Trace Amine-Associated Receptor Agonists: Synthesis and Evaluation of Thyronamines and Related Analogues

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Received June 16, 2005

We have previously shown that several thyronamines, decarboxylated and deiodinated metabolites of the thyroid hormone, potently activate an orphan G protein-coupled receptor in vitro (TAAR1) and induced hypothermia in vivo on a rapid time scale [Scanlan, T. S.; Suchland, K. L.; Hart, M. E.; Chiellini, G.; Huang, Y.; Kruzich, P. J.; Frascarelli, S.; Crossley, D. A.; Bunzow, J. R.; Ronca-Testoni, S.; Lin, E. T.; Hatton, D.; Zucchi, R.; Grandy, D. K. 3-Iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nat. Med.* **2004**, *10* (6), 638−642]. Herein, we report the synthesis of these thyronamines. Additionally, a large number of thyroamine derivatives were synthesized in an effort to understand the molecular basis of TAAR1 activation and hypothermia induction. Several derivatives were found to potently activate both rTAAR1 and mTAAR1 in vitro (compounds **77**, **85**, **91**, and **92**). When administered to mice at a 50 mg/kg dose, these derivatives all induced significant hypothermia within 60 min and exhibited a hypothermic induction profile analogous to 3-iodothyronamine (**1**, T_1AM) except **91**, which proved to be more efficacious. On the basis of this result, a dose-dependent profile for **91** was generated and an ED_{50} of 30 μmol/kg was calculated. Compound **91** proved to be more potent than T_1AM for TAAR1 activation and exhibits increased potency and efficacy for hypothermia induction. These data further strengthen the pharmacological correlation linking TAAR1 activation by thyronamines and hypothermia induction in mice.

Introduction

Thyroid hormone (TH) is crucial for normal physiology and development in vertebrates.[2] The predominant secreted form of TH is thyroxine (T_4; Figure 1), which is deiodinated in target tissue to 3,5,3′-triiodothyronine (T_3; Figure 1), the high-affinity ligand for thyroid hormone receptors (TRs). The TRs regulate TH target gene transcription in a T_3-dependent manner, and like all transcriptional regulation, these processes occur on a relatively slow time scale. However, there are many rapid effects associated with TH, especially in the cardiovascular system, that occur in seconds to minutes, a time scale precluding a T_3−TR transcriptional mechanism.[3,4] Some examples of these nongenomic effects include sodium channel activation[5] and increased isolated cardiac myocyte contractile function.[6] Additionally, there is evidence that rapid effects of TH could have therapeutic implications.[7] Patients suffering from congestive heart failure can experience a rapid increase in cardiac performance upon a bolus injection of T_3.

Recently, we demonstrated that a novel metabolite of the TH, 3-iodothyronamine (**1**, T_1AM; Figure 1), elicited rapid responses in vitro and in vivo.[1] In HEK293 cells expressing an orphan G protein-coupled receptor, the trace amine receptor[8,9] (TAR)-now officially referred to as the trace amine-associated receptor (TAAR)[10]-T_1AM potently increased cAMP accumulation (rTAAR1, EC_{50} = 14 nM; mTAAR1, EC_{50} = 112 nM). In mice, T_1AM rapidly induces hypothermia and bradycardia and leads to behavioral inactivity. In a rat working heart preparation, T_1-AM treatment leads to a rapid decrease in cardiac drive with a more potent inhibition of inotropy than chronotropy. Herein, we describe the synthesis and properties of a number of thyronamines and related analogues. These compounds were screened in vitro for TAAR1 activation, and selected compounds were evaluated in vivo for induction of hypothermia.

Results and Discussion

Synthesis. Utilizing a divergent synthetic route, we synthesized the entire panel of thyronamines from commercially available starting materials. Synthesis of the right-hand portion of the scaffold begins with the protection of tyramine **2** to give **3** (Scheme 1). Selective iodination of **3** was a crucial component to our synthetic route, and many electrophilic iodine sources were screened.[11−13] We found that in situ generation of ICl in methanol gave a mixture of the mono- and diiodinated products **4** and **5** favoring the former (method A).[14] The diiodinated product **5** can be synthesized in good yields with an excess of iodine monochloride and butylamine (method B). The synthesis of the left-hand portion of the scaffold begins with the protection of commercially available phenol **6** as either the silyl ether **7** or the MOM-protected **8**. The aryl bromides were lithiated followed by reaction with triisopropyl borate to give the desired boronic acids **9** and **10**.[15,16]

With the appropriate boronic acid and phenols in hand, the biaryl ether moiety was constructed. Boronic acid **9** was coupled with phenols **3**−**5** utilizing stoichiometric copper(II) acetate to give ethers **11**−**13**, respectively (Scheme 2).[17−19] In our hands, this coupling procedure proved to be variable with good to moderate yields reported. The ethers were treated with tetrabutylammonium fluoride, and the resulting phenols were iodinated. Utilizing method A outlined above for phenol **16** proved to be problematic. An inseparable impurity arising from iodination adjacent to the biaryl ether bridge contaminated the desired

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10.1021/jm0505718 CCC: $33.50 © 2006 American Chemical Society
Published on Web 01/11/2006

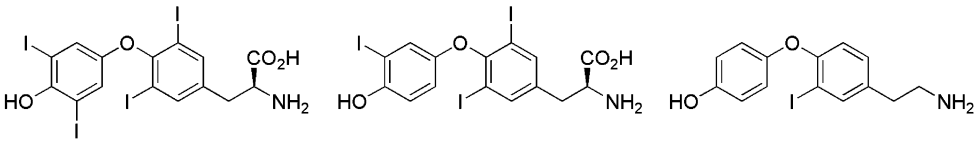
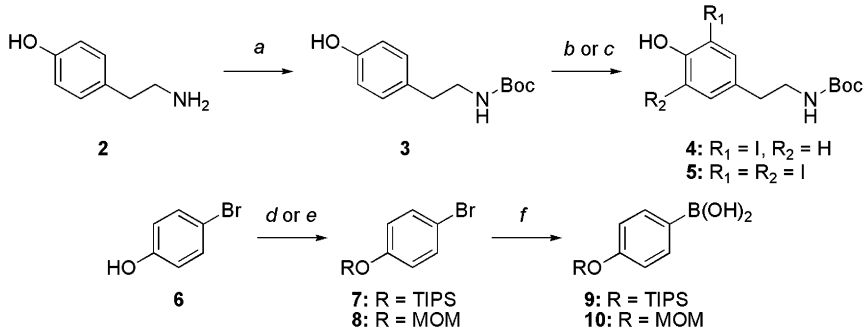


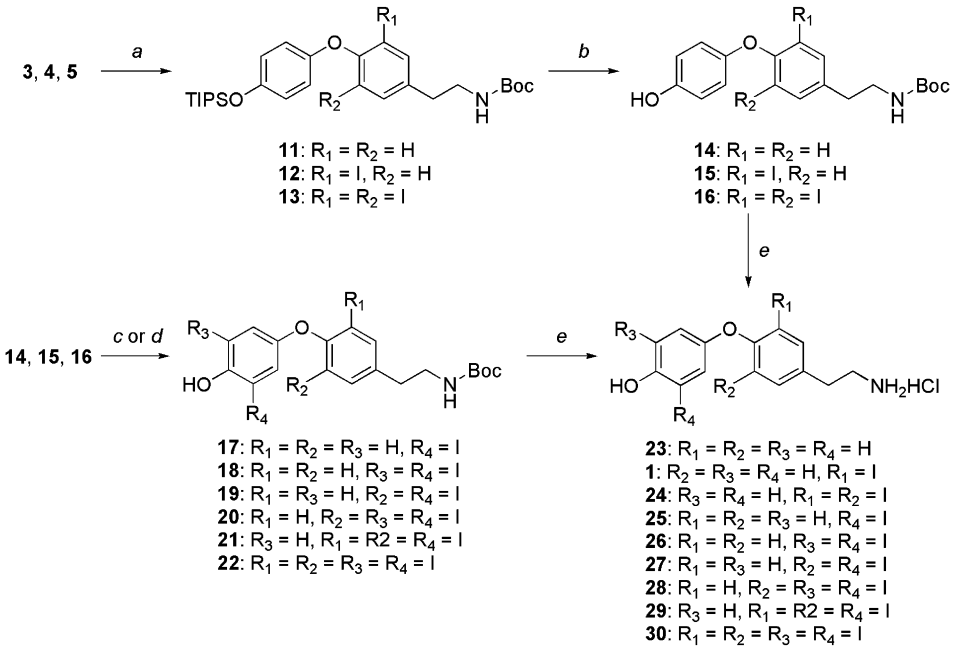
Figure 1. Predominant TH produced by the thyroid gland, thyroxine (T_4); the active TH, 3,3′,5-triiodothyronine (T_3); and a novel metabolite, 3-iodothyronamine (**1**, T_1AM).

Scheme 1. Synthesis of Thyronamine Fragments[a]



[a] Reagents and conditions: (a) Boc_2O, $NaHCO_3$, THF/H_2O, room temperature. (b) NaI, NaOCl, KOH, MeOH, 0 °C. (c) ICl, $BuNH_2$, DCM, 0 °C. (d) TIPSCl, imidazole, DCM, room temperature. (e) NaH, MOMCl, THF, room temperature. (f) (i) *n*-BuLi, THF, −78 °C; (ii) $B(OiPr)_3$, THF, −78 °C to room temperature; (iii) 0.5 M HCl, 0 °C.

Scheme 2. Synthesis of Thyronamines[a]



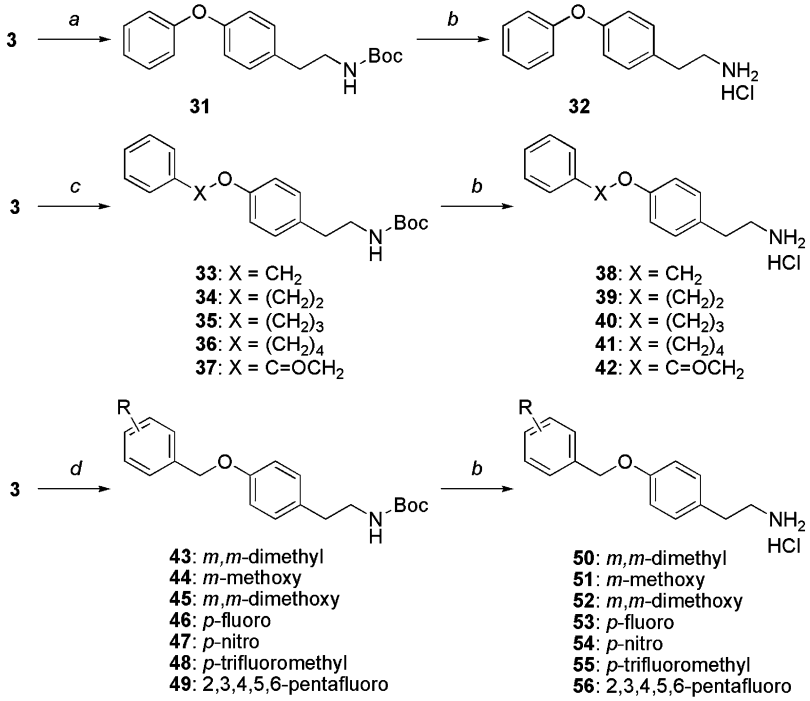
[a] Reagents and conditions: (a) $Cu(OAc)_2$, **9**, Et_3N, pyridine, 4 Å powdered molecular sieves, DCM, room temperature. (b) TBAF, THF, 0 °C. (c) KI_3, $BuNH_2$, THF/H_2O, 0 °C. (d) ICl, $BuNH_2$, THF, 0 °C. (e) 3 N HCl (anhydrous) in EtOAc.

product. However, KI_3 and butylamine provided the requisite monoiodinated product, albeit in low yields.[20] Deprotection of **14**−**22** with 1−3 N HCl in anhydrous ethyl acetate gave the desired thyronamines **23** (T_0AM), **1** (T_1AM), **24** (T_2AM), **25** (3′-T_1AM), **26** (3′,5′-T_2AM), **27** (3,3′-T_2AM), **28** (rT_3AM), **29** (T_3AM), and **30** (T_4AM) in excellent yields.[21] In all cases, the hydrochloride salts were sufficiently pure and required no additional purification.

In an effort to explore the structural requirements of TAAR1 activation, several derivatives of the thyronamines were pursued. These analogues included removal of the phenol hydroxyl, an increase in the distance between the two aryl rings, a change in the electronic and steric requirements on the aryl ring distal to the amine functionality, alkylation or modification of the amine, and replacement of the 3-iodo substituent with an alkyl group.

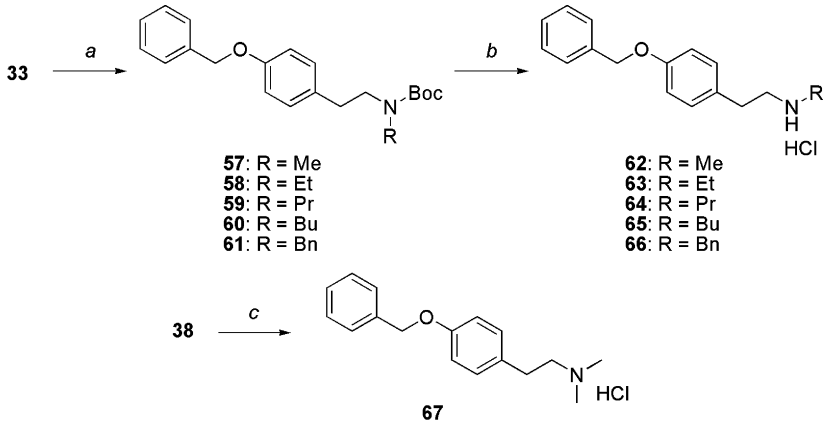
Protected tyramine **3** was coupled with phenyl boronic acid utilizing the copper(II)-mediated procedure outlined above to give biaryl ether **31** (Scheme 3). Deprotection gave the hydrochloride salt of the des-hydroxythyronamine **32**. Alkylation of **3** with a variety of aryl-substituted alkyl halides followed by subsequent deprotection gave derivatives **38**−**42**, with an increased chain between the two aryl rings. In an effort to examine the steric and electronic requirements of the distal aryl ring, protected tyramine **3** was alkylated with a variety of substituted benzyl halides followed by subsequent deprotection providing derivatives **50**−**56**.

Scheme 3. Synthesis of *O*-Substituted Analogues[a]



[a] Reagents and conditions: (a) Phenyl boronic acid, $Cu(OAc)_2$, Et_3N, pyridine, 4 Å powdered molecular sieves, DCM, room temperature. (b) 3 N HCl (anhydrous) in EtOAc. (c) $Ph(CH_2)_nBr$ ($n = 1-4$) or $PhC{=}OCH_2Br$, K_2CO_3, DMF. (d) $ArCH_2Br$, K_2CO_3, DMF.

Scheme 4. Alkylated Amine Derivatives[a]



[a] Reagents and conditions: (a) RBr, K_2CO_3, DMF, room temperature. (b) 3 N HCl (anhydrous) in EtOAc. (c) Formic acid, formaldehyde, reflux.

The benzylated intermediate **33** was alkylated with a variety of alkyl halides in the presence of potassium carbonate in DMF to give **57**−**61** in moderate yields (Scheme 4). Deprotection with 3 N HCl in anhydrous ethyl acetate gave **62**−**66** as white solids in excellent yields. The hydrochloride salts were sufficiently pure and used without any further purification. Treatment of **38** under Eschwieler−Clark conditions followed by treatment with anhydrous HCl gave the dimethylated derivative **67** in acceptable yields.

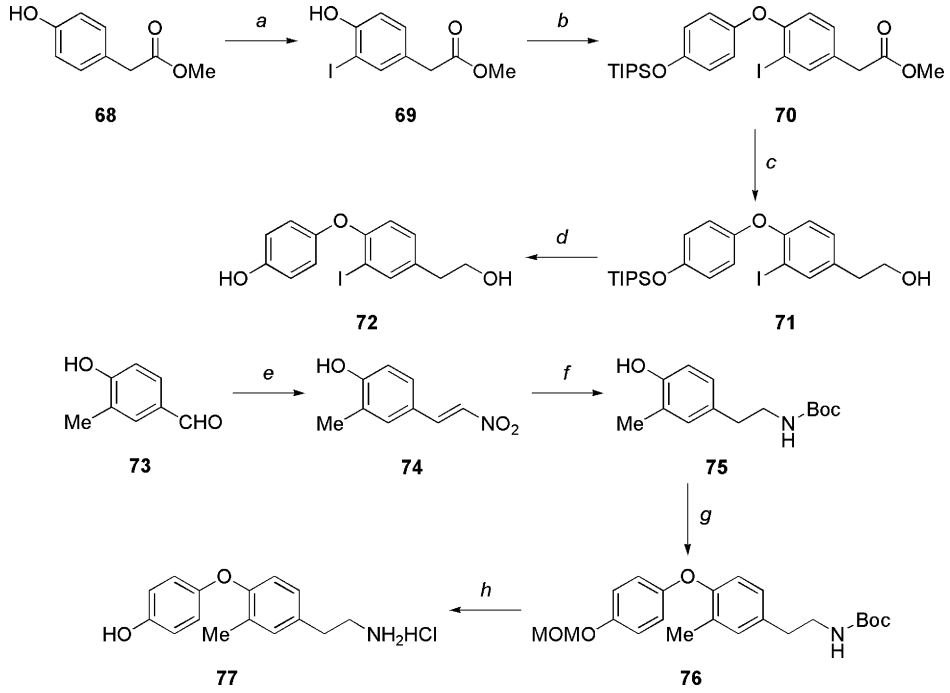
To examine the requirement of the amine, we synthesized a derivative replacing this functionality with a hydroxyl (Scheme 5). Commercially available phenol **68** was iodinated in the presence of iodine monochloride and butylamine to give **69** in low yields. Copper(II)-mediated coupling with boronic acid **9** gave **70** in moderate yields. Reduction of the ester under standard diisobutyl aluminum hydride conditions, followed by deprotection with tetrabutylammonium fluoride, gave **72** in good yield.

We also synthesized a T_1AM derivative replacing the 3-iodo substituent with a methyl group (Scheme 5). Aldehyde **73** was condensed with nitromethane to give the nitro compound **74**.[22] Reduction with lithium aluminum hydride followed by protection gave **75** in respectable yields.[22] Copper(II)-mediated coupling of **75** with boronic acid **10** gave the biaryl ether **76**. Concomitant hydroxyl and amine deprotection in the presence of 3 N anhydrous HCl in ethyl acetate gave derivative **77** in excellent yields.

The second generation thyronamines that were synthesized incorporated elements from T_1AM and the first generation derivatives described above. In particular, we wanted to investigate combinations of electron-withdrawing groups on the aryl ring distal to the amine, the iodine on the aryl ring proximal to the amine, and *N*-alkylation. We examined both *O*-benzyl tyramine and thyroanmine scaffolds with these modifications.

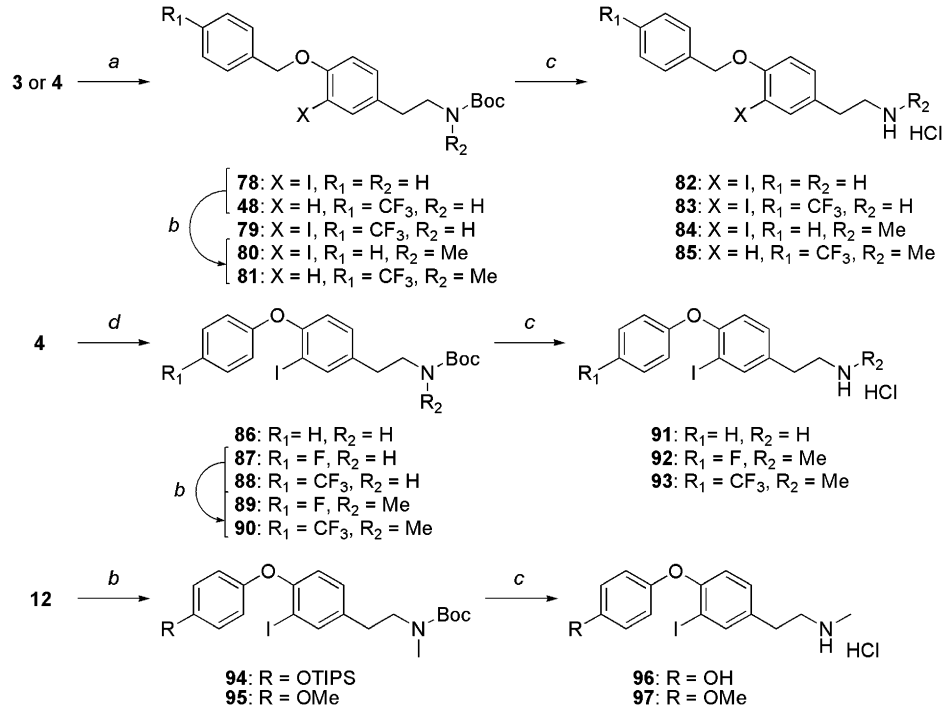
To this end, the iodinated tyramine intermediate **4** was alkylated with either benzyl bromide or 4-trifluoromethylbenzyl bromide under standard conditions to give **78** and **79**, respectively, in acceptable yields (Scheme 6). The alkylated product **78** and intermediate **48** described above were *N*-alkylated in the presence of sodium hydride and iodomethane to give **80**

Scheme 5. Synthesis of 3-Iodothyronamine Analogues[a]



[a] Reagents and conditions: (a) ICl, $BuNH_2$, THF, −40 °C. (b) $Cu(OAc)_2$, **9**, Et_3N, Pyr, DCM, 4 Å molecular sieves. (c) DIBAL-H, THF, −78 °C. (d) TBAF, THF, 0 °C. (e) CH_3NO_2, NH_4OAc, reflux. (f) (i) $LiAlH_4$, THF, reflux; (ii) Boc_2O, $NaHCO_3$, THF/H_2O. (g) $Cu(OAc)_2$, **10**, $EtNiPr_2$, pyridine, DCM, 4 Å molecular sieves, room temperature. (h) 3 N HCl (anhydrous in EtOAc).

Scheme 6. Synthesis of Second Generation Analogues[a]



[a] Reagents and conditions: (a) Benzyl bromide, K_2CO_3, DMF. (b) NaH, MeI, THF, room temperature. (c) 3 N HCl (anhydrous) in EtOAc. (d) Aryl boronic acid, $Cu(OAc)_2$, pyridine, Et_3N, DCM, 4 Å molecular sieves.

and **81** in good yields. Intermediates **78**−**81** were deprotected in the presence of 3 N HCl in anhydrous ethyl acetate to give the hydrochloride salts **82**−**85** in excellent yields and were used without any further purification.

To examine the biaryl ether scaffold, the iodinated tyramine **4** was subjected to the copper(II)-mediated coupling conditions described above in the presence of either phenyl-, *p*-fluorophenyl-, or *p*-trifluoromethylphenyl boronic acid to give **86**, **87**, and **88** in moderate yields. Ethers **87** and **88** were treated with sodium hydride and iodomethane to give the *N*-alkylated products **89** and **90**. Intermediates **86**, **89**, and **90** were then deprotected in the presence of 3 N HCl in anhydrous ethyl acetate to give the corresponding hydrochloride salts **91**−**93** in excellent yields. Finally, *N*-*t*-Boc-3-iodothyronamine **12** was treated with sodium hydride and iodomethane; however, the desired *N*-alkylated product **94** was only a minor product. The

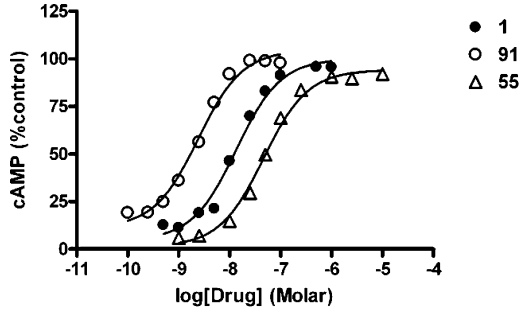
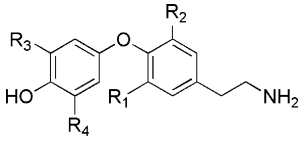


Figure 2. Dose-dependent cAMP accumulation. Curves representing dose-dependent increase in cAMP accumulation in cultured HEK293 cells stably expressing rTAAR1. Data reported for 3-iodothyronamine **1** (T_1AM) (●), *O*-phenyl-3-iodotyramine **91** (○), and *O*-(*p*-trifluoromethyl)benzyl tyramine **55** (△) are expressed as a percent of a forskolin control (%FSK). Concentration−response curves were plotted, and EC_{50} values were calculated with Prism software as described in the Experimental Section. The standard error of the mean was less than 0.1 log units from the average EC_{50} value in all cases.

Table 1. Thyronamines Activate rTAAR1 and mTAAR1



					EC_{50}	
#	R_1	R_2	R_3	R_4	rTAAR1	mTAAR1
23	H	H	H	H	131	∼1000
1	I	H	H	H	14	112
24	I	I	H	H	56	371
29	I	I	H	I	87	>1000
30	I	I	I	I	>1000	>1000
27	H	I	H	I	41	∼1000
28	H	I	I	I	>1000	>1000
26	H	H	I	I	>1000	>1000
25	H	H	H	I	800	>1000

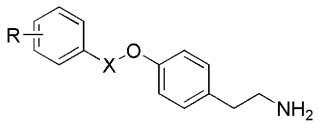
[a] Values represent the average EC_{50} of multiple experiments and were calculated using Prism software as described in the Experimental Section. The standard error of the mean was less than 0.1 log units from the average EC_{50} value in all cases.

predominate product, **95**, resulted from hydride-promoted desilylation followed by subsequent methylation of the phenol. These products were subsequently deprotected in the presence of 3 N HCl in anhydrous ethyl acetate to give the corresponding hydrochloride salts, **96** and **97**.

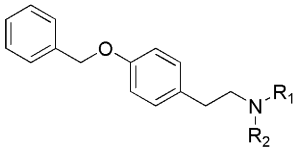
Receptor Activation. Previously, we reported rTAAR1 and mTAAR1 activation by thyronamines.[1] Both mTAAR1 and rTAAR1 are $G\alpha_s$-coupled G protein-coupled receptors that in vitro stimulate adenylyl cyclase leading to cAMP accumulation in response to agonists. A typical dose−response curve for **1**, T_1AM, is shown in Figure 2. As the results for the thyronamines indicate, the number of iodines on the scaffold and relative position directly affect potency (Table 1). T_1AM was the most potent at both rTAAR1 and mTAAR1, with EC_{50} values of 14 and 112 nM, respectively.

The first generation thyronamine analogues described above were evaluated in the cAMP accumulation assay with cells stably expressing either rTAAR1 or mTAAR1 (Table 2). The *O*-phenyltyramine derivative **32** exhibited increased potency at TAAR1 of both species as compared to **23**, T_0AM (by approximately 3-fold). Increasing the distance between the two aryl rings resulted in different potencies at rTAAR1 and mTAAR1. The benzylated derivative **38** was less potent at rTAAR1 than mTAAR1. The addition of another methylene group in the spacer was also deleterious (compound **39**); however, significant activity was rescued with a three or four carbon spacer (compounds **40** and **41**, respectively). Incorpora-

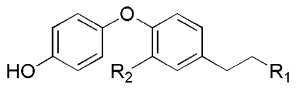
Table 2. First Generation Analogues of Thyronamines Activate rTAAR1 and mTAAR1



			EC_{50}[a]	
#	X	R	rTAAR1	mTAAR1
32	-	H	38	296
38	CH_2	H	209	168
39	$(CH_2)_2$	H	203	207
40	$(CH_2)_3$	H	89	102
41	$(CH_2)_4$	H	43	80
42	$(CO)CH_2$	H	309	83
50	CH_2	*m*,*m*-dimethyl	137	98
51	CH_2	*m*-methoxy	141	194
52	CH_2	*m*,*m*-dimethoxy	333	123
53	CH_2	*p*-fluoro	72	38.5
54	CH_2	*p*-nitro	64	21.5
55	CH_2	*p*-trifluoromethyl	55	20.2
56	CH_2	2,3,4,5,6-pentafluoro	>1000	>1000



			EC_{50}[a]	
#	R_1	R_2	rTAAR1	mTAAR1
62	Me	H	119	54
63	Et	H	>1000	71
64	Pr	H	>1000	>1000
65	Bu	H	>1000	>1000
66	Bn	H	>1000	>1000
67	Me	Me	>1000	192



			EC_{50}[a]	
#	R_1	R_2	rTAAR1	mTAAR1
72	OH	I	>1000	>1000
77	NH_2	CH_3	33	116

[a] Values represent the average EC_{50} of multiple experiments and were calculated using Prism software as described in the Experimental Section. The standard error of the mean was less than 0.1 log unit from the average EC_{50} value in all cases.

tion of a carbonyl in the spacer exhibited reduced potency at rTAAR1 and increased potency at mTAAR1 (compound **42**). In general, the addition of bulky and/or electron-donating groups to the benzyl group was tolerated by both rTAAR1 and mTAAR1 (compounds **50**−**52**). Incorporating electron-withdrawing substituents on the benzyl group significantly increased the potency toward TAAR1 (compounds **53**−**55**), except for the pentafluorobenzyl derivative **56**, which was inactive. This suggests that these derivatives may be forming an edge-to-π interaction crucial for receptor activation.[23,24] Of the benzyl derivatives examined, the *p*-trifluoromethylbenzyl derivative **55** was the most potent toward rTAAR1 and mTAAR1 (calculated EC_{50} values of 55 and 20.2 nM, respectively). A typical dose−response curve for **55** vs rTAAR1 is shown in Figure 2.

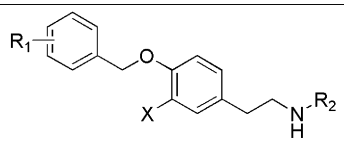
Because the TAAR1 is most closely related to the receptors for the biogenic amines, we anticipated that the amine functionality would be required for activation. The *N*-methylated analogue of benzyl tyramine **38** (compound **62**) exhibited increased potency; however, larger alkyl substituents greatly decreased activation of both rTAAR1 and mTAAR1 (compounds **64**−**66**). The notable exception is the ethyl-substituted derivative **63**, which was equipotent to **62** at mTAAR1 but inactive against rTAAR1. *N*,*N*-Dimethylation was also deleterious for rTAAR1 activation while mTAAR1 exhibited moderate activation (compound **67**). In the case of compound **72**, where the amine has been replaced with a hydroxyl, no TAAR1 activation was observed.

Replacement of the 3-iodo substituent with an alkyl isostere was also examined. Derivative **77** with a methyl group at the 3-position of the thyronamine scaffold was nearly as potent as T_1AM against both rTAAR1 and mTAAR1 (calculated EC_{50} values of 33 and 116 nM, respectively).

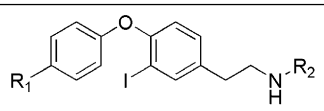
The second generation analogues were also assayed for rTAAR1 and mTAAR1 activation (see Table 3). The benzyl-substituted tyramine derivative **82** with the iodine exhibited an increase in rTAAR1 activation and slightly attenuated mTAAR1 activation relative to the parent compound **38**. However, inclusion of the iodine and methylation of the amine, compound **84**, led to an increase in potency of activation for TAAR1. Interestingly, **83**, which contained an electron-withdrawing group, a trifluoromethyl, and the iodine, failed to activate rTAAR1 significantly and only weakly activated mTAAR1. However, **85**, which contained the same electron-withdrawing group and the methylated amine, potently activated both rTAAR1 and mTAAR1 (calculated EC_{50} values of 61 and 12 nM, respectively). The *N*-methylated T_1AM derivative **96** exhibited slightly increased potency relative to T_1AM at rTAAR1 (In a comparative study, T_1AM exhibited an EC_{50} of 25 nM) but slightly attenuated potency at mTAAR1. Methylation of the phenol, derivative **97**, was deleterious to mTAAR1 and rTAAR1 activation. Replacing the phenolic hydroxyl with a large electron-withdrawing group was also deleterious. Compound **93** failed to activate the two TAARs examined to a significant level. However, compound **92**, which contains a fluorine atom, exhibited increased potency at both rTAAR1 and mTAAR1. The derivative lacking the phenolic hydroxyl **91** was the most potent agonist of heterologously expressed rTAAR1 and one of the most potent at heterologously expressed mTAAR1 (calculated EC_{50} values of 2.4 and 35 nM, respectively). A typical dose−response curve for **91** activation of rTAAR1 is shown in Figure 2.

In Vivo Pharmacology. We previously reported that in mice, T_1AM induced a rapid, dose-dependent drop in core body temperature.[1] The most potent derivatives from this study, compounds **77**, **85**, **91**, and **92**, were also examined for hypothermia induction in mice. When adult male C57BL/6J mice were administered a 50 mg/kg dose of **77**, **85**, **91**, and **92** (i.p.), rapid induction of hypothermia was observed (Figure 3A). Furthermore, all four of the compounds induced a significant drop in body temperature relative to vehicle control and similar to the degree of hypothermia seen with 50 mg/kg T_1AM. Compounds **77**, **85**, and **92** were as efficacious as T_1AM at this dose with mean minimal body temperatures of 29.6, 26.7, and 28.3 °C, respectively. Mice treated with T_1AM typically reached a minimal body temperature of 28.5 °C. Compound **91** was more efficacious than T_1AM, dropping the average body temperature of the mice from 36.7 to 23.6 °C within 120 min; however, this derivative proved to be toxic at this dose. After 24 h, the mice treated with **91** exhibited stiffening of the hind limbs and several expired (died). Similarly, those mice administered derivative **85** became cold, assumed a hunched posture, and had distended abdomens 8 days after injection, at which time the animals were euthanized.

Table 3. Second Generation Analogues of Thyronamines Activate rTAAR1 and mTAAR1



#	X	R_1	R_2	EC_{50}[a] rTAAR1	EC_{50}[a] mTAAR1
82	I	H	H	77	221
83	I	CF_3	H	>1000	284
84	I	H	Me	68	106
85	H	CF_3	Me	61	12



#	R_1	R_2	EC_{50}[a] rTAAR1	EC_{50}[a] mTAAR1
91	H	H	2.4	35
92	F	Me	2.7	32.5
93	CF_3	Me	>1000	>1000
96	OH	Me	18	221
97	OMe	Me	107	>1000

[a] Values represent the average EC_{50} of multiple experiments and were calculated using Prism software as described in the Experimental Section. The standard error of the mean was less than 0.1 log unit from the average EC_{50} value in all cases.

A dose range study was performed with **91** but not with the other derivatives because of the observed toxicity. Mice were treated with 2, 10, 25, and 50 mg/kg doses of **91** (Figure 3B). Mice administered 25 and 50 mg/kg doses exhibited significant hypothermia relative to the vehicle control. On the basis of the above data, we calculated the dose to induce half-maximal stimulation of hypothermia (ED_{50}) for **91** to be 30 μmol/kg. This compares with the 59 μmol/kg ED_{50} of T_1AM for hypothermia induction.

Discussion. We previously showed that certain thyronamines proposed to arise from deiodination and decarboxylation of T_4 are potent agonists of mouse and rat TAAR1.[1] 3-Iodothy-

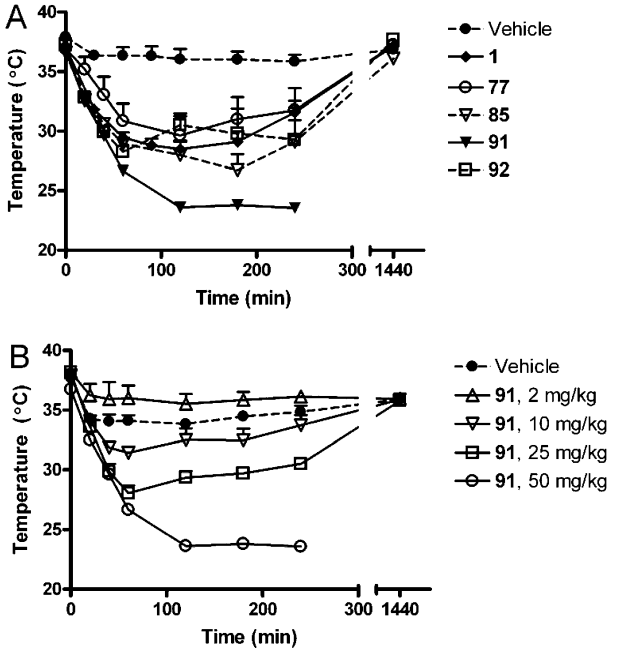


Figure 3. Effect of thyronamine analogues on rectal temperature of mice. (A) Effects of intraperatoneal injection (i.p.) of compounds **77** (○), **85** (▽), **91** (▼), and **92** (□) at 50 mg/kg as compared to **1** (T_1AM) (50 mg/kg, ◆) and vehicle control (100 μL of DMSO, ●) in adult male C57BL/6J mice maintained at 25 °C. The baseline temperature is determined immediately before each mouse was injected (time 0 min). All compounds significantly reduced the rectal temperature as compared to vehicle control. (B) Compound **91** reduces the rectal temperature in a dose-dependent manner. Effects of i.p. injection of **91** at 2, 10, 25, and 50 mg/kg as compared to vehicle control (200 μL of DMSO, ●) in adult male C57BL/6J mice maintained at 25 °C. Data reported for compounds **77**, **85**, **91**, and **92** are averages of 2−4 mice.

ronamine (**1**, T_1AM) was found to be the most potent agonist for both mouse and rat TAAR1 and was also found to be an endogenous component of extracts from rodent brain, peripheral organs, and blood. In pharmacological studies, T_1AM (and **23**, T_0AM) rapidly induces hypothermia and bradycardia in mice and rapidly reduces cardiac output in an ex vivo working rat heart preparation. The purpose of the present study was to understand the structure−activity relationship (SAR) of thyronamine/TAAR activation, and toward this goal, a large number of thyronamine derivatives were synthesized and evaluated as TAAR1 agonists.

Analysis of the TAAR1 activation data reported herein suggests the following requirements for TAAR activation: (i) A basic amino group at Cα is required; (ii) monomethylation of the amine can be beneficial although larger alkyl groups and bis-alkylation are deleterious; (iii) mTAAR1 and rTAAR1 differ with respect to their tolerance of changes in the diaryl linker, both in length and in functionality; (iv) within the thyronamine scaffold, an iodine or methyl substituent at the 3-position is optimal; and (v) *H* at the 4′-position vs OH is optimal, and substituents larger than OH are deleterious.

The requirement for a basic amine at Cα is consistent with the SARs of other biogenic amine GPCRs that belong to the same family as the TAARs. Likewise, the toleration of *N*-alkylation is consistent although somewhat more limited in the case of TAAR1. For example, isoproterenol, which carries an *N*-isopropyl substituent, is a substantially more potent β-adrenergic receptor agonist than the endogenous ligand norepinephrine, whereas monomethylation marks the rough limit for *N*-alkylation of thyronamine/TAAR1 agonists and only a modest potency improvement is seen. The observed sensitivity to diaryl linker length is a useful property as we found that the *O*-benzyl compounds (containing a linker length of two atoms) were significantly easier to prepare than the diaryl ether thyronamine derivatives (containing a one atom linker). In terms of the SAR, this suggests flexibility in the TAAR1 ligand-binding pocket where ligands that are longer than thyronamines can be accommodated. Although the ability to substitute methyl for iodide at the 3-position of the inner ring is not unusual, it is somewhat surprising that this substitution does not lead to a decrease in potency. In the context of the nuclear TRs, a similar methyl for iodine substitution results in a 100-fold decrease in agonist potency.[25] Finally, the observation that the 4′-OH of the thyronamine is not required is also divergent from the thyronine/nuclear TR SAR where removal of the 4′-OH results in about a 10-fold decrease in binding affinity and potency.[25] In addition, the 4′-OH is an important site of sulfation and glucoronidation, which are important clearance mechanisms.[26]

Compounds **77**, **85**, **91**, and **92** were found to be more potent agonists at either rat or mouse TAAR1 than **1** (T_1AM). Upon administration to mice, all of these compounds induced hypothermia with the same rapid kinetics as T_1AM. In addition, all of the compounds except **91** lowered body temperature to the same level as T_1AM. Compound **91** was found to have greater efficacy of hypothermia induction than T_1AM and in a dose ranging study was found to be more potent than T_1AM by a factor of 2. This further strengthens the pharmacological correlation linking TAAR1 activation by thyronamines and hypothermia induction in mice.[1] Compounds **85**, **91**, and **92** all exhibited obvious toxicity within a week of the hypothermia measurements; this was not seen with T_1AM. A common structural feature of these three derivatives is the lack of a 4′-OH, which as mentioned above is the site of sulfation/glucoronidation modification in thyronines, and, by analogy, may play a similar role in the clearance mechanism for thyronamines. We speculate, therefore, that impaired clearance may be a factor in the observed toxicity of these compounds.

Summary

In summary, the synthesis of a family of decarboxylated TH analogues, called thyronamines, is reported. Additionally, we synthesized a family of thyronamine derivatives to explore the SAR of TAAR1 activation and induced hypothermia in mice. In the case of rTAAR1 activation, derivatives **77**, **91**, and **92** were the most potent. In the case of mTAAR1, derivatives **85**, **91**, and **92** were among the most potent. When administered to mice at a 50 mg/kg dose, these derivatives all induced significant hypothermia within 60 min. All of these derivatives exhibited a hypothermic induction profile analogous to **2**, T_1AM, except **91**, which proved to be more efficacious. On the basis of this result, a dose-dependent profile for **91** was generated and an ED_{50} of 30 μmol/kg was calculated. The data for **91** taken as a whole indicate that it is more potent then T_1AM for TAAR1 activation and exhibits increased potency and efficacy for hypothermia induction.

Materials and Methods

General. ^1H and ^{13}C NMR spectra were taken on a Varian 400 (400 and 100 MHz, respectively). Data reported were calibrated to internal TMS (0.0 ppm) for all solvents unless otherwise noted and are reported as follows: chemical shift, multiplicity (app, apparant; par obsc, partially obscured; ovrlp, overlapping; br, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant, and integration. High-resolution mass spectrometry (HRMS) using electrospray ionization was performed by the National Bio-Organic, Biomedical Mass Spectrometry Resource at UCSF. Inert atmosphere

operations were conducted under argon passed through a Drierite drying tube in flame-dried or oven-dried glassware unless otherwise noted. Anhydrous THF, DCM, diethyl ether, pyridine, and diisopropyl ethylamine were filtered through two columns of activated basic alumina and transferred under an atmosphere of argon gas in a solvent purification system designed and manufactured by J. C. Meyer (University of California, Irvine). Anhydrous DMF was obtained by passing through two columns of activated molecular sieves. All other anhydrous solvents and reagents were purchased from Aldrich, Sigma-Aldrich, Fluka, or Acros and were used without any further purification unless otherwise stated. Final compounds were judged to be >95% pure by ^{1}H NMR analysis and confirmed by LC/MS and HPLC. LC/MS was performed on an Waters AllianceHT LC/MS with a gradient of 0−100% methanol (0.05% TFA) over 7 min. HPLC was performed on a Waters AllianceHT LC with a gradient of 0−100% acetonitrile (0.05% TFA) over 7 min.

In Vitro cAMP Assays. HEK293 cells stably transfected with either rTAAR1 or mTAAR1 were harvested in Krebs−Ringer−HEPES buffer (KRH) and preincubated in KRH with 200 μM 3-isobutyl-1-methylxanthine (IBMX). Cells were incubated in KRH with 100 μM IBMX with the test compound, forskolin (10 μM), or vehicle (DMSO) for 1 h at 37 °C (400 μL total volume). The cells were then boiled for 20 min after adding an equal volume of 0.5 mM sodium acetate buffer and centrifuged to remove cellular debris. An aliquot of the resulting extract (200 μL) was analyzed for cAMP content using competitive binding of [^{3}H]cAMP to a cAMP binding protein (Diagnostic Products Corp., Los Angeles, CA). Data were reported relative to the forskolin control and expressed as %cAMP. Concentration−response curves were plotted, and EC_{50} values were calculated with Prism software (GraphPad, San Diego, CA). The R^2 values in all cases were greater than 0.9. Experiments were run in triplicate, and the standard error of the mean (SEM) was less than 0.1 log units from the average EC_{50} value in all cases.

In Vivo Induced Hypothermia. C57BL/6J male mice aged about 7−10 weeks were obtained from Jackson Laboratories. Mice were housed in groups of 3−6 per cage and had ad libitum access to food (PMI rodent lab chow) and water. The vivarium was maintained at 21−22 °C on a 12 h/12 h light/dark cycle with lights on at 06:00. All studies were conducted between 09:30 and 13:30 in a room with an ambient temperature of 19−21 °C. All experiments were done in accordance with approved institutional and National Institutes of Health (NIH) guidelines for the use and care of animals.

All drugs were dissolved in 100% dimethyl sulfoxide (DMSO) with the exceptions of T_1AM, which was dissolved in 60% DMSO and physiological saline (pH7.4), and **91** (65% DMSO and physiological saline). On the test day, before drug administration, basal body weights and rectal temperatures (THM 100, Indus Instruments) were determined. After basal measures, mice received an i.p. injection of **77**, **85**, **91**, **92**, **1** (T_1AM) (2, 10, 25, and 50 mg/kg), or vehicle (100% DMSO, 60% DMSO and 40% saline, or 65% DMSO and 35% saline) and were returned to the home cages. The rectal temperature was measured at 30, 60, 120, 180, 240, and 1440 min after injection. Temperature data were analyzed by a two-way analysis of variance (ANOVA). Significance was set at $P < 0.05$. After a significant overall ANOVA, Bonferroni posthoc comparisons were done across the treatment groups.

General Procedure for *t*-Boc Deprotection. The protected amine (31.2 mg, 0.054 mmol) was dissolved in a 1 or 3 N HCl solution in ethyl acetate (2 mL, anhydrous), and the reaction mixture was stirred at ambient temperature for 5−15 h. A white precipitate formed after several minutes. Additional HCl was added as needed (2 mL), and the reaction mixture was stirred until complete by TLC. The reaction was completed as described below.

General Procedure for Silyl Deprotection. To a stirred solution of the protected phenol (1.0 mmol) in THF (10 mL) was added TBAF (1.5 mL, 1.5 mmol, 1 M solution in THF) dropwise. The reaction mixture was stirred for 10−30 min until complete by TLC analysis and then diluted with ethyl acetate. The reaction mixture was washed with 0.5 M HCl, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were sequentially washed with water and brine and then dried over $MgSO_4$. The crude product was purified as described below.

Thyronamine Hydrochloride (23, T_0AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was concentrated in vacuo and dried under high vacuum pressure to give **23** as a slightly tan solid (32.9 mg, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.37 (s, 1 H), 7.90 (br s, 3 H), 7.20 (d, J = 8.4 Hz, 1 H), 6.86 (ovrlp d, J = 8.8 Hz, 1 H), 6.85 (ovrlp d, J = 8.4 Hz, 1 H), 6.78 (d, J = 8.8 Hz, 1 H), 2.99 (app br q, J = 8.0 Hz, 2 H), 2.81 (t, J = 8.2 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{15}NO_2$: calcd, 229.1103; found, 229.1107. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 4.78 min; purity, 100%; $[M - NH_2]^+$ calcd, 213.09; found, 213.37 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.22 min; purity, 95%.

3-Iodothyronamine Hydrochloride (1, T_1AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude precipitate was filtered and washed with ether to give **1** as a white solid (816 mg, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.44 (s, 1 H), 8.12 (br s, 3 H), 7.76 (s, 1 H), 7.20 (d, J = 8.0 Hz, 1 H), 6.79 (s, 4 H), 6.68 (d, J = 8.4 Hz, 1 H), 2.98 (app br q, J = 7.2 Hz, 2 H), 2.84 (t, J = 7.4 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{14}INO_2$ $[M - NH_3]^+$: calcd, 337.9804; found, 337.9812. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.32 min; purity, 100%; $[M + H]^+$: calcd, 356.01; found, 356.44 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.73 min; purity, 100%.

3,5-Diiodothyronamine Hydrochloride (24, T_2AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was concentrated in vacuo and dried under high vacuum pressure to give **24** as a white solid (26.7 mg, 96% yield). ^{1}H NMR (400 MHz, D_2O): δ 7.97 (s, 2 H), 6.89 (d, J = 6.8 Hz, 2 H), 6.79 (d, J = 7.2 Hz, 2 H), 3.29 (app t, J = 6.4 Hz, 2 H), 3.01 (app t, J = 6.4 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{13}I_2NO_2$: calcd, 480.9036; found, 480.9050. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.45 min; purity, 100%; $[M + H]^+$: calcd, 481.91; found, 482.30 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.91 min; purity, 95%.

3′-Iodothyronamine Hydrochloride (25, 3′-T_1AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was concentrated in vacuo and dried under high vacuum pressure to give **25** as a white solid (12.7 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.24 (s, 1 H), 7.86 (s, 3 H), 7.30 (d, J = 2.4 Hz, 1 H), 7.23 (d, J = 8.4 Hz, 2 H), 6.96−6.86 (m, 4 H), 3.01 (br s, 2 H), 2.83 (app t, J = 7.6 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{14}INO_2$ $[M - NH_3]^+$: calcd, 337.9804; found, 337.9809. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.48 min; purity, 100%; $[M + H]^+$: calcd, 356.01; found, 356.44 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.84 min; purity, 100%.

3′,5′-Diiodothyronamine Hydrochloride (26, 3′,5′-T_2AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitated product was collected via vacuum filtration to give **26** as a white solid (32.3 mg, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.41 (s, 1 H), 7.95 (s, 3 H), 7.39 (s, 2 H), 7.27 (d, J = 8.4 Hz, 2 H), 6.96 (d, J = 8.4 Hz, 2 H), 3.02 (br s, 2 H), 2.86 (app br t, J = 8.0 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{13}I_2NO_2$ $[M - NH_3]^+$: calcd, 463.8770; found, 463.8748. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.83 min; purity, 100%; $[M + H]^+$: calcd, 482.91; found, 482.30 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.18 min; purity, 100%.

3,3′-Diiodothyronamine Hydrochloride (27, 3,3′-T_2AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was concentrated in vacuo and dried under high vacuum pressure to give **27** as a white solid (14.6 mg,

100% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1 H), 7.96 (br s, 3 H), 7.79 (d, J = 1.6 Hz, 1 H), 7.25 (ovrlp dd, J = 8.4, 2.0 Hz, 1 H), 7.23 (ovrlp d, J = 2.8 Hz, 1 H), 6.92 (ovrlp d, J = 8.8 Hz, 1 H), 6.87 (ovrlp dd, J = 8.8, 2.8 Hz, 1 H), 6.81 (d, J = 8.0 Hz, 1 H), 3.03 (app br s, 2 H), 2.84 (br t, J = 7.6 Hz, 2 H). LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.78 min; purity, 100%; [M + H]$^+$: calcd, 481.91; found, 482.24 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.15 min; purity, 98%.

3,3′,5′-Triiodothyronamine Hydrochloride (28, rT$_3$AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **28** as a white solid (27.1 mg, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (s, 1 H), 7.92 (br s, 3 H), 7.81 (d, J = 2.0 Hz, 1 H), 7.29 (ovrlp dd, J = 8.0, 2.0 Hz, 1 H), 7.29 (ovrlp s, 2 H), 6.95 (d, J = 8.4 Hz, 1 H), 3.05 (br s, 2 H), 2.85 (t, J = 7.6 Hz, 2 H). LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 6.10 min; purity, 100%; [M + H]$^+$: calcd, 607.81; found, 608.24 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.49 min; purity, 99%.

3,3′,5-Triiodothyronamine Hydrochloride (29, T$_3$AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction was concentrated in vacuo and dried under high vacuum pressure to give **29** as a tan solid (9.6 mg, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1 H), 7.86 (ovrlp s, 2 H), 7.80 (ovrlp br s, 3 H), 6.98 (d, J = 2.8 Hz, 1 H), 6.83 (d, J = 9.2 Hz, 1 H), 6.65 (dd, J = 8.8, 3.2 Hz, 1 H), 3.11 (t, J = 7.2 Hz, 2 H), 2.84 (t, J = 7.2 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{12}I_3NO_2$: calcd, 606.8002; found, 606.8010. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.90 min; purity, 100%; [M + H]$^+$: calcd, 607.81; found, 608.16 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.35 min; purity, 95%.

3,3′,5,5′-Tetraiodothyronamine Hydrochloride (30, T$_4$AM). Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction was concentrated in vacuo and dried under high vacuum pressure to give **30** as a tan solid (13.8 mg, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (s, 1 H), 7.87 (s, 2 H), 7.11 (s, 2 H), 3.12 (app br s, 2 H), 2.85 (t, J = 7.2 Hz, 2 H). LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 6.12 min; purity, 100%; [M + H]$^+$: calcd, 733.70; found, 733.89 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.60 min; purity, 97%.

***O*-Phenyl-tyramine Hydrochloride (32).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction was concentrated in vacuo and dried under high vacuum pressure to give **32** as a tan solid (18.3 mg, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (br s, 3 H), 7.38 (app t, J = 7.6 Hz, 2 H), 7.28 (d, J = 8.4 Hz, 2 H), 7.13 (t, J = 7.4 Hz, 1 H), 7.02−6.94 (m, 4 H), 3.02 (app br t, J = 8.0 Hz, 2 H), 2.90 (app t, J = 8.4 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{15}NO$: calcd, 213.1154; found, 213.1158. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.45 min; purity, 100%; [M + H]$^+$: calcd, 214.12; found, 214.46 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.79 min; purity, 100%.

***O*-Benzyl-tyramine Hydrochloride (38).** Refer to general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **38** as a white solid (156 mg, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (s, 3 H), 7.46−7.30 (m, 5 H), 7.17 (app d, J = 8.8 Hz, 2 H), 6.97 (app d, J = 8.4 Hz, 2 H), 5.08 (s, 2 H), 2.97 (app t, J = 7.5 Hz, 2 H), 2.81 (app t, J = 7.5 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{15}H_{17}NO$: calcd, 227.1310; found, 227.1316. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.45 min; purity, 100%; [M + H]$^+$: calcd, 228.14; found, 228.35 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.84 min; purity, 100%.

***O*-(2′-Phenyl)ethyl-tyramine Hydrochloride (39).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitate was collected by vacuum filtration to give **39** as a white solid (22.4 mg, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (br s, 3 H), 7.16−7.23 (m, 5 H), 7.12 (d, J = 8.4 Hz, 2 H), 6.86 (d. J = 8.0 Hz, 2 H), 4.13 (t, J = 6.8 Hz, 2 H), 2.98 (ovrlp t, J = 7.0 Hz, 2 H), 2.40 (ovrlp app t, J = 8.0 Hz, 2 H), 2.75 (app t, J = 8.0 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{16}H_{19}NO$: calcd, 241.1467; found, 241.1457. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.68 min; purity, 100%; [M + H]$^+$: calcd, 242.15; found, 242.49 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.06 min; purity, 100%.

***O*-(3′-Phenyl)propyl-tyramine Hydrochloride (40).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was concentrated in vacuo and dried under high vacuum pressure to give **40** as a white solid (80 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (br s, 2 H), 7.33−7.15 (m, 8 H), 6.88 (d, J = 8.0 Hz, 2 H), 3.94 (br t, J = 6.0 Hz, 2 H), 2.97 (app br t, J = 8.4 Hz, 2 H), 2.81 (app br t, J = 8.4 Hz, 2 H), 2.73 (app br t, J = 6.0 Hz, 2 H), 2.02−1.99 (m, 2 H). ^{13}C NMR (100 MHz, methanol-d_4): δ 160.0, 142.9, 130.08, 129.5, 129.4, 126.9, 116.0, 68.0, 42.1, 33.7, 32.2. HRMS (EI$^+$, free base) *m*/*z* for $C_{17}H_{21}NO$: calcd, 255.1623; found, 255.1619. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.95 min; purity, 100%; [M + H]$^+$: calcd, 256.17; found, 256.50 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.30 min; purity, 100%.

***O*-(4′-Phenyl)butyl-tyramine Hydrochloride (41).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was concentrated in vacuo and dried under high vacuum pressure to give **41** as a white solid (95 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (br s, 2 H), 7.28−7.14 (m, 8 H), 6.87 (d, J = 8.0 Hz, 2 H), 3.94 (br t, J = 6.0 Hz, 2 H), 2.94 (app br t, J = 8.4 Hz, 2 H), 2.81 (app br t, J = 8.4 Hz, 2 H), 2.62 (app br t, J = 6.0 Hz, 2 H), 1.73−1.62 (m, 4 H). ^{13}C NMR (100 MHz, methanol-d_4): δ 160.0, 143.5, 130.8, 129.6, 129.4, 129.3, 126.8, 68.9, 42.2, 36.6, 33.7, 29.9, 29.1. HRMS (EI$^+$, free base) *m*/*z* for $C_{18}H_{23}NO$ [M − CH_3NH + H]$^+$: calcd, 240.1514; found, 240.1512. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 6.18 min; purity, 100%; [M + H]$^+$: calcd, 270.19; found, 270.58 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.54 min; purity, 97%.

***O*-(Phenylmethanone)methyl-tyramine Hydrochloride (42).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction was diluted with ether, and the precipitate was collected by vacuum filtration to give **42** as a white solild (45 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (app br d, J = 7.6 Hz, 2 H), 7.70 (t, J = 7.6 Hz, 1 H), 7.58 (t, J = 7.6 Hz, 2 H), 7.16 (d, J = 8.8 Hz, 2 H), 6.93 (d, J = 8.8 Hz, 2 H), 5.55 (s, 2 H), 2.98 (app br t, J = 8.0 Hz, 2 H), 2.81 (app br t, J = 6.0 Hz, 2 H). ^{13}C NMR (100 MHz, methanol-d_4): δ 196.9, 158.9, 135.1, 130.9, 130.5, 129.1, 116.3, 71.7, 42.9, 33.7. HRMS (EI$^+$, free base)-*m*/*z* for $C_{16}H_{17}NO_2$ [M − CH_4N + H]$^+$: calcd, 226.0994; found, 226.0996. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 4.93 min; purity, 100%; [M + H]$^+$: calcd, 256.13; found, 256.43 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.45 min; purity, 100%.

***O*-(*m*,*m*-Dimethyl)benzyl-tyramine Hydrochloride (50).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitate was collected by vacuum filtration to give **50** as a white solid (28.6 mg, 86% yield). ^{1}H NMR (400 MHz, DMOS-d_6): δ 7.97 (br s, 3 H), 7.17 (d, J = 8.4 Hz, 2 H), 7.03 (s, 2 H), 6.96 (ovrlp d, J = 8.4 Hz, 2 H), 6.95 (ovrlp s, 1 H), 4.99 (s, 2 H), 2.97 (br s, 2 H), 2.81 (app t, J = 8.0 Hz, 2 H), 2.27 (s, 6 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{17}H_{21}NO$: calcd, 255.1623; found, 255.1633. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 6.02 min; purity, 100%; [M + H]$^+$: calcd, 256.17; found, 256.56 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.43 min; purity, 100%.

***O*-(*m*-Methoxy)benzyl-tyramine Hydrochloide (51).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitate was collected by vacuum filtration to give **51** as a white solid (67.0 mg, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (br s, 3 H), 7.30 (t, J = 8.0 Hz, 1 H), 7.17 (d, J = 8.4 Hz, 2 H), 6.94−7.20 (m, 4 H), 6.88 (app d, J = 7.2 Hz, 1 H), 5.06 (s, 2 H), 3.75 (s, 3 H), 2.98 (br s, 2 H), 2.79 (app t, J = 7.8 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{16}H_{19}NO_2$: calcd, 257.1416; found: 257.1416. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.45 min; purity, 100%; [M + H]$^+$: calcd, 258.15; found, 258.55 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.87 min; purity, 100%.

***O*-(*m*,*m*-Dimethoxy)benzyl-tyramine Hydrochloride (52).** Refer to the general procedure for *t*-Boc deprotection outlined above. The precipitate was filtered to give **52** as a white solid (136 mg, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (br s, 3 H), 7.17 (d, J = 8.4 Hz, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 6.58 (d, J = 1.6 Hz, 2 H), 6.44 (d, J = 1.6 Hz, 1 H), 5.02 (s, 2 H), 3.73 (s, 6 H), 2.98 (app t, J = 7.8 Hz, 2 H), 2.79 (app t, J = 7.8 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{17}H_{21}NO_3$: calcd, 287.1521; found, 287.1522. LC/MS(LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.52 min; purity, 100%; [M + H]$^+$: calcd, 288.16; found, 288.55 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.97 min; purity, 100%.

***O*-(*p*-Fluoro)benzyl-tyramine Hydrochloride (53).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitate was collected by vacuum filtration to give **53** as a white solid (50.4 mg, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (br s, 3 H), 7.45 (app dd, J = 8.4, 5.6 Hz, 2 H), 7.22 (ovrlp app t, J = 8.8 Hz, 2 H), 7.18 (d, J = 8.8 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 5.07 (s, 2 H), 2.98 (app t, J = 7.8 Hz, 2 H), 2.80 (app t, J = 8.0 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{15}H_{16}HNO$: calcd, 245.1216; found, 245.1214. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.50 min; purity, 100%; [M + H]$^+$: calcd, 246.13; found, 246.45 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.92 min; purity, 99%.

***O*-(*p*-Nitro)benzyl-tyramine Hydrocloride (54).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitate was collected by vacuum filtration to give **54** as a white solid (59.1 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 8.8 Hz, 2 H), 7.95 (br s, 3 H), 7.71 (d, J = 8.8 Hz, 2 H), 7.21 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 5.27 (s, 2 H), 3.01−2.95 (m, 2 H), 2.81 (app t, J = 8.0 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{15}H_{16}N_2O_3$: calcd, 272.1161; found, 272.1163. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.42 min; purity, 100%; [M − NH_2 + H]$^+$: calcd, 257.10; found, 257.46 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.95 min; purity, 100%.

***O*-(*p*-Trifluoromethyl)benzyl-tyramine Hydrochloride (55).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitate was collected by vacuum filtration to give **55** as a white solid (37.3 mg, 84% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (s, 3 H), 7.77 (d, J = 8.4 Hz, 2 H), 7.66 (d, J = 8.0 Hz, 2 H), 7.19 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 5.22 (s, 2 H), 2.99 (app t, J = 8.0 Hz, 2 H), 2.80 (app t, J = 7.8 Hz, 2 H). LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.97 min; purity, 100%; [M − NH_2 + H]$^+$: calcd, 280.11; found, 280.49 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.41 min; purity, 100%.

***O*-(2′,3′,4′,5′,6′-Pentafluoro)benzyl-tyramine Hydrochloride (56).** Refer to the genereal procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the precipitate was collected by vacuum filtration to give **56** white crystalline solid (72.7 mg, 95% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (br s, 3 H), 7.19 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 5.15 (s, 2 H), 2.98 (app t, J = 7.6 Hz, 2 H), 2.79 (app t, J = 7.6 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{15}H_{12}F_5NO$: calcd, 317.0839; found, 317.0843. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.87 min; purity, 100%; [M − NH_2 + H]$^+$: calcd, 302.07; found, 302.50 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.28 min; purity, 100%.

***N*-Methyl-*O*-benzyl-tyramine Hydrochloride (62).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was concentrated in vacuo to give **62**, which was dried under high vacuum (118 mg, 89% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.90 (br s, 1H), 7.45−7.32 (m, 5 H), 7.18 (d, J = 8.4 Hz, 2 H), 6.75 (d, J = 8.4 Hz, 2 H), 5.08 (s, 2H), 3.33 (s, 1H) 3.05 (br s, 2H) 2.86 (t, J = 8.8 Hz, 2H) 2.54 (s, 3H). HRMS (EI$^+$, free base) *m*/*z* for $C_{16}H_{19}NO$ [M + H]$^+$: calcd, 242.1547; found, 242.1549. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.42 min; purity, 100%; [M + H]$^+$: calcd, 242.15; found, 242.49 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.94 min; purity, 100%.

***N*-Ethyl-*O*-benzyl-tyramine Hydrochloride (63).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **63** as a white solid (38.9 mg, 92% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (br s, 2 H), 7.45−7.30 (m, 5 H), 7.18 (d, J = 8.4 Hz, 2 H), 6.97 (d, J = 8.4 Hz, 2 H), 5.09 (s, 2 H), 3.08 (app t, J = 7.6 Hz, 2 H), 2.95 (q, J = 7.2 Hz, 2 H), 2.85 (app t, J = 8.2 Hz, 2 H), 1.19 (t, J = 7.2 Hz, 3 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{17}H_{21}NO$: calcd, 255.1623; found, 255.1616. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.50 min; purity, 100%; [M + H]$^+$: calcd, 256.17; found, 256.56 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.03 min; purity, 100%.

***N*-Propyl-*O*-benzyl-tyramine Hydrochloride (64).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **64** as a white solid (35.9 mg, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (br s, 2 H), 7.45−7.30 (m, 5 H), 7.17 (d, J = 8.4 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 5.09 (s, 2 H), 308 (app t, J = 8.2 Hz, 2 H), 2.89−2.84 (m, 4 H), 1.62 (sextet, J = 7.5 Hz, 2 H), 0.91 (t, J = 7.6 Hz, 3 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{18}H_{23}NO$: calcd, 269.1780; found, 269.1771. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.62 min; purity, 100%; [M + H]$^+$: calcd, 270.19; found, 270.58 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.19 min; purity, 100%.

***N*-Butyl-*O*-benzyl-tyramine Hydrochloride (65).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **65** as a white solid (32.1 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (br s, 2 H), 7.45−7.30 (m, 5 H), 7.17 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 5.09 (s, 2 H), 3.08 (app t, J = 8.2 Hz, 2 H), 2.92−2.84 (m, 4 H), 1.58 (quintet, J = 7.7 Hz, 2 H), 1.33 (sextet, J = 7.4 Hz, 2 H), 0.89 (t, J = 7.2 Hz, 3 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{19}H_{25}NO$ [M + H]$^+$: calcd, 284.2014; found, 284.2015. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.78 min; purity, 100%; [M + H]$^+$: calcd, 284.20; found, 284.59 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.39 min; purity, 100%.

***N*,*O*-Dibenzyl-tyramine Hydrochloride (66).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **66** as a white solid (66.2 mg, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (br s, 2 H), 7.56−7.30 (m, 10 H), 7.16 (d, J = 8.4 Hz, 2 H), 6.97 (d, J = 8.4 Hz, 2 H), 5.08 (s, 2 H), 4.16 (br s, 2 H), 3.09 (br s, 2 H), 2.91 (app t, J = 8.2, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{22}H_{23}NO$: calcd, 317.1780; found, 317.1780. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.93 min; purity, 100%; [M + H]$^+$: calcd, 318.19; found, 318.63 *m*/*z*. HPLC

(gradient 0−100% MeCN [0.05% TFA]): retention time, 4.51 min; purity, 100%.

***N,N*-Dimethyl-*O*-benzyl-tyramine Hydrochloride (67).** *O*-Benzyl tyramine hydrochloride **38** (0.22 mmol) was dissolved in water, treated with potassium carbonate (>0.22 mmol), and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated to give the free amine. A solution of free amine (0.22 mmol) in formic acid (>1.10 mmol, 88% in water solution) and formaldehyde (>1.10 mmol, 37% in water solution) was stirred at 80 °C for ∼20 h. After it was cooled to room temperature, the reaction was diluted with water, adjusted to pH ∼ 10 with K_2CO_3, and extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was treated with 3 N anhydrous HCl/ethyl acetate (1 mL), exposed to diethyl ether, and filtered to give **67** as a white solid (84.6 mg, 60% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.46 (br s, 1 H), 7.42−7.26 (m, 5 H), 7.15 (app d, J = 8.4 Hz, 2 H), 6.94 (app d, J = 8.8 Hz, 2 H), 3.21−3.13 (m, 2 H), 2.93−2.86 (m, 2 H), 2.73 (d, J = 4.0 Hz, 6 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{17}H_{21}NO$: calcd, 255.1623; found, 255.1617. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.38 min; purity, 100%; [M + H]$^+$: calcd, 256.17; found, 256.56 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.05 min; purity, 95%.

2-[3-Iodo-4-(*p*-hydroxy)phenoxyphenyl]ethanol (72). Refer to the general procedure for silyl deprotection described above. The crude product was purified via flash SiO_2 [eluted with hexane/ethyl acetate (2:1)] to give **72** as a white solid (35 mg, 85% yield). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.71 (d, J = 2.4 Hz, 1 H), 7.09 (dd, J = 2.4, 8.8 Hz, 1 H), 6.87 (d, J = 9.2 Hz, 2 H), 6.79 (d, J = 9.2 Hz, 2 H), 6.70 (d, J = 8.8 Hz, 1 H), 5.58 (br s, 1H), 3.85 (t, J = 6.4 Hz, 2 H), 2.80 (t, J = 6.8 Hz, 2 H), 1.69 (br s, 1H). ^{13}C NMR (100 MHz, chloroform-*d*): δ 156.2, 152.0, 150.2, 140.1, 135.1, 130.2, 120.2, 117.5, 116.1, 88.0, 63.5, 37.8. HRMS (EI$^+$) *m*/*z* for $C_{14}H_{13}IO_3$: calcd, 355.9909; found, 355.9906. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 6.28 min; purity, 100%; [M − H + K]$^+$: calcd, 393.95; found, 393.43 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.49 min; purity, 99%.

3-Methyl-thyronamine (77). Thyronamine derivative **76** (160 mg, 0.41 mmol) was dissolved in 3 N HCl solution in ethyl acetate (2 mL, anhydrous), and the reaction mixture was stirred at ambient temperature overnight. The crude mixture was concentrated in vacuo and dried under high vacuum pressure to give the pure product **77** as a white solid (110 mg, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.27 (br, 1 H), 7.94 (br, 2 H), 7.16 (s, 1 H), 7.02 (d, J = 8.4 Hz, 1 H), 6.76 (m, 3 H), 6.67 (d, J = 8.2 Hz, 2 H), 3.01 (m, 2 H), 2.81 (m, 2 H), 2.19 (s, 3 H). ^{13}C NMR (100 MHz, methanol-d_4): δ 156.7, 154.3, 151.3, 132.6, 132.1, 130.3, 128.3, 120.5, 118.9, 117.1, 42.1, 33.8, 16.3. HRMS (EI$^+$, free base) *m*/*z* for $C_{15}H_{17}NO_2$: calcd, 243.1259; found, 243.1296. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.08 min; purity, 100%; [M − NH_2]$^+$: calcd, 227.11; found, 227.45 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.52 min; purity, 95%.

***O*-Benzyl-3-iodotyramine Hydrochloride (82).** Refer to the general procedure for the *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **82** as a white solid (18.6 mg, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (br s, 3 H), 7.69 (d, J = 2.0 Hz, 1 H), 7.48 (d, J = 7.2 Hz, 2 H), 7.40 (t, J = 7.4 Hz, 2 H), 7.32 (app t, J = 7.2 Hz, 1 H), 7.23 (dd, J = 8.4, 2.0 Hz, 1 H), 7.03 (d, J = 8.8 Hz, 1 H), 5.17 (s, 2 H), 2.99 (br s, 2 H), 2.78 (t, J = 7.8 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{15}H_{16}INO$: calcd, 353.0277; found, 353.0280. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.90 min; purity, 100%; [M + H]$^+$: calcd, 354.04; found, 354.46 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.31 min; purity, 100%.

***O*-(*p*-trifluoromethyl)benzyl-3-iodotyramine Hydrochloride (83).** Refer to the general procedure for *t*-Boc deprotection. The precipitate was collected by filtration to give **83** as a white solid (94.9 mg, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (br s, 3 H), 7.75 (d, J = 8.0 Hz, 2 H), 6.67 (ovrlp d, J = 1.6 Hz, 1 H), 7.66 (ovrlp d, J = 8.0 Hz, 2 H), 7.21 (dd, J = 2.0 Hz, 1 H), 6.99 (d, J = 8.4 Hz, 1 H), 5.26 (s, 2 H), 2.95 (app t, J = 7.8 Hz, 2 H), 2.78 (app t, J = 7.6 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{16}H_{15}F_3INO$: calcd, 421.0150; found, 421.0136. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 6.33 min; purity, 100%; [M + H]$^+$: calcd, 422.02; found, 422.47 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.78 min; purity, 100%.

***N*-Methyl-*O*-benzyl-3-iodotyramine Hydrochloride (84).** Refer to the general procedure for *t*-Boc deprotection described above. The crude reaction mixture was diluted with ether, and the white precipitate was collected by vacuum filtration to give **84** as a white solid (35.9 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (br s, 2 H), 7.71 (d, J = 2.0 Hz, 1 H), 7.49 (d, J = 7.2 Hz, 2 H), 7.41 (app t, J = 7.3 Hz, 2 H), 7.33 (app t, J = 7.4 Hz, 1 H), 7.24 (dd, J = 8.2, 2.2 Hz, 1 H), 7.05 (d, J = 8.4 Hz, 1 H), 5.18 (s, 2 H), 3.10 (br s, 2 H), 2.83 (app t, J = 7.8 Hz, 2 H), 2.55 (br s, 3 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{16}H_{18}INO$ [M + H]$^+$: calcd, 368.0513; found, 368.0509. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.88 min; purity, 100%; [M + H]$^+$: calcd, 368.05; found, 368.47 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.44 min; purity, 100%.

***N*-Methyl-*O*-(*p*-trifluoromethyl)benzyl-tyramine Hydrochloride (85).** Refer to the general procedure for *t*-Boc deprotection described above. The precipitate was filtered to give **85** as a white solid (93.4 mg, 88% yield). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.77 (br s, 2 H), 7.76 (d, J = 8.4 Hz, 2 H), 7.66 (d, J = 7.6 Hz, 2 H), 7.19 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 5.22 (s, 2 H), 3.08 (br s, 2 H), 2.86 (app br t, J = 8.0, 2 H), 2.55 (ovrlp br s, 3 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{17}H_{18}F_3NO$: calcd, 309.1340; found, 309.1331. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.97 min; purity, 100%; [M + H]$^+$: calcd, 310.14; found, 310.63 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.54 min; purity, 100%.

***O*-Phenyl-3-iodotyramine Hydrochloride (91).** Refer to the general procedure for *t*-Boc deprotection described above. The precipitate was collected by filtration to give **91** as a white solid (250 mg, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (br s, 3 H), 7.80 (d, J = 2.0 Hz, 1 H), 7.33 (app t, J = 8.0 Hz, 2 H), 7.27 (dd, J = 8.2, 2.2 Hz, 1 H), 7.08 (t, J = 7.4 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 1 H), 6.87 (app d, J = 8.6 Hz, 2 H), 3.07−2.97 (m, 2 H), 2.83 (app t, J = 7.8 Hz, 2 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{14}H_{14}INO$: calcd, 339.0120; found, 399.0128. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.78 min; purity, 100%; [M + H]$^+$: calcd, 340.02; found, 340.45 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.20 min; purity, 100%.

***O*-(*p*-Fluoro)phenyl-3-iodotyramine Hydrochloride (92).** Refer to the general procedure for *t*-Boc deprotection above. The reaction was concentrated to dryness and dried in vacuo to give **92** as a slightly yellow residue (43.6 mg, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (br s, 2 H), 7.79 (d, J = 0.8 Hz, 1 H), 7.25 (dd, J = 8.4, 1.2 Hz, 1 H), 7.17 (app t, J = 8.8 Hz, 2 H), 6.94−6.87 (m, 3 H), 3.08 (app t, J = 8.0 Hz, 2 H), 2.86 (app t, J = 7.8 Hz, 2 H), 2.51 (s, 3 H). HRMS (EI$^+$, free base) *m*/*z* for $C_{15}H_{15}$-FICO: calcd, 371.0182; found, 371.0178. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI$^+$): retention time, 5.87 min; purity, 100%; [M + H]$^+$: calcd, 372.03; found, 372.50 *m*/*z*. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.37 min; purity, 98%.

***O*-(*p*-trifluromethyl)phenyl-3-iodotyramine (93).** Refer to the general procedure for *t*-Boc deprotection above. The reaction was concentrated to dryness and dried in vacuo to give **93** as a slightly yellow residue (34.5 mg, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (br s, 2 H), 7.85 (s, 1 H), 7.68 (d, J = 8.4 Hz, 2 H), 7.34 (app d, J = 8.0 Hz, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 6.99 (d,

J = 8.8 Hz, 2 H), 3.12 (t, J = 7.6 Hz, 2 H), 2.92 (t, J = 7.6 Hz, 2 H), 2.52 (s, 3 H). HRMS (EI^+, free base) m/z for $C_{16}H_{15}F_3INO$ $[M + H]^+$: calcd, 422.0229; found, 422.0222. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI^+): retention time, 6.20 min; purity, 100%; $[M + H]^+$: calcd, 422.02; found, 422.47 m/z. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.76 min; purity, 98%.

***N*-Methyl-3-iodothyronamine Hydrochoride (96).** Refer to the general procedures for silyl deprotection and *t*-Boc deprotection described above. The crude deprotected product was submitted to *t*-Boc deprotection conditions without further purification. The precipitate was filtered to give **96** as a white solid (7.7 mg, 60% yield for both steps). ^1H NMR (400 MHz, DMSO-d_6): δ 9.39 (s, 1 H), 8.57 (br s, 2 H), 7.78 (d, J = 2.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.4 Hz, 1 H), 6.82 (app dt, J = 9.2, 2.8 Hz, 2 H), 6.78 (app dt, J = 9.2, 2.8 Hz, 2 H), 6.71 (d, J = 8.2 Hz, 1 H), 3.12 (app br d, J = 6.0 Hz, 2 H), 2.86 (app br t, J = 7.8 Hz, 2 H), 2.56 (br s, 3 H). HRMS (EI^+, free base) m/z for $C_{15}H_{16}INO_2$ $[M - NHCH_3 + H]^+$: calcd, 339.9960; found, 339.9941. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI^+): retention time, 5.28 min; purity, 100%; $[M + H]^+$: calcd, 370.03; found, 370.46 m/z. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 3.76 min; purity, 100%.

***N*,*O*-Dimethyl-3-iodothyronamine Hydrochloride (97).** Refer to the general procedure for *t*-Boc deprotection described above. The precipitate was filtered to give **97** as a white solid (34.9 mg, 89% yield). ^1H NMR (400 MHz, DMSO-d_6): δ 8,82 (br s, 2 H), 7.80 (d, J = 2.0 Hz), 7.25 (dd, J = 8.4, 2.0 Hz, 1 H), 6.95 (app dt, J = 9.2, 2.6 Hz, 2 H) 6.91 (app dt, J = 9.2, 2.6 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 1 H), 3.74 (s, 3 H), 3.16−3.08 (br m, 2 H), 2.89 (app t, J = 7,8 Hz, 2 H), 2.57−2.53 (br m, 3 H). HRMS (EI^+, free base) m/z for $C_{16}H_{18}INO_2$: calcd, 383.0382; found, 383.0391. LC/MS (LC: gradient 0−100% MeOH [0.05% TFA], MS: EI^+): retention time, 5.80 min; purity, 100%; $[M + H]^+$: calcd, 384.05; found, 384.47 m/z. HPLC (gradient 0−100% MeCN [0.05% TFA]): retention time, 4.24 min; purity, 99%.

Acknowledgment. This research was supported by grants from the National Institutes of Health (Grant DK52798 to T.S.S.) and by the Sandler Family Supporting Foundation (to T.S.S.).

Supporting Information Available: Experimental procedures for all intermediates and LC/MS and HPLC data for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM0505718