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Further Structure−Activity Relationship Studies on 4-((((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol: Identification of Compounds with Triple Uptake Inhibitory Activity as Potential Antidepressant Agents

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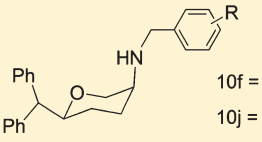
Supporting Information

ABSTRACT: To investigate structural alterations of the lead triple uptake inhibitor molecule, disubstituted 4-((((3*S*,6*S*)-6-benzhydryltetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol, we have carried out structure−activity relationship (SAR) studies to investigate the effect of alteration of aromatic substitutions and introduction of heterocyclic aromatic moieties on this molecular template. The novel compounds were tested for their affinities for the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET) in the brain by measuring their potency in inhibiting the uptake of [^{3}H]DA, [^{3}H]5-HT, and [^{3}H]NE, respectively. SAR results indicate dopamine norepinephrine reuptake inhibitory (DNRI) type activity in thiophene (**10g**) and pyrrole (**10i**) derivatives. On the other hand, 3-hydroxyphenyl derivative **10f** and 4-methoxyphenyl derivative **10j** exhibited a triple reuptake inhibitory (TUI) activity profile, as these molecules exhibited potent uptake inhibition for all the monoamine transporters (K_i of 31.3, 40, 38.5 and K_i of 15.9, 12.9, 29.3 for DAT, SERT, and NET for **10f** and **10g**, respectively). Compound **10f** was further evaluated in the rat forced swim test to evaluate its potential antidepressant effect. The results show significant reduction of immobility by TUI **10f** at 10 mg/kg dose, indicating potential antidepressant activity.



R	DAT Ki (nM)	SERT Ki (nM)	NET Ki (nM)
10f = -3-OH	31.3	40	38.5
10j = -4-OCH3	15.9	12.9	29.3

INTRODUCTION

Depression, especially major depression disorder, significantly affects a high percentage of the population (15−20%) and is regarded as a significant health problem. Unipolar depression is ranked as number 1 before all other somatic and psychiatric illnesses.[1,2] It is believed that at least 20% of all individuals suffer from a depressive episode at least once in their lifetime. Depression is potentially fatal, since most sufferers consider life threatening acts and suicide.[3,4]

Selective monoamine uptake inhibitors have been used in the treatment of depression.[5] Among those, especially serotonin (5-HT) and norepinephrine (NE) transporter blockers have been used in the therapy for depression.[6,7] However, in spite of developments of different arrays of antidepressants, there still remains a significant unmet need for more improved therapy, as a large number of depressed people are still refractory to the current existing therapies.[8] Also, a significant number of people relapse after treatment with current therapies.[9] Although current pharmacotherapies of depression do not address the dopaminergic component, there is ample clinical and biochemical evidence pointing toward a strong dopaminergic component in depression.[10,11] It is hypothesized that a triple uptake inhibitor (TUI) interacting with all three monoamine transporters would display reduced side effects associated with selective serotonin reuptake inhibitors (SSRIs).[12,13] Recently, TUIs have been shown to be potent antidepressants in animal models and therefore are being advanced as novel treatment tools offering certain advantages.[14−16] Because of their interaction at three monoamine transporters, this class of drug could potentially provide faster onset of action. The enhanced efficacy of a TUI as an antidepressant may be due to the additional dopaminergic component, which can effectively relieve depression by activating mesocorticolimbic dopaminergic pathways, reducing anhedonia associated with a deficit in dopaminergic transmission.

In recent years a number of TUIs, e.g., DOV 21,947 and PRC200-SS, have been developed and have been characterized in animal antidepressant models.[17,18] Some of these molecules are shown in Figure 1. In our previous studies on monoamine transporters, we developed a unique pyran template as a bioisosteric extension of piperidine derivatives, which we originally synthesized for targeting the dopamine transporter (DAT).[19−27] Initially, we identified unique asymmetric di- and trisubstituted pyran derivatives inhibiting uptake of all three monoamine transporters with higher potency for the 5-HT transporter (SERT) and NE transporter (NET) and modest potency for

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the dopamine transporter (DAT). Dual acting inhibitors as blockers of both SERT and NET as well as selective blockers for NET were also identified. Asymmetric synthesis methods have been developed by us to generate these molecules.[26,27] The results indicated stereospecific requirement for interaction of these molecules with the monoamine transporters, as the interaction was mainly exhibited in the (−)-isomers. One of our lead TUIs, **1c** (D-161) (Figure 2), was recently shown to possess antidepressant-like activity in animal studies.[28]

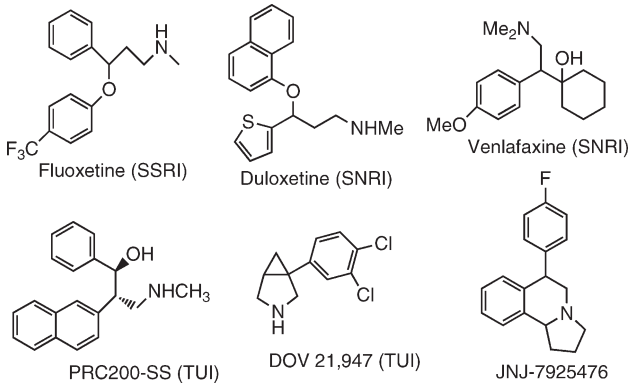


Figure 1. Molecular structures of known clinical and preclinical antidepressants.

In our current work, we extended our SAR studies further with asymmetric disubstituted pyran derivatives to understand the effect of different aromatic substitutions on affinity and selectivity for different monoamine transporters.

CHEMISTRY

Scheme 1 describes the synthesis of the key amine intermediate **8**, which was used toward the synthesis of target compounds as shown in Schemes 2 and 3. Briefly, regioselective ring-opening of the (*R*)-epoxide **1** with allylmagnesium chloride in the presence of a catalytic amount of copper(I) iodide afforded alcohol **2** in good yield. Trans-vinylation of alcohol **2** with ethyl vinyl ether in the presence of mercury(II) trifluoroacetate at room temperature provided compound **3**, which was immediately converted to cyclic olefin **4** by ring-closing metathesis. Hydroboration of olefin **4** with 9-BBN in THF followed by oxidation gave an inseparable mixture containing mostly trans-isomer **5a**. The mixture of compounds **5a** and **5b** was mesylated with methanesulfonyl chloride in dichloromethane in the presence of triethylamine and separated by column chromatography to give the trans-compound **6a** in 74.7% yield and cis-compound **6b** in 12.4% yield (trans/cis = 6:1). Compound **6a** was then treated with sodium azide in DMF to give azide **7**, which was finally hydrogenated with Pd/C in methanol to obtain the optically active *cis*-amine intermediate **8** in quantitative yield.

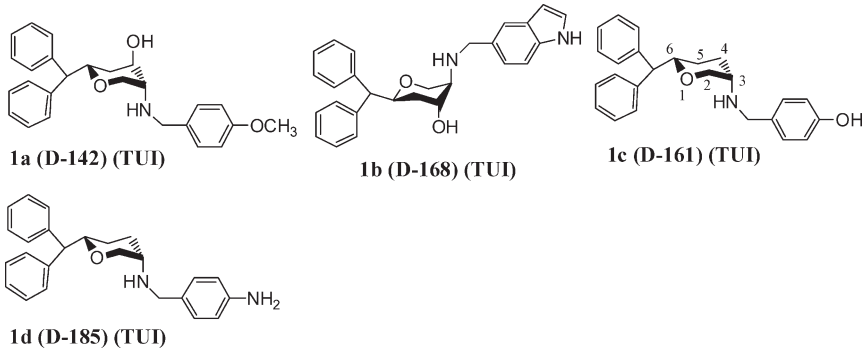
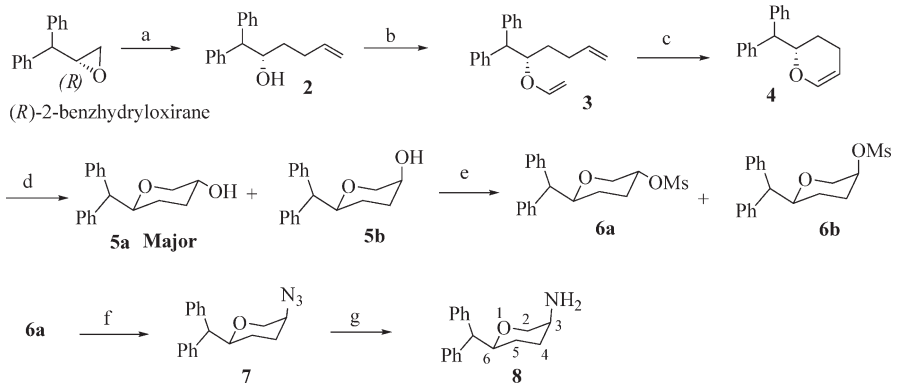


Figure 2. Molecular structures of lead asymmetric pyran TUIs.

Scheme 1[a]



[a] Reagents and conditions: (a) allylmagnesium chloride, ether, −78 °C to room temp, overnight, 82.4%; (b) ethylvinyl ether, $Hg(OCOCF_3)_2$, room temp, 4 h, 63.4%; (c) first generation Grubb's catalyst, benzene, reflux, 2 h, 67.6%; (d) (i) 9-BBN, THF, room temp, overnight; (ii) 10% NaOH, 30% H_2O_2, 50 °C, 1 h, 90%; (e) CH_3SO_2Cl, Et_3N, dichloromethane, room temp, 2 h, 74.7% for **6a**, 12.4% for **6b**; (f) NaN_3, DMF, 80 °C, overnight, 81.1%; (g) H_2, Pd−C, MeOH, 50 psi, 2 h, quantitative yield.

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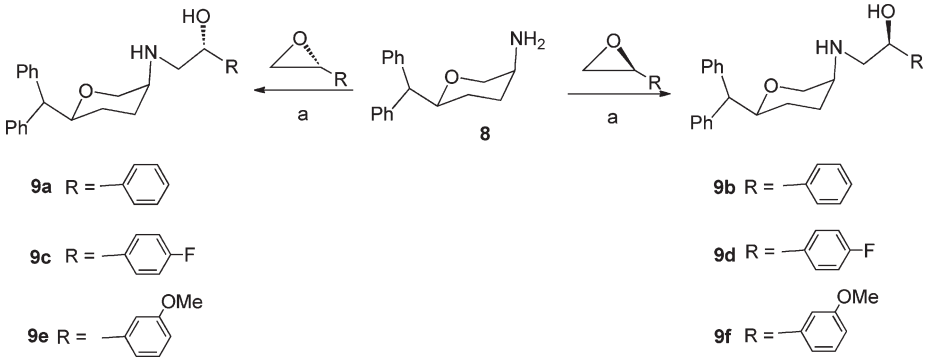
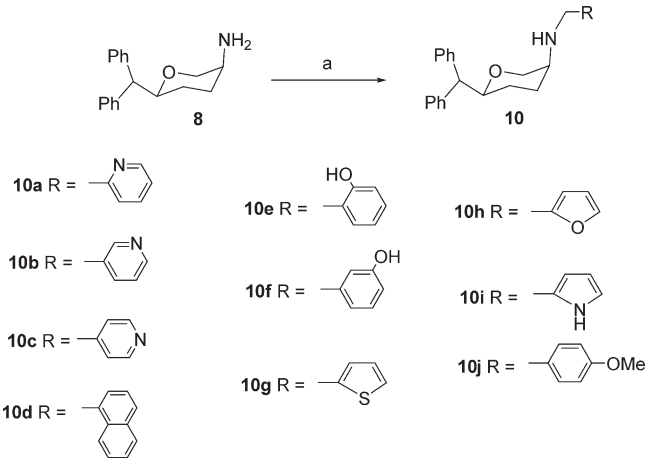
Scheme 2[a]



[a] Reagents and conditions: (a) epoxide, EtOH, reflux, overnight.

Scheme 3[a]



[a] Reagents and conditions: (a) RCHO, $NaCNBH_3$, AcOH, 1,2-dichloroethane, room temp, overnight.

Scheme 2 outlines the synthesis of the final compounds **9a**−**f** by treating amine **8** with corresponding optically active (*R*)- and (*S*)-epoxides.

Similarly, reductive amination of amine **8** with various aldehydes furnished target compounds **10a**−**j** as shown in Scheme 3.

RESULTS AND DISCUSSION

We have successfully developed an improved version of the synthesis of asymmetric disubstituted pyran derivative precursor as described in Scheme 1. This involved fewer synthetic steps to make 3,6-disubstituted compounds compared to our previous published report.[27]

In our previous SAR studies, we have shown that substitutions on the *N*-benzylic aromatic ring had a significant influence on the profile of monoamine uptake inhibition. One of the interesting findings from those studies was that the presence of H-bond forming functionality in the aromatic ring conferred higher potency for the NET. Compounds **1d** (D-185), **1b** (D-168), and **1c** (Figure 2) with amino and hydroxyl groups at the para position exhibited a TUI profile with potent activity at the NET.[27] In the current SAR studies, we wanted to further explore 3,6-disubstituted compounds by introducing various aromatic substitutions and side chain expansion on the exocyclic N-atom.

Scheme 2 describes epoxide ring-opening from 3,6-disubstituted amine precursor **8**. The rationale behind designing these compounds stems from the observation that in the GBR class of compounds such side chain extension via opening of epoxide led to development of potent molecules for DAT and SERT.[29] Regioselective ring-opening of different substituted (*R*)-styrene epoxides by the amine precursor **8** produced (*R*)-hydroxy compounds **9a**, **9c**, and **9e**. On the other hand, regioselective ring-opening of similar (*S*)-epoxides by the same amine precursor yielded (*S*)-hydroxy compounds **9b**, **9d**, and **9f**. None of the (*R*)-hydroxy compounds exhibited potent activity except 4-fluorophenyl substituted compound **9c** which displayed moderate potency at DAT (K_i = 71 nM). Similarly, corresponding diastereomers (*S*)-hydroxy compounds **9d** and **9f** did not exhibit much potent activity except **9b** which exhibited moderate potency at DAT (K_i = 54 nM).

In our next series, we planned to systematically explore the influence of heterocyclic and substituted aromatic moieties in the disubstituted pyran template. Since the initial development of pyran derivatives, influences of N-heterocyclic substitutions have not been explored. In the starting pyridine series, 2- (**10a**), 3- (**10b**), and 4-substituted (**10c**) pyridines were designed and synthesized. Interestingly, the 4-pyridine substituted compound **10c** exhibited selective interaction with DAT (K_i of 28.3, 889, and 462 for DAT, SERT, and NET, respectively (Tables 1 and 2)) whereas the other two pyridine compounds were weak at all three transporters. This indicates the importance of the position of the N-atom in the pyridine ring in interacting with the monoamine transporters. In our next exploration of heterocyclic aromatic moieties, thiophene derivative **10g**, furan derivative **10h**, and pyrrole derivative **10i** were designed and synthesized. Thiophene derivative **10g** and pyrrole derivative **10i** exhibited interesting dual DAT/NET potency (K_i (DAT and NET) of 41.4 and 47.2 nM for **10g** and 43.2 and 39.6 nM for **10i**), whereas furan derivative **10h** exhibited 2-fold selective potency for NET (K_i of 59.8 nM for NET vs K_i of 110 and 115 nM for DAT and SERT, respectively (Tables 1 and 2).

In our next series of molecules, we focused on phenyl substituted compounds. In our exploration to evaluate the effect of enhanced hydrophobicity on N-aromatic substitution, we replaced the phenyl moiety by a naphthalene ring to produce **10d**. However, such replacement only produced moderate potency for SERT (K_i = 88.8 nM). Next we wanted to explore the positional effect of the hydroxyl group on the aromatic ring in **1c**,

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Table 1. Affinity of Drugs at DAT, SERT, and NET in Rat Brain

	K_i, nM		
compd	DAT uptake, [^{3}H]DA[a]	SERT uptake, [^{3}H]-5-HT[a]	NET uptake, [^{3}H]NE[a]
GBR 12909	16.2 ± 1.6	198 ± 19	48.5 ± 7.4
reboxetine	ND[b]	503 ± 61	0.826 ± 0.25
fluoxetine	1092 ± 98	12.2 ± 2.4	120 ± 41
1a	37.4 ± 3.9	14.7 ± 2.1	29.3 ± 7.9
1b	85.2 ± 8.2	25.0 ± 8.4	25.5 ± 9.6
1c	42.0 ± 3.3	29.1 ± 3.5	30.5 ± 7.8
9a	145 ± 16	936 ± 68	162 ± 34.6
9b	54.0 ± 8.5	796 ± 94	298 ± 45
9c	71.8 ± 13.6	1,140 ± 208	546 ± 97
9d	106 ± 28	825 ± 169	222 ± 62
9e	125 ± 31	1,092 ± 161	429 ± 245
9f	137 ± 9	646 ± 118	299 ± 34
10a	209 ± 20	483 ± 63	505 ± 220
10b	145 ± 51	152 ± 11	353 ± 60
10c	28.3 ± 11.6	889 ± 61	462 ± 86
10d	473 ± 134	88.8 ± 21.7	232 ± 54
10e	200 ± 28	440 ± 96	160 ± 38
10f	31.3 ± 10.6	40.1 ± 4.9	38.5 ± 6.0
10g	41.4 ± 8.9	186 ± 43	47.2 ± 15.4
10h	110 ± 23	115 ± 5	59.8 ± 0.6
10i	43.2 ± 1.8	141 ± 2	39.6 ± 3.5
10j	15.9 ± 1.7	12.9 ± 1.3	29.3 ± 4.8

[a] For uptake by DAT, SERT, and NET, [^{3}H]DA, [^{3}H]-5-HT, and [^{3}H]NE accumulation was measured. Results are average ± SEM of three to eight independent experiments assayed in triplicate. [b] Not done.

Table 2. Selectivity of Drugs (Ratio of K_i) in Inhibiting Uptake by Monoamine Transporters

compd	DAT uptake/SERT uptake[a]	DAT uptake/NET uptake[a]	SERT uptake/NET uptake[a]
9a	0.15	0.9	5.78
9b	0.07	0.18	2.67
9c	0.06	0.13	2.09
9d	0.13	0.48	3.72
9e	0.11	0.29	2.55
9f	0.21	0.46	2.16
10a	0.43	0.41	0.96
10b	0.95	0.41	0.43
10c	0.03	0.06	1.92
10d	5.33	2.04	0.38
10e	0.45	1.25	2.75
10f	0.78	0.81	1.04
10g	0.22	0.88	3.94
10h	0.96	1.84	1.92
10i	0.31	1.09	3.56
10j	1.23	0.54	0.44

[a] Ratio of K_i values.

through compounds **10e** and **10f**. The 3-hydroxyl substituted compound **10f** (K_i of 31. 40 and 38 for DAT, SERT, and NET, respectively) exhibited a TUI-like profile very similar to **1c**, whereas 2-hydroxyl substituted **10e** was much less potent at the three transporters. The low activity of **10e** might be due to the location of the hydroxyl group at the 2-position, giving rise to an unfavorable steric interaction. Next we wanted to evaluate **10j**, which is a methoxylated derivative of **1c**. The uptake inhibition results indicate higher potencies for DAT and SERT compared to **1c** in the methoxylated derivative (K_i of 15.9 and 12.9 vs 42 and 29 nM for DAT and SERT, respectively, for **10j**).

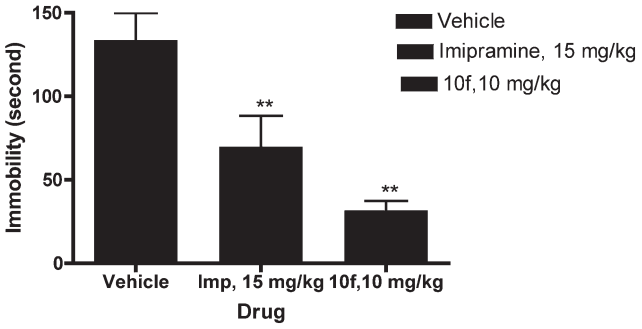

Figure 3. Effect of subchronic administration of vehicle (10% β-hydroxypropylcyclodextrin solution), **10f**, and imipramine on the duration of immobility in the forced swimming test in rats. One-way ANOVA analysis demonstrated significant effect among treatments: $F(4,95) = 13.70$ ($P < 0.008$). Dunnett's analysis showed that the effect of **10f** at 10 mg/kg dose on immobility was statistically significantly different compared to vehicle ($P < 0.01$). The effect of imipramine (15 mg/kg) on immobility was also statistically significantly different ($P < 0.05$) from vehicle. Asterisks indicate a statistically significant difference toward control group that received saline ip: (**) $P < 0.05$ or 0.01. Each treatment group contained six to seven rats.

Finally, we subjected one of our lead TUIs, **10f**, to the forced swim test (FST) in rats to measure its potential antidepressant effect. Extended CNS receptor screening of this compound at 10 μM indicated less than 50% inhibition with the majority of the receptor target sites and greater than 50% inhibition at a few other target sites (only marginally so in some cases; see Supporting Information for the data). The forced swim test has been used widely as a preclinical model for screening drugs for antidepressant activity and has been applied to characterize a broad spectrum of antidepressants.[30,31] This assay, with some limitations, is considered a very good predictor of antidepressant activity of a test compound. On the basis of our previous experience, we chose 10 mg/kg as a moderately high dose to study the effect of this compound on immobility. It is evident from the results (Figure 3) that compound **10f** at 10 mg/kg exhibited significant reduction of immobility compared to vehicle, as did the reference drug imipramine at 15 mg/kg dose. Thus, the results suggest that compound **10f** may have antidepressant activity.

CONCLUSION

We have carried out further SAR studies with disubstituted pyran derivatives. Introduction of exocyclic hydroxyl groups on the *N*-alkylphenyl moiety did not produce any further improvement of activity. Replacement of the phenyl ring in compound **1c** by the heterocyclic 4-pyridine moiety produced potent activity for the DAT in compound **10c**. Further replacement by five-membered heterocycles, e.g., furan, thiophene, and pyrole, produced interesting dopamine norepinephrine reuptake inhibitor (DNRI) type activity in **10g** and **10i**. Furthermore, compounds

10f and **10j** exhibited triple uptake inhibitory activity. Finally, in the rat FST experiment, compound **10f** exhibited high efficacy in reducing immobility, indicating a potential antidepressant effect. In this regard, **10f** was more efficacious than imipramine which might indicate higher efficacy of TUI in this animal model. In the near future we plan to examine this molecule further for its potential antidepressant property.

EXPERIMENTAL SECTION

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Dry solvents were obtained according to the standard procedures. All reactions were performed under inert atmosphere (N_2) unless otherwise noted. Analytical silica gel coated TLC plates (Si 254F) were purchased from Baker Inc. and were visualized with UV light or by treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker silica gel (40 μm). ^{1}H NMR and ^{13}C spectra were routinely recorded with a Varian 400 spectrometer operating at 400 and 100 MHz, respectively. The NMR solvent used was $CDCl_3$ as indicated. TMS was used as an internal standard. NMR and rotation of free bases were recorded. Salts of free bases were used for biological characterization. Elemental analyses were performed by Atlantic Microlab Inc., and results were within ±0.4% of the theoretical value.

[Ring 2,5,6-^{3}H]dopamine (38.7 Ci/mmol), [1,2-^{3}H]serotonin (28.0 Ci/mmol), and levo-[ring-2,5,6-^{3}H]norepinephrine (44.6 Ci/mmol) were obtained from Perkin-Elmer (Boston, MA, U.S.). Imipramine, fluoxetine, reboxetine, and GBR 12909 dihydrochloride (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine) were purchased from Sigma-Aldrich (St. Louis, MO, U.S.).

(*S*)-1,1-Diphenylhex-5-en-2-ol (2). To a stirred solution of (*R*)-2-benzhydryloxirane[26] (4.5 g, 21.40 mmol) in anhydrous diethyl ether (90 mL) was added copper(I) iodide (0.41 g, 2.14 mmol) and allylmagnesium chloride (13.37 mL, 2 M solution in tetrahydrofuran, 26.75 mmol) at −78 °C. After being stirred overnight at room temperature under nitrogen atmosphere, the reaction mixture at 0 °C was quenched by addition of saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4, and solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography using 10% ethyl acetate in hexanes to give compound **2** (4.45 g, 82%) as a thick colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44−1.64 (m, 3H), 2.12−2.21 (m, 1H), 2.25−2.34 (m, 1H), 3.89 (d, J = 8.4 Hz, 1H), 4.34−4.40 (m, 1H), 4.93−5.04 (m, 2H), 5.72−5.83 (m, 1H), 7.18−7.42 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.41, 34.42, 59.14, 73.40, 115.13, 126.82, 127.14, 128.50, 128.92, 129.05, 129.09, 138.72, 141.69, 142.60.

(*S*)-(2-(Vinyloxy)hex-5-ene-1,1-diyl)dibenzene (3). To a stirred solution of alcohol **2** (2.6 g, 10.30 mmol) in excess of ethyl vinyl ether (100 mL) was added mercury(II) trifluoroacetate (0.88 g, 2.06 mmol) at room temperature, and stirring was continued for 4 h under a nitrogen atmosphere. The solvent was removed under reduced pressure at room temperature. The crude product was dissolved in 5% ethyl acetate in hexanes and filtered through a basic alumina pad quickly, and the filtrate was concentrated under reduced pressure at room temperature to give product **3** (1.82 g, 63%) as a thick light-yellow syrup. The unreacted starting material **2** (0.65 g, 25%) was also recovered by washing the used basic alumina pad with 15% ethyl acetate in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55−1.72 (m, 2H), 2.05−2.22 (m, 2H), 3.83 (dd, J = 1.6, 6.4 Hz, 1H), 4.10 (d, J = 7.6 Hz, 1H), 4.20 (dd, J = 1.6, 14.0 Hz, 1H), 4.45 (dt, J = 4.0, 7.6 Hz, 1H), 4.80−5.06 (m, 2H), 5.68−5.78 (m, 1H), 6.12 (dd, J = 6.4, 14.0 HZ, 1H), 7.16−7.36 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.70, 32.57, 56.21, 82.10, 88.20, 115.45, 126.72, 126.84, 128.56, 128.81, 128.85, 129.24, 138.22, 141.62, 142.28, 152.23.

(*S*)-2-Benzhydryl-3,4-dihydro-2*H*-pyran (4). To a stirred solution of compound **3** (1.65 g, 5.93 mmol) in anhydrous benzene (80 mL) was added Grubb's (first generation) catalyst (0.24 g, 0.3 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was slowly heated to reflux, and the refluxing was continued for 2 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude residue was purified by column chromatography using 5% ethyl acetate in hexanes and recrystallized in hexanes to give compound **4** (1 g, 68%) as a white solid. Mp: 68−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52−1.62 (m, 1H), 1.72−1.82 (m, 1H), 1.92−2.10 (m, 2H), 4.05 (d, J = 8.8 Hz, 1H), 4.57 (dt, J = 2.4, 9.2 Hz, 1H), 4.67−4.72 (m, 1H), 6.35 (d, J = 6.0 Hz, 1H), 7.16−7.42 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.01, 26.49, 56.46, 76.64, 100.86, 126.66, 126.85, 128.60, 128.70, 128.88, 142.12, 142.42, 144.06.

6-Benzhydryltetrahydro-2*H*-pyran-3-ol (Mixture of 5a and 5b). To a stirred solution of compound **4** (2.8 g, 11.18 mmol) in anhydrous THF (10 mL) was added 9-BBN (56 mL, 0.5 M solution in tetrahydrofuran, 27.96 mmol) under a nitrogen atmosphere. After being stirred overnight at room temperature, the reaction mixture was cooled to 0 °C, quenched by the addition of ethanol (15 mL), and stirred for 10 min. Next, aqueous 10% NaOH solution (15 mL) and 30% H_2O_2 (10 mL) were added, and the resulting solution was heated to 50 °C for 1 h. After cooling to room temperature, the reaction mixture was treated with water (40 mL) and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with water (40 mL), brine (40 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography using 25% ethyl acetate in hexanes to give mixture of inseparable compounds **5a** and **5b** (2.7 g, 90%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34−1.45 (m, 3H), 1.53−1.61 (m, 1H), 2.01−2.09 (m, 1H), 3.14 (t, J = 10.0 Hz, 1H), 3.62−3.70 (m, 1H), 3.91 (d, J = 9.2 Hz, 1H), 3.95−4.04 (m, 2H), 7.16−7.37 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.68, 33.01, 57.55, 66.24, 73.18, 79.09, 126.68, 126.92, 128.73, 128.78, 128.81, 128.86, 128.99, 142.57, 142.64, 142.96.

(3*R*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-yl Methanesulfonate (6a). To an ice-cooled stirred mixture of compounds **5a** and **5b** (2.7 g, 10.06 mmol) and triethylamine (2.8 mL, 20.12 mmol) in anhydrous dichloromethane (60 mL) was added methanesulfonyl chloride (1.17 mL, 15.09 mmol) under a nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was extracted with ethyl acetate (3 × 75 mL) and water (40 mL). The combined organic layers were washed with water (40 mL), brine (40 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 25% ethyl acetate in hexanes to elute the trans compound **6a** (2.6 g, 75%) first as a white solid followed by cis compound **6b** (0.43 g, 12%) as a white solid. Spectral data for **6a**. Mp: 110−112 °C. $[\alpha]^{25}_D$ (−)48.4° (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42−1.52 (m, 1H, H-5ax), 1.62−1.78 (m, 2H, H-4ax, H-5eq), 2.21−2.30 (m, 1H, H-4eq), 2.99 (s, 3H, CH_3), 3.37 (t, J = 10.4 Hz, 1H, H-2ax), 3.89 (d, J = 8.8 Hz, 1H, Ph_2CH), 4.02 (dt, J = 2.0, 9.2 Hz, 1H, H-6ax), 4.10−4.18 (m, 1H, H-2eq), 4.58−4.66 (m, 1H, H-3ax), 7.14−7.32 (m, 10H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.51, 30.58, 38.68, 57.12, 69.87, 75.27, 79.04, 126.73, 126.96, 128.59, 128.65, 128.68, 128.93, 141.97, 142.34.

(2*S*,5*S*)-5-Azido-2-benzhydryltetrahydro-2*H*-pyran (7). To a stirred solution of compound **6a** (2.5 g, 7.22 mmol) in DMF (60 mL) was added sodium azide (2.35 g, 36.08 mmol). After being stirred overnight at 80 °C, the reaction mixture was cooled to room temperature, treated with water (40 mL), and extracted with ethyl ether (3 × 75 mL). The combined organic layers ware washed with water (40 mL),

brine (40 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography using 5% ethyl acetate in hexanes to give compound **7** (1.72 g, 81%) as a white solid. Mp: 93−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32−1.38 (m, 1H), 1.59−1.70 (m, 1H), 1.73−1.82 (m, 1H), 1.94−2.20 (m, 1H), 3.52−3.57(m, 1H), 3.63 (dd, J = 1.6, 12.0 Hz, 1H), 3.95−4.10 (m, 3H), 7.16−7.38 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.43, 27.68, 55.58, 57.55, 69.80, 79.45, 126.56, 126.81, 128.57, 128.64, 128.73, 128.84, 142.23.

(3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-amine (8). Azide **7** (0.65 g, 2.21 mmol) in methanol (40 mL) was hydrogenated (50 psi) in the presence of 10% Pd−C (65 mg, 10 wt %) for 2 h. The reaction mixture was filtered through a short bed of Celite, and the solvent was removed under reduced pressure to afford amine **8** (0.65 g) as a light yellow solid in quantitative yield. The product was pure enough for continuation to the next step. Mp: 92−94 °C. $[\alpha]^{25}_D$ (−)76.8° (c 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24−1.44 (m, 3H), 1.52−1.62 (m, 1H), 1.63−1.80 (m, 2H), 2.89 (br s, 1H), 3.62−3.66 (m, 1H), 3.74−3.80 (m, 1H), 3.96 (d, J = 8.8 Hz, 1H), 4.04 (dt, J = 2.4, 8.8 Hz, 1H), 7.12−7.37 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.86, 31.06, 45.55, 57.58, 73.92, 79.60, 126.50, 126.69, 128.56, 128.72, 128.76, 142.40, 142.65.

Procedure A. (*R*)-2-((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-ylamino)-1-phenylethanol (9a). A mixture of amine **8** (50 mg, 0.19 mmol) and (*R*)-2-phenyloxirane (27 mg, 0.22 mmol) in anhydrous ethanol (3 mL) was refluxed under nitrogen atmosphere overnight. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography using 3% methanol in ethyl acetate to afford compound **9a** (40 mg, 56%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28−1.34 (m, 1H), 1.45−1.55 (m, 1H), 1.67 (tt, J = 4.0, 13.6 Hz, 1H), 1.82−1.92 (m, 1H), 2.57 (dd, J = 9.6, 12.4 Hz, 1H), 2.65 (br s, 1H), 2.91 (dd, J = 3.6, 12.4 Hz, 1H), 3.58 (dd, J = 1.2, 11.6 Hz, 1H), 3.90−3.98 (m, 2H), 4.05 (dt, J = 2.0, 10.4 Hz, 1H), 4.63 (dd, J = 3.6, 9.6 Hz, 1H), 7.12−7.40 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.63, 26.64, 51.16, 53.74, 57.12, 68.84, 71.83, 79.11, 125.66, 125.97, 126.28, 127.49, 128.02, 128.14, 128.20, 128.29, 141.91, 142.00, 142.28. $[\alpha]^{25}_D$ (−)100.6° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 275−277 °C. Anal. ($C_{26}H_{29}NO_2\cdot$HCl) C, H, N.

(*S*)-2-((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-ylamino)-1-phenylethanol (9b). Amine **8** (0.1 g, 0.37 mmmol) was treated with (*S*)-2-phenyloxirane (45 mg, 0.37 mmol) in anhydrous ethanol (5 mL) using procedure A. The residue was purified by column chromatography using 4% methanol in ethyl acetate to afford compound **9b** (90 mg, 62%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26−1.34 (m, 1H), 1.48−1.59 (m, 1H), 1.67 (tt, J = 4.0, 13.6 Hz, 1H), 1.92−1.99 (m, 1H), 2.65 (dd, J = 9.2, 12.0 Hz, 1H), 2.74 (br s, 1H), 3.05 (dd, J = 3.2, 12.0 Hz, 1H), 3.48−3.52 (m, 1H), 3.96−4.06 (m, 4H), 4.78 (dd, J = 2.8, 9.2 Hz, 1H), 7.12−7.38 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.82, 26.47, 51.53, 54.37, 57.12, 70.12, 70.99, 79.30, 125.72, 126.23, 126.50, 127.51, 128.28, 128.37, 128.40, 128.47, 128.53, 141.92, 142.04, 142.09. $[\alpha]^{25}_D$ (−)40.6° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 215−217 °C. Anal. ($C_{26}H_{29}NO_2\cdot$HCl) C, H, N.

(*R*)-2-(((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-yl)amino)-1-(4-fluorophenyl)ethanol (9c). Amine **8** (60 mg, 0.22 mmol) was treated with (*R*)-2-(4-fluorophenyl)oxirane (35 mg, 0.25 mmol) in anhydrous ethanol (3 mL) using procedure A. The residue was purified by silica gel column chromatography using 3% methanol in ethyl acetate as the eluent to afford compound **9c** (51 mg, 59%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20−1.56 (m, 2H), 1.56−1.76 (m, 1H), 1.86−2.04 (m, 1H), 2.62−2.72 (m, 1H), 2.75 (s, 1H), 2.84 (dd, J = 3.5, 12.0 Hz, 1H), 3.25−3.65 (m, 3H), 3.82−3.94 (m, 2H), 3.97−4.09 (m, 1H), 4.75 (dd, J = 3.5, 9.4 Hz, 1H), 6.90−7.05 (m, 2H), 7.06−7.36 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 27.4, 51.0, 54.3, 57.2, 69.7, 71.2, 79.3, 114.9, 115.2, 126.2, 126.4, 127.3, 127.4, 128.3, 128.4, 138.1, 141.9, 142.0, 160.9, 163.3. $[\alpha]^{25}_D$ (−)54.6° (c 1, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 260−265 °C. Anal. ($C_{26}H_{28}NO_2F\cdot$HCl) C, H, N.

(*S*)-2-(((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-yl)amino)-1-(4-fluorophenyl)ethanol (9d). Amine **8** (60 mg, 0.22 mmol) was treated with (*S*)-2-(4-fluorophenyl)oxirane (35 mg, 0.25 mmol) in anhydrous ethanol (3 mL) using procedure A. The residue was purified by silica gel column chromatography using 3% methanol in ethyl acetate as the eluent to afford compound **9d** (48 mg, 56%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17−1.38 (m, 2H), 1.56−1.76 (m, 1H), 1.96−2.08 (m, 1H), 2.75 (t from dd, J = 10.0 Hz, 1H), 2.88 (br s, 1H), 3.10 (dd, J = 2.3, 12.0 Hz, 1H), 3.44 (d, J = 12.3 Hz, 1H), 4.02−4.12 (m, 3H), 4.95 (d, J = 9.1 Hz, 1H), 5.63 (br s, 1H), 6.93−7.04 (m, 2H), 7.13−7.40 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.4, 52.0, 54.1, 56.8, 69.2, 69.5, 69.6, 79.3, 115.1, 115.3, 126.2, 126.5, 127.3, 127.4, 128.2, 128.3, 128.4, 128.5, 136.9, 137.0, 141.8, 141.9, 160.9, 163.4. $[\alpha]^{25}_D$ (−)34.6° (c 1, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 248−256 °C. Anal. ($C_{26}H_{28}NO_2F\cdot$HCl$\cdot$0.4H_2O) C, H, N.

(*R*)-2-(((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-yl)amino)-1-(3-methoxyphenyl) ethanol (9e). Amine **8** (60 mg, 0.22 mmol) was treated with (*R*)-2-(3-methoxyphenyl)oxirane (38 mg, 0.25 mmol) in anhydrous ethanol (3 mL) using procedure A. The residue was purified by silica gel column chromatography using 3% methanol in ethyl acetate as the eluent to afford compound **9e** (55 mg, 59%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76−0.89 (m, 1H), 1.10−1.50 (m, 3H), 1.56−1.74 (m, 1H), 1.80−1.98 (m, 1 H), 2.63−2.73 (m, 2H), 2.82 (dd, J = 3.5, 12.0 Hz, 1H), 3.41 (br s, 2H), 3.56 (dd, J = 1.5, 12.0 Hz, 1H), 3.74 (s, 3H), 3.82−3.96 (m, 2H), 3.96−4.07 (m, 1H), 4.69 (dd, J = 3.5, 9.1 Hz, 1H), 6.73−6.80 (m, 1H), 6.84−6.91 (m, 2H), 7.07−7.32 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7, 26.9, 51.3, 53.9, 55.1, 57.1, 68.9, 71.2, 79.3, 111.0, 113.2, 118.0, 126.2, 126.4, 128.2, 128.4, 129.3, 141.8, 143.6, 159.6. $[\alpha]^{25}_D$ (−)69.5° (c 1, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 140−150 °C. Anal. ($C_{27}H_{31}NO_3\cdot$HCl$\cdot$0.2H_2O) C, H, N.

(*S*)-2-(((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-yl)amino)-1-(3-methoxyphenyl)ethanol (9f). Compound **8** (0.18 g, 0.67 mmol) was treated with (*S*)-2-(3-methoxyphenyl)oxirane (0.1 g, 0.67 mmol) in anhydrous ethanol (10 mL) using procedure A. The residue was purified by column chromatography using 5% methanol in ethyl acetate to afford compound **9f** (0.16 g, 57%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24−1.34 (m, 2H), 1.42−1.56 (m, 1H), 1.65 (tt, J = 4.0, 13.2 Hz, 1H), 1.90−1.98 (m, 1H), 2.62 (dd, J = 9.6, 12.4 Hz, 1H), 2.71 (br s, 1H), 3.03 (dd, J = 3.2, 12.4 Hz, 1H), 3.48−3.54 (m, 1H), 3.80 (s, 3H), 3.94−4.08 (m, 3H), 4.72 (dd, J = 2.8, 9.2 Hz, 1H), 6.81 (dd, J = 2.4, 8.0 Hz, 1H), 6.90−6.96 (m, 2H), 7.12−7.34 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.15, 26.92, 51.68, 54.60, 55.50, 57.46, 70.56, 71.37, 79.58, 111.25, 113.47, 118.29, 126.51, 126.77, 128.56, 128.66, 128.72, 128.81, 129.65, 142.32, 142.39, 144.14, 159.99. $[\alpha]^{25}_D$ (−)53.2° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 210−212 °C. Anal. ($C_{27}H_{31}NO_3\cdot$HCl) C, H, N.

Procedure B. (3*S*,6*S*)-6-Benzhydryl-*N*-(pyridin-2-ylmethyl) tetrahydro-2*H*-pyran-3-amine (10a). To a stirred solution of amine **8** (60 mg, 0.22 mmol) and 2-pyridinecarboxaldehyde (21 μL, 0.22 mmol) in 1,2-dichloroethane (6 mL) was added glacial acetic acid (13 μL, 0.22 mmol). After the mixture was stirred for 30 min, $NaCNBH_3$ (28 mg, 0.44 mmol) was added portionwise followed by methanol (1 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution at 0 °C and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4, and solvent was removed under reduced pressure. Crude product was purified by column chromatography using 3% methanol in dichloromethane to give compound **10a** (45 mg, 56%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28−1.36 (m, 1H), 1.50−1.74 (m, 1H), 1.91−2.04 (m,

1H), 2.74 (s, 1H), 3.28 (br s, 1H), 3.58 (dd, J = 1.8, 12.0 Hz, 1H), 3.85−4.14 (m, 5H), 7.07−7.42 (m, 12H), 7.62 (t, J = 7.6 Hz, 1H), 8.52 (d, J = 3.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 27.2, 51.1, 52.1, 57.0, 70.1, 79.3, 121.9, 122.1, 126.1, 126.4, 128.2, 128.5, 136.5, 142.2, 142.3, 149.1, 159.3. $[\alpha]^{25}_D$ (−)65.0° (c 1, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 220−230 °C. Anal. ($C_{24}H_{26}N_2O\cdot 2HCl$) C, H, N.

(3*S*,6*S*)-6-Benzhydryl-*N*-(pyridin-3-ylmethyl)tetrahydro-2*H*-pyran-3-amine (10b). Compound **8** (60 mg, 0.22 mmol) was reacted with 3-pyridinecarboxaldehyde (21 μL, 0.22 mmol), glacial acetic acid (13 μL, 0.22 mmol), and $NaCNBH_3$ (28 mg, 0.44 mmol)) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using 3% methanol in dichloromethane to afford compound **10b** (45 mg, 56%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24−1.36 (m, 2H), 1.48−1.70 (m, 2H), 1.90−1.98 (m, 1H), 2.64 (br s, 1H), 3.56 (dd, J = 1.6, 12.0 Hz, 1H), 3.81 (br s, 2H), 3.94−4.10 (m, 3H), 7.10−7.38 (m, 11H), 7.72 (d, J = 7.2 Hz, 1H), 8.50 (d, J = 3.6 Hz, 1H), 8.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.35, 27.55, 48.26, 50.62, 57.50, 70.37, 79.53, 123.64, 126.52, 126.72, 128.56, 128.72, 128.75, 128.77, 136.11, 142.34, 142.57, 148.70, 149.92. $[\alpha]^{25}_D$ (−)77.2° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 258−260 °C. Anal. ($C_{24}H_{26}N_2O\cdot 2HCl$) C, H, N.

(3*S*,6*S*)-6-Benzhydryl-*N*-(pyridin-4-ylmethyl)tetrahydro-2*H*-pyran-3-amine (10c). Compound **8** (60 mg, 0.22 mmol) was reacted with 4-pyridinecarboxaldehyde (21 μL, 0.22 mmol), glacial acetic acid (13 μL, 0.22 mmol), and $NaCNBH_3$ (28 mg, 0.44 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using 3% methanol in dichloromethane to afford compound **10c** (46 mg, 58%) as a thick syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35−1.43 (m, 1H), 1.46−1.60 (m, 1H), 1.72 (tt, J = 4.0, 13.4 Hz, 1H), 1.86−1.95 (m, 1H), 2.58 (s, 1H), 3.61 (dd, J = 1.2, 11.6 Hz, 1H), 3.89−4.02 (m, 4H), 4.06−4.13 (m, 1H), 7.16−7.40 (m, 10H), 7.67 (d, J = 6.1 Hz, 2H), 8.48 (d, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.1, 27.5, 49.1, 50.9, 57.4, 70.2, 79.3, 124.9, 126.3, 126.5, 128.3, 128.4, 128.6, 128.5, 141.9, 142.1, 146.7, 157.6. $[\alpha]^{25}_D$ (−)69.5° (c 1, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 224−230 °C. Anal. ($C_{24}H_{26}N_2O\cdot 1.8HCl$) C, H, N.

(3*S*,6*S*)-6-Benzhydryl-*N*-(naphthalen-1-ylmethyl)tetrahydro-2*H*-pyran-3-amine (10d). Compound **8** (60 mg, 0.22 mmol) was reacted with 1-naphthaldehyde (30 μL, 0.22 mmol), glacial acetic acid (13 μL, 0.22 mmol), and $NaCNBH_3$ (28 mg, 0.44 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using 3% methanol in dichloromethane to afford compound **10d** (51 mg, 56%) as a thick syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33−1.41 (m, 1H), 1.55−1.66 (m, 1H), 1.73 (tt, J = 4.0, 13.4 Hz, 1H), 1.99−2.08 (m, 1H), 3.63 (dd, J = 1.2, 11.6 Hz, 1H), 4.01 (d, J = 8.9 Hz, 1H), 4.07−418 (m, 2H), 4.28 (dd, J = 13.1, 37.5 Hz, 2H), 7.17−7.35 (m, 8 H), 7.37−7.58 (m, 6 H), 7.81 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.3, 27.7, 48.4, 50.9, 57.2, 70.1, 79.3, 123.7, 125.4, 125.9, 126.0, 126.2, 126.4, 127.7, 128.3, 128.4, 128.5, 128.6, 131.8, 133.8, 135.8, 142.2, 142.4. $[\alpha]^{25}_D$ (−)69.5° (c 1, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 140−150 °C. Anal. ($C_{29}H_{29}NO\cdot HCl\cdot 0.4H_2O$) C, H, N.

2-(((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-ylamino)methyl)phenol (10e). Compound **8** (60 mg, 0.22 mmol) was reacted with 2-hydroxybenzaldehyde (24 μL, 0.22 mmol), glacial acetic acid (13 μL, 0.22 mmol), and $NaCNBH_3$ (28 mg, 0.44 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using 2% methanol in dichloromethane to afford compound **10e** (65 mg, 77%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34−1.52 (m, 2H), 1.68 (tt, J = 4.0, 13.6, 1H), 1.90−2.00 (m, 1H), 2.70 (br s, 1H), 3.54−3.60 (m, 1H), 3.90−3.96 (m, 2H), 4.00−4.12 (m, 3H), 6.78 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 6.8 Hz, 1H), 7.14−7.38 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.48, 27.28, 49.61, 49.80, 57.89, 69.72, 79.69, 116.69, 119.20, 112.50, 126.63, 126.85, 128.58, 128.67, 128.86, 129.01, 142.21, 142.27, 158.72. $[\alpha]^{25}_D$ (−)86.2° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 315−317 °C (dec). Anal. ($C_{25}H_{27}NO_2\cdot HCl\cdot 0.3H_2O$) C, H, N.

3-((((3*S*,6*S*)-6-Benzhydryltetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol (10f). Compound **8** (60 mg, 0.22 mmol) was reacted with 3-hydroxybenzaldehyde (24 μL, 0.22 mmol), glacial acetic acid (13 μL, 0.22 mmol), and $Na(OAc)_3BH$ (84 mg, 0.44 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using 2% methanol in dichloromethane to afford compound **10f** (64 mg, 76%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29−1.39 (m, 1H), 1.44−1.58 (m, 1H), 1.68 (tt, J = 4.3, 13.7 Hz, 1H), 2.05−2.11 (m 1H), 2.82 (br s, 1H), 3.31−3.35 (m, 1H), 3.52 (d, J = 12.5 Hz, 1H), 3.82 (dd, J = 13.1, 29.9 Hz, 2H), 3.94 (d, J = 9.2 Hz, 1H), 3.99−4.09 (m, 2H), 6.68 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.96 (s, 1H), 7.09−7.31 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.8, 49.2, 49.9, 56.9, 67.9, 79.4, 115.4, 115.7, 120.0, 126.3, 126.5, 128.2, 128.5, 129.8, 141.7, 141.8, 157.4. $[\alpha]^{25}_D$ (−)55.4° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 190−200 °C. Anal. ($C_{25}H_{27}NO_2\cdot HCl\cdot 0.5H_2O$) C, H, N.

(3*S*,6*S*)-6-Benzhydryl-*N*-(thiophen-2-ylmethyl)tetrahydro-2*H*-pyran-3-amine (10g). Compound **8** (60 mg, 0.22 mmol) was reacted with 2-thiophenecarboxaldehyde (25 mg, 0.22 mmol), glacial acetic acid (13 μL, 0.22 mmol), and $NaCNBH_3$ (18 mg, 0.29 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using 3% methanol in dichloromethane to afford compound **10g** (65 mg, 79%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24−1.34 (m, 1H), 1.44−1.58 (m, 1H), 1.64 (tt, J = 4.0, 13.2 Hz, 1H), 1.86−1.94 (m, 1H), 2.69 (br s, 1H), 3.55 (dd, J = 2.0, 12.0 Hz, 1H), 3.92−4.08 (m, 6H), 6.88−6.91 (m, 1H), 6.92−6.95 (m, 1H), 7.14−7.36 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.51, 27.87, 45.85, 50.22, 57.60, 70.43, 79.56, 124.53, 124.75, 126.54, 126.74, 126.83, 128.63, 128.78, 128.82, 142.49, 142.68, 145.09. $[\alpha]^{25}_D$ (−)78.4° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 256−258 °C. Anal. ($C_{23}H_{25}NOS\cdot HCl\cdot 0.1H_2O$) C, H, N.

(3*S*,6*S*)-6-Benzhydryl-*N*-(furan-2-ylmethyl)tetrahydro-2*H*-pyran-3-amine (10h). Compound **8** (50 mg, 0.19 mmol) was reacted with furfural (18 mg, 0.19 mmol), glacial acetic acid (11 μL, 0.19 mmol), and $NaCNBH_3$ (24 mg, 0.37 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using 45% ethyl acetate in hexanes to afford compound **10h** (45 mg, 69%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28−1.34 (m, 1H), 1.45−1.58 (m, 1H), 1.59−1.74 (m, 2H), 1.84−1.94 (m, 1H), 2.65 (br s, 1H), 3.55 (dd, J = 2.0, 12.0 Hz, 1H), 3.77 (dd, J = 14.4, 22.8 Hz, 2H), 3.90−4.00 (m, 2H), 4.02−4.10 (m, 1H), 6.15 (d, J = 2.8 Hz, 1H), 6.30 (t, J = 2.8 Hz, 1H), 7.10−7.40 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.36, 27.82, 43.76, 50.50, 57.42, 70.30, 79.51, 106.96, 110.32, 126.47, 126.67, 128.55, 128.70, 128.72, 128.76, 141.98, 142.49, 142.65, 154.27. $[\alpha]^{25}_D$ (−)75.4° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 228−230 °C. Anal. ($C_{23}H_{25}NO_2\cdot HCl\cdot 0.3H_2O$) C, H, N.

(3*S*,6*S*)-*N*-((1*H*-Pyrrol-2-yl)methyl)-6-benzhydryltetrahydro-2*H*-pyran-3-amine (10i). Compound **8** (50 mg, 0.19 mmol) was reacted with pyrrole-2-carboxaldehyde (18 mg, 0.19 mmol), glacial acetic acid (11 μL, 0.19 mmol), and $NaCNBH_3$ (24 mg, 0.37 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude product was purified by column chromatography using 5% methanol in ethyl acetate to afford compound **10i** (50 mg, 77%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32−1.36 (m, 1H), 1.64−1.68 (m, 2H), 1.96−2.00

(m, 1H), 2.72 (br s, 1H), 3.46 (d, J = 12.4 Hz, 1H), 3.88−4.08 (m, 5H), 4.99 (br s, 1H), 6.07 (br s, 1H), 6.14 (br s, 1H), 6.77 (br s, 1H), 7.10−7.36 (m, 10H), 9.48 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.11, 26.55, 43.13, 50.30, 57.43, 69.54, 79.63, 107.93, 108.22, 118.58, 126.48, 126.79, 127.41, 128.55, 128.67, 128.78, 128.83, 142.34, 142.49. $[\alpha]^{25}_D$ (−)77.8° (c 0.5, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 234−236 °C. Anal. ($C_{23}H_{26}N_2O \cdot HCl \cdot 0.3H_2O$) C, H, N.

(3*S*,6*S*)-6-Benzhydryl-*N*-(4-methoxybenzyl)tetrahydro-2*H*-pyran-3-amine (10j). Compound **8** (60 mg, 0.22 mmol) was reacted with 4-methoxybenzaldehyde (31 mg, 0.22 mmol), glacial acetic acid (13 μL, 0.22 mmol), and $NaCNBH_3$ (28 mg, 0.44 mmol) in 1,2-dichloroethane (6 mL) using procedure B. The crude residue was purified by column chromatography using ethyl acetate to afford compound **10j** (40 mg, 46%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28−1.36 (m, 1H), 1.50−1.70 (m, 2H), 1.81 (br s, 1H), 1.90−1.98 (m, 1H), 2.65 (br s, 1H), 3.57 (d, J = 11.6 Hz, 1H), 3.73 (dd, J = 12.8, 24.8 Hz, 2H), 3.82 (s, 3H), 3.96−4.10 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 7.16−7.40 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.45, 27.84, 50.40, 50.46, 55.51, 57.45, 70.49, 79.49, 114.01, 126.46, 126.64, 128.52, 128.73, 128.75, 128.82, 129.43, 132.96, 142.48, 142.76, 158.82. $[\alpha]^{25}_D$ (−) 67.3° (c 1, MeOH). The product was converted into the corresponding hydrochloride salt. Mp: 136−138 °C. Anal. ($C_{26}H_{29}NO_2 \cdot HCl \cdot 0.3H_2O$) C, H, N.

In Vitro Experiments. *Monoamine Transport Inhibition.* The ability of test compounds to inhibit substrate uptake by rat monoamine transporters was monitored as described by us previously.[28,32] Briefly, uptake of [^{3}H]dopamine by DAT was measured in rat striatum, and uptake of [^{3}H]serotonin by SERT and [^{3}H]norepinephrine by NET was monitored in rat cerebral cortex. At least five triplicate concentrations of each test compound were studied, spaced evenly around the IC_{50}. IC_{50} was estimated by nonlinear computer curve-fitting procedures and converted to K_i with the Cheng−Prusoff equation, as we described previously.[32]

CNS Receptor Screening. Compound **10f** was characterized in several CNS receptor binding assays to assess the selectivity and specific interactions of **10f** with the monoamine transporters. The assays were carried out generously by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract NO1MH32004 (NIMH PDSP). The NIMH PDSP is Directed by Bryan L. Roth, MD, Ph.D., at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda, MD, U.S. (http://pdsp.med.unc.edu/).

Compound **10f** was evaluated in primary binding assays targeting, among others, cloned human dopamine receptor subtypes, serotonin receptor subtypes, α-adrenergic receptors, and opioid receptors. The description of all receptors targeted and corresponding radioligand used is provided in the Supporting Information. The default concentration for primary binding experiments was 10 μM. Compounds with inhibition of >50% in the primary assay were moved into the secondary assay with full concentration curves of the test compound in order to calculate the K_i value for inhibition. For experimental details refer to the PDSP Web site http://pdsp.med.unc.edu/ and click on "Binding Assay" or "Functional Assay" on the menu bar (experimental details have been updated!).

In Vivo Experiments. *Animals.* Male Sprague−Dawley rats (200−225 g) were purchased from Harlan. Animals were housed in a temperature and humidity controlled room with 12 h light/dark cycle. Food and water were accessible to animals freely throughout the duration of study. All testing occurred during the light component. All animal procedures were reviewed and approved by Wayne State University animal investigation committee consistent with AALAC guidelines.

*Effect of Compound **10f** in the Rat Forced Swimming Test as a Measure of Its Antidepressant Property.* The subjects were male Swiss Sprague−Dawley rats (Harlam Sprague−Dawley Inc., Indianapolis, IN, U.S.) weighing 200−225 g housed in cages for at least 1 week prior to testing. Animals were maintained in a temperature-controlled environment under a 12 h light/dark cycle. All subjects were naive and used only once.

Rats were transported to the testing room at least for 1 h prior to testing for acclimatization and adaptation purposes. Experimental sessions were conducted between 9 a.m. to 2 p.m. daily. Animals were assigned randomly and were placed individually in a glass cylinder (24.5 cm × 35.5 cm) filled with water at room temperature to a depth of 22 cm. All the test sessions were recorded by a video camera. The water was changed in the beginning of each session, and the temperature was maintained constant at 24−25 °C. Rats were judged to be immobile if making minimum movement to barely keep afloat.

The procedure consisted of a pretest and a test session separated by 24 h.[30] During the pretest period, rats were placed in the swim chamber for 15 min. Followed by the initial swim exposure, rats were patted dry and were transferred to the individual cages. Drugs or vehicle was then administered (ip) 15 min after the initial swim exposure, and the rats were then transported to their home cages. On the following day the rats were brought back to the testing room at least 1 h before the beginning of test session. Rats were administered either drugs or vehicle 1 h before the swim test. Each rat underwent a 5 min swim session, which was videotaped and scored later. In the case of imipramine, the pretreatment time was 30 min.

All drugs were prepared freshly on the test days. Compound **10f** and imipramine were dissolved in 10% β-hydroxypropylcyclodextrin solution. All drugs and vehicles were administered ip. **10f** was administered at a dose of 10 mg/kg and the volume of injections was maintained at 2 mL/kg. Imipramine was administered at 15 mg/kg. All drugs and vehicles were administered 1 h prior to testing for FST. Imipramine was administered 30 min prior to testing. An individual, blinded to the treatment, scored the videotapes for immobility. Immobility scores were analyzed by one-way ANOVA test.

■ ASSOCIATED CONTENT

Supporting Information. Spectral data for **6b**, binding affinity of **10f**, and elemental analysis data for all final targets. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

DAT, dopamine transporter; SERT, serotonin transporter; NET, norepinephrine transporters; TUI, triple uptake inhibitor; SAR, structure−activity relationship; GBR 12909 dihydrochloride, (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine); SSRI, selective serotonin reuptake inhibitor; DNRI, dopamine norepinephrine reuptake inhibitor; NE, norepinephrine; 5-HT, serotonin; FST, forced swim test

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