Further Structural Exploration of Trisubstituted Asymmetric Pyran Derivatives (2*S*,4*R*,5*R*)-2-Benzhydryl-5-benzylamino-tetrahydropyran-4-ol and Their Corresponding Disubstituted (3*S*,6*S*) Pyran Derivatives: A Proposed Pharmacophore Model for High-Affinity Interaction with the Dopamine, Serotonin, and Norepinephrine Transporters

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In our previous report, we described a novel series of asymmetric pyran derivatives (2*S*,4*R*,5*R*)-2-benzhydryl-5-benzylamino-tetrahydropyran-4-ol and their enantiomers as blockers of monoamine transporters in the brain. In this report, we describe the further exploration of this series of molecules by incorporating functional groups in the molecular template, which should promote the formation of H bonds with the transporters. In addition, a new synthetic scheme for the asymmetric synthesis of disubstituted *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-benzylamine analogues and their biological characterization is reported. All synthesized derivatives 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. The compounds were also tested for their binding potency at the DAT by their ability to inhibit binding of [^{3}H]WIN 35, 428. The results indicated that the presence of functional groups, such as −OH, $-NH_2$, and the bioisosteric 5-substituted indole moiety in both di and trisubstituted compounds, significantly increased their potencies for the SERT and NET, especially for the NET. Among the trisubstituted compounds, (−)-**4b** exhibited the highest potency for the NET and the SERT (K_i of 2.13 and 15.3 nM, respectively) and was a serotonin norepinephrine reuptake inhibitor (SNRI). Compound (−)-**4a** exhibited the highest selectivity for the NET. Among the disubstituted compounds, a number of compounds, such as (−)-**9a**, (+)-**9b**, (−)-**9b**, and (+)-**9d**, exhibited significant low-nanomolar potencies for the SERT and the NET. Interestingly, compound (−)-**9d** exhibited appreciable potencies at all three transporters. On the basis of our present and past findings, we propose a qualitative model for the interaction of these compounds with monoamine transporters, which will be refined further in the future.

Introduction

Synaptic transmission involves the regulated release of neurotransmitters into the synaptic cleft for interaction with postsynaptic receptors.[1] The removal of biogenic amine transmitters from the cleft and from the extraneuronal space by their respective transporters enables the termination of the signal by its reuptake back into the presynaptic terminal, allowing a high constant level of neurotransmitters in the neuron and a low extraneuronal concentration.[2] Monoamine transporters, including the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET), play an important role in maintaining the concentration of biogenic amine neurotransmitters in the central nervous system (CNS). These transporters are involved in different pathological processes and have been implicated in many neurological disorders.[3−8] DAT is believed to be the main target for mediating cocaine's reinforcing and behavioral effects, although several lines of evidence also implicate the involvement of the serotonergic system in some capacity.[9−12] It is believed that dysfunctional SERT and NET systems in the CNS play an important role in the etiology of depression.[13,14]

Structurally diverse molecules have been developed for targeting monoamine transporter systems in search of medications for various diseases such as cocaine addiction and depression. Especially, for the past one and half decades, the DAT has been a target for developing medications for cocaine addiction. In this respect, compounds with diverse structures have been developed as extensively reviewed in recent articles.[15−17] Similarly, various structurally different molecules have been developed for the inhibition of the SERT known as SSRIs, for example, fluoxetine (Figure 1).[18,19] SSRIs are known to possess pharmacological activity against depression and are used extensively as antidepressant agents.[19−21] However, selective agents for the NET are relatively rare, compared to those for the DAT and the SERT. Recently, the highly selective NET blocker reboxetine (Figure 1) has been advanced for its strong antidepressant effect.[22−24] Compounds that are potent at both the SERT and the NET are known as SNRIs. Two well-known molecules belonging to the SNRI category are duloxetine and venlafaxine (Figure 1).[25] SNRIs such as venlafaxine exhibit antidepressant activity in clinical trials and produce a somewhat greater response and remission rates compared to those of SSRIs.[26]

In our effort to design and discover novel templates for developing pharmacotherapies for cocaine addiction and other related neuro disorders, we recently developed 3,6-disubstituted and 2,4,5-trisubstituted tetrahydro-pyran derivatives targeting

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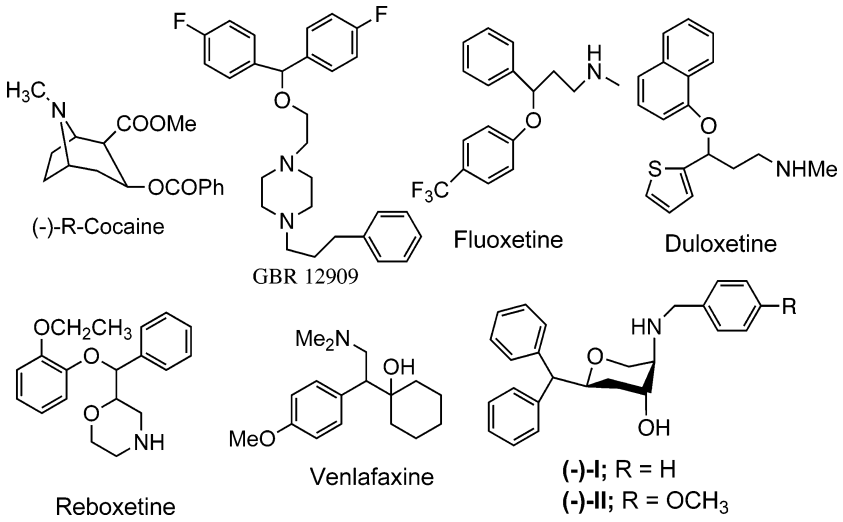


Figure 1. Molecular structures of selected dopamine, serotonin, and norepinephrine transporter blockers.

monoamine transporter systems.[27−29] In a recent report, we demonstrated the development of asymmetric trisubstituted pyran derivatives in different stereo- and regio-selective isomers with respect to the location of the hydroxyl and amino substitutions on the pyran ring.[29] Biological results indicate that the regioselective location of the hydroxyl group at the 4-position on the pyran ring, as shown in compounds **I** and **II** in Figure 1, is an important requirement for the binding interaction with the transporters. In addition, the stereoselective orientation of the hydroxyl group is important because the (−)-isomers exhibited higher potency compared to that of the corresponding (+)-isomers. Our earlier results indicated the preferential interaction of certain *cis*-3,6-disubstituted pyran derivatives with the NET, whereas (2*S*,4*R*,5*R*)-2,4,5-trisubstituted pyran derivatives bound selectively or nonselectively mainly to the SERT or NET.[28,29] For trisubstituted derivatives, the selectivity for different transporters could be manipulated by modifying the substituents in the phenyl ring of the *N*-benzyl moiety.[29] Thus, compound **I** exhibited high potency and selectivity for the NET, whereas compound **II** exhibited dual activity by being potent for both the SERT and NET.[29] We now report an extrapolation of this initial result. In the class of compounds presented here, the moieties capable of hydrogen bonding have been introduced at the *N*-benzyl position in both the di and trisubstituted series. Thus, in one instance, either hydroxyl or amino groups were introduced in the phenyl ring, and in another case, the phenyl moiety was replaced by a 5-substituted indole moiety.

In our attempt to synthesize the asymmetric trisubstituted derivatives, we have followed our previously established synthetic procedure. In addition, we have developed a novel asymmetric synthetic procedure for the synthesis of 3,6-disubstituted derivatives.

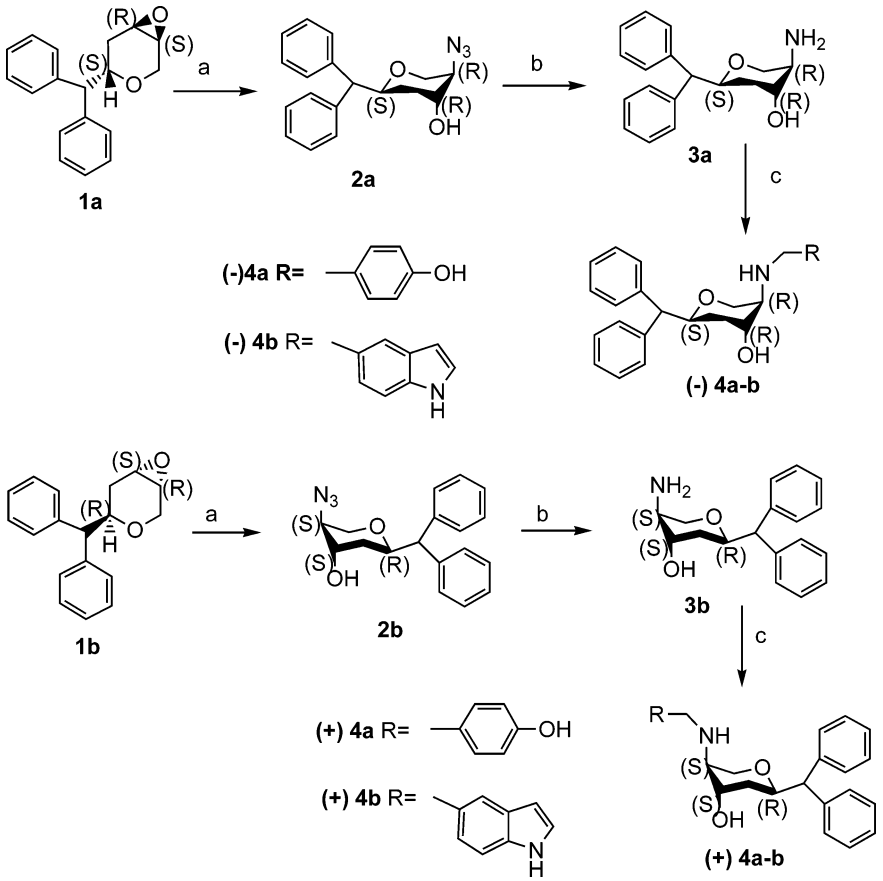
Chemistry. The route of synthesis of all final compounds is presented in Schemes 1−3. Scheme 1 describes the synthesis of (−)-**4a**, (+)-**4a**, (−)-**4b**, and (+)-**4b**. The *trans*-epoxide derivative **1a**,[29] was reacted with NaN_3 in the presence of NH_4-Cl in CH_3OH-H_2O to regioselectively give only **2a**.[30,31] Compound **2a** was hydrogenated in the presence of a palladium-C catalyst in methanol to produce amine **3a** in good yield. The reductive amination of **3a** with 4-hydroxy-benzaldehyde and 1*H*-indol-5-carbanaldehyde produced (−)-**4a** and (−)-**4b**, respectively. The same procedure starting with **1b** regioselectively produced enantiomeric compounds (+)-**4a** and (+)-**4b** in good yield.

Scheme 2 presents the asymmetric synthesis of disubstituted (−)-**9a**, (−)-**9b**, (−)-**9c**, and (−)-**9d**. The *trans*-epoxide derivative **1a** was reduced by lithium aluminum hydride (LAH) in hexane/ether (100:1) to give **5a** and **5c** as a mixture of products, which were mesylated without further separation. Pure mesylate **6a** could be separated by column chromatography. The detailed structural characterization of **6a** is included in the Supporting Information. *trans*-(3*R*,6*S*)-Benzhydryl-tetrahydro-pyran-3-ol (**5a**) was converted to **8a** through three reaction steps as reported in our previous publication.[28] Thus, mesylation with methanesulfonyl chloride in dry dichloromethane produced **6a**, which was then treated with sodium azide in DMF to produce azide **7a** with inversion of configuration. This azido displacement reaction resulted in the production of the *cis*-isomer **7a** from *trans*-**5a**. Finally, the catalytic hydrogenation of azide **7a** with Pd/C produced the amine precursors **8a** in good yield. The reductive amination of **8a** with 4-hydroxy-benzaldehyde, 1*H*-indol-5-carnaldehyde, and 4-nitro-benzaldehyde produced (−)-**9a**, (−)-**9b**, and (−)-**9c**, respectively. Compound (−)-**9d** was synthesized from (−)-**9c** via the reduction of the nitro group in the presence of $SnCl_2$ in ethanol and ethyl acetate.

The synthesis of compounds (+)-**9a**, (+)-**9b**, (+)-**9c**, and (+)-**9d** is presented in Scheme 3. The same procedure we have described in Scheme 2 produced the enantiomeric compounds (+)-**9a**, (+)-**9b**, (+)-**9c**, and (+)-**9d** from the starting compound *trans*-**1b**.

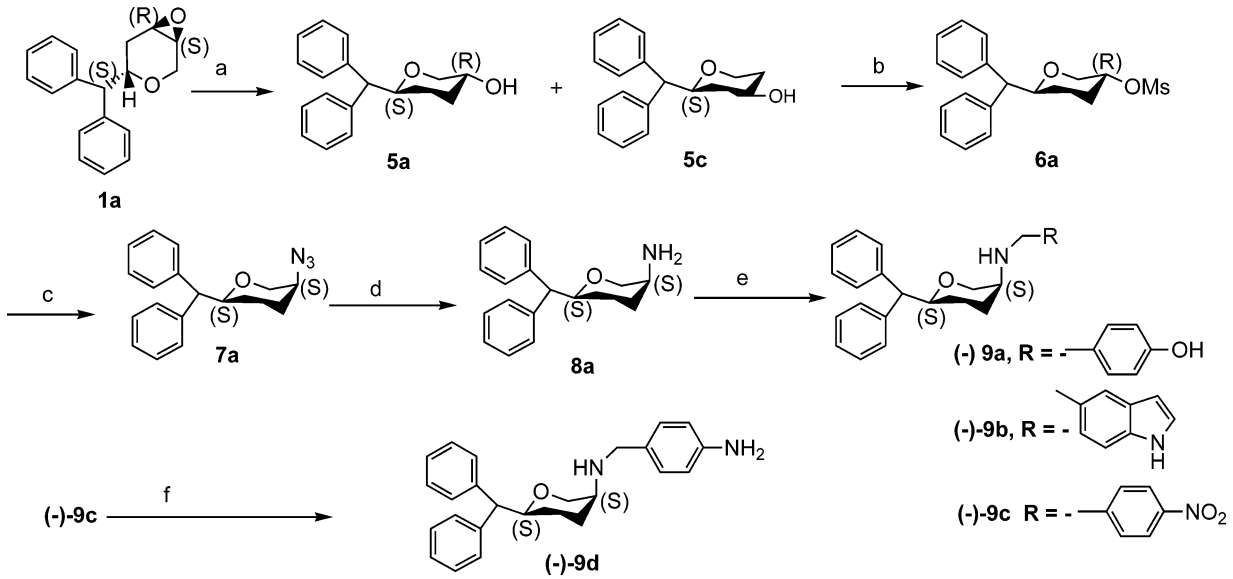
In our initial article, we extensively characterized the structure of the final target compounds and the epoxide intermediates by proton NMR analysis.[29] We demonstrated that the highest activity in the 2-benzhydryl-5-benzylaminotetrahydropyran-4-ol analogues resides in the (2S,4R,5R) absolute configuration. Furthermore, we showed by NMR analysis that the equatorial biphenyl group is in a cis relationship with the axial amino group. We also demonstrated that the hydroxyl group located in the 4-position on the pyran ring is oriented in an axial position and in a trans stereochemistry relationship with the vicinal amino substitution and in a trans relationship with respect to the benzyl group at the 2-position. We have now unambiguously confirmed our proposed structure by a crystal structure of compound **II** (Figure 2). The crystal structure confirms the (2S,4R,5R) absolute configuration stereochemistry that we proposed earlier.[29]

Scheme 1[a]



[a] (a) $NaN_3/NH_4Cl/CH_3OH-H_2O$ (8:1), 80 °C, overnight. (b) $H_2/Pd-C$, MeOH, 4 h. (c) Aldehyde/AcOH/$NaCNBH_3$, $ClCH_2CH_2Cl$, room temperature, 4 h.

Scheme 2[a]

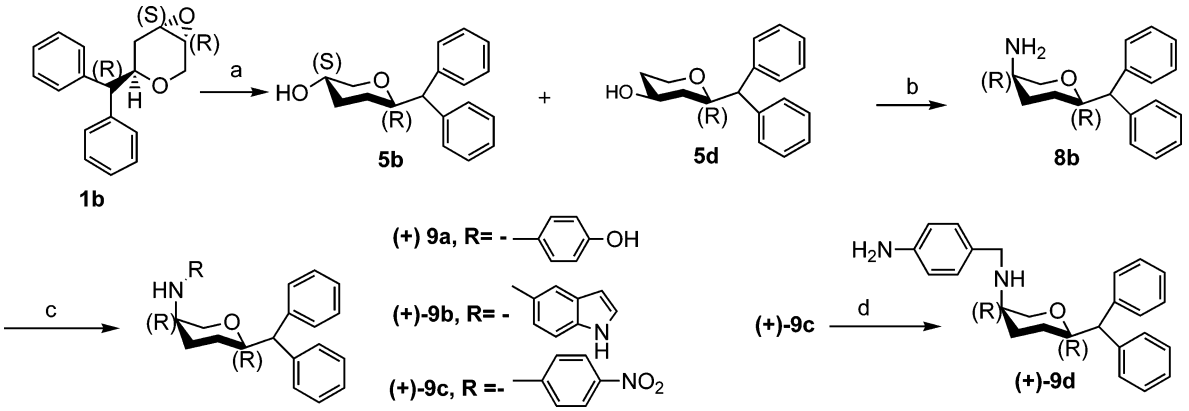


[a] (a) $LiAlH_4$/hexane/ether (100:1), room temperature, 20 h. (b) (i) $MeSO_2Cl/Et_3N/CH_2Cl_2$, room temperature, overnight. (ii) Separation by chromatography. (c) NaN_3/DMF, 100 °C, overnight. (d) $H_2/Pd-C$, MeOH, 4 h. (e) Aldehyde/AcOH/$NaCNBH_3$, 4 h. (f) $SnCl_2$/EtOH/EtOAc, reflux, 1.5 h.

Results and Discussion

In this report, we describe the biological properties of rationally designed novel asymmetric pyran derivatives as an extension of our earlier findings.[28,29] The current compounds have been designed with H bond forming functionalities incorporated in the *N*-benzyl substitution to explore their effect on potency and selectivity in interacting with monoamine transporters. The design of these compounds was prompted by our earlier observation that either the introduction of a hydroxyl and an amino group in the benzyl aromatic ring or the replacement of the 4-hydroxyphenyl group by a bioisosteric 5-substituted indole ring in 3,6-disubstituted pyran derivatives produces compounds with potent affinity at the NET.[28] Furthermore, in our initial study on trisubstituted compounds, we

Scheme 3[a]



[a] (a) $LiAlH_4$/pentane, rt, 20 h. (b) (i) $MeSO_2Cl/Et_3N/CH_2Cl_2$, rt, overnight. (ii) Separation by column. (iii) NaN_3/DMF, 100 °C, overnight. (iv) H_2/Pd−C. (c) Aldehyde/AcOH/$NaCNBH_3$. (d) $SnCl_2$/EtOH/EtOAc, reflux, 1.5 h.

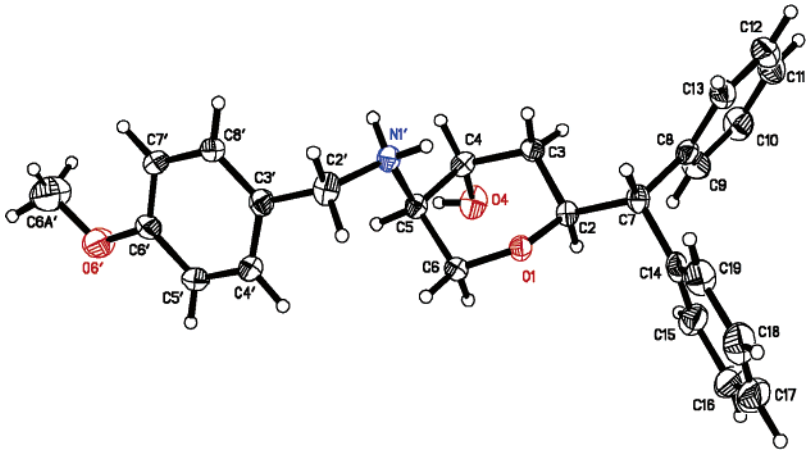


Figure 2. View of ((2*S*,4*R*,5*R*)-5-(4-methoxybenzylamino)-2-benzhydryl-tetrahydro-2*H*-pyran-4-ol) (**II**) with the thermal displacement parameters shown at the 30% level. The bromine atom and water molecule have been omitted for clarity.

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

compd	DAT binding, K_i, nM, [^{3}H]WIN 35, 428[a]	DAT uptake, K_i, nM, [^{3}H]DA[a]	SERT uptake, K_i, nM, [^{3}H]5-HT[a]	NET uptake, K_i, nM [^{3}H]NE[a]
GBR 12909[b]	8.56 ± 1.5	10.6 ± 2.2	91.1 ± 12.8	102 ± 32
(−)-I-(D-165)[b]	1500 ± 570	446 ± 59	707 ± 30	4.92 ± 0.92
(−)-II-(D-142)[b]	183 ± 32	115 ± 12	25.9 ± 3.6	15.8 ± 5.3
(+)-4a(D-158)	125 ± 5	91.5 ± 7.4	2540 ± 430	94.4 ± 18.5
(−)-4a(D-152)	234 ± 18	172 ± 20	237 ± 12	10.4 ± 1.0
(+)-4b(D-167)	399 ± 78	184 ± 16	223 ± 45	13.2 ± 4.0
(−)-4b (D-168)	570 ± 142	120 ± 8	15.3 ± 1.3	2.13 ± 0.41
(+)-9a (D-155)	114 ± 2	67.4 ± 4	187 ± 25	40.9 ± 6
(−)-9a (D-161)	226 ± 6	85 ± 5.9	37.7 ± 2.6	5.09 ± 0.92
(+)-9b(D-186)	467 ± 48	142 ± 43	11.8 ± 1.6	15.6 ± 2.3
(−)-9b(D-187)	338 ± 40	214 ± 11	14.5 ± 2.7	6.56 ± 1.01
(+)-9c (D-200)	64.6 ± 12.4	59.9 ± 14.2	64.6 ± 11.8	81.6 ± 9.7
(−)-9c (D-199)	38.4 ± 10.3	34.6 ± 6.5	19.9 ± 1.5	54.3 ± 9.8
(+)-9d(D-184)	118 ± 18	43.9 ± 5.2	45.7 ± 17.7	25.6 ± 3.6
(−)-9d(D-185)	142 ± 18	62.4 ± 5.6	16.1 ± 1.6	12.6 ± 3.7

[a] For binding, the DAT was labeled with [^{3}H]WIN 35, 428. For uptake by the DAT, SERT, and NET, the [3H]DA, [3H]5-HT, and [3H]NE accumulation were measured. Results are average ± SEM of three to eight independent experiments assayed in triplicate. [b] See ref 29.

observed the significant influence of substituents in the aromatic ring on affinity and selectivity for the SERT and the NET. Our model for the qualitative prediction of potency and selectivity of these compounds for monoamine transporter systems is based upon the results from the current studies as well as from our previously published data.[29]

Compounds (+)-**4a**, (−)-**4a**, (+)-**4b** and (−)-**4b** incorporate phenolic hydroxy and 5-substituted indole moieties. Consonant with our earlier results on disubstituted compounds,[28] both (−)-**4a** and (−)-**4b** (Scheme 1) exhibited high potency for the NET (K_i: 10.39 and 2.13 nM, respectively), and additionally, the indole derivative (−)-**4b** exhibited high potency for the SERT (K_i: 15.3 nM) (Table 1). Thus, (−)-**4b** is a dual active serotonin−norepinephrine transporter blocker and can be designated as an SNRI. As we found enantioselective activity in our earlier study,[29] the enantiomeric (+)-**4a** was much weaker than (−)-**4a** at the NET. However, no appreciable enantioselectivity was observed for the two indole enatiomers (+)-**4b**

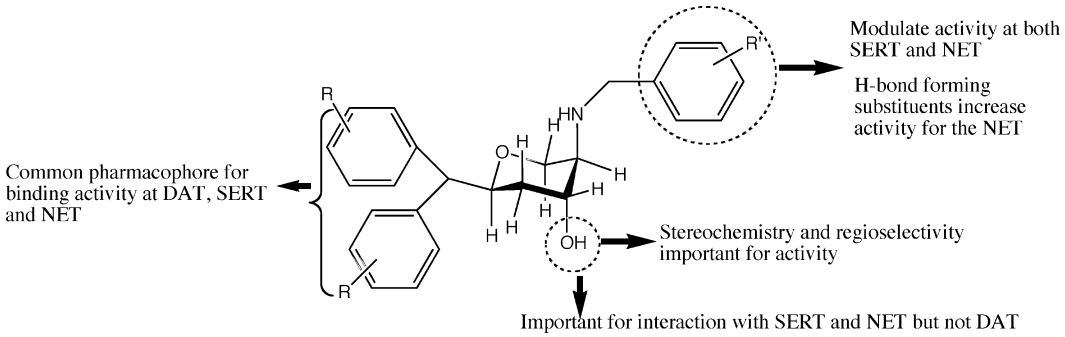


Figure 3. Proposed interaction model of pyran derivatives with monoamine transporters molecules.

and (−)-**4b** because both enantiomers exhibited potent affinity for the NET (K_i: 13.2 and 2.13 nM, respectively). However, for the interaction with the SERT, an enantioselectivity was observed because (−)-**4b** was more potent than (+)-**4b** (K_i: 15.3 vs 223 nM). It is evident from these results that the potency for the NET has increased significantly in these molecules compared to that of the SERT, reflecting a possible contribution of enhanced H-bonding interaction with the NET.

As described in the Chemistry section, we have developed an asymmetric synthesis pathway for the 3,6-disubstituted compounds to circumvent our earlier problems related to resolution. Similar *N*-benzyl modifications were introduced for our disubstituted derivatives as described above for the above trisubstituted compounds. The results indicate potent activity for the NET in these optically active disubstituted compounds. The hydroxy compounds (+)-**9a** and (−)-**9a** (Scheme 2) exhibited differential activity for the monoamine transporters with (−)-**9a** displaying an SNRI profile (K_i: 37.7 and 5.09 nM for SERT and NET, respectively). In this context, the counterpart of disubstituted compound (−)-**9a**, the trisubstituted compound (−)-**4a**, exhibited low-nanomolar potency at the NET and was weak at the SERT. Evidently, compound (−)-**9a** without the hydroxyl group on the pyran ring has increased affinity for the SERT. However, indole derivatives (−)-**9b** and (+)-**9b** were potent at both the SERT and the NET with (−)-**9b** being twice as potent at the NET than (+)-**9b** (K_i: 6.56 vs 15.6 nM, Table 1); their potencies at the SERT were comparable (K_i: 14.5 and 11.8 nM, respectively). In addition, the potency of (−)-**4b** and (−)-**9b** was also comparable. However, unlike enantiomeric (+)-**4b**, compound (+)-**9b** retained low-nanomolar affinity for the SERT (223 vs 11.8 nM).

Furthermore, we synthesized two enantiomeric amino derivatives as shown in structures (+)-**9d** and (−)-**9d**. The profile of the interaction with the monoamine transporters of these two derivatives bears similarities to that for (+)-**9b** and (−)**9b**. All molecules exhibited potent interaction with the NET and SERT, indicating the potential involvement of an H-bonding interaction with the amino moiety. In this regard, compound (−)-**9d** exhibited activity for all three transporters and was thus a triple acting molecule. Interestingly, much of the potency for the NET was decreased when the electron withdrawing substituent nitro was introduced in compounds (+)-**9c** and (−)-**9c**. Thus, compound (−)-**9c** was more than 4- and 8-fold less potent than (−)-**9d** and (−)-**9b** (54.3 vs 12.6 and 6.56 nM, Table 1). An interesting observation was that the disubstituted derivatives compared to their trisubstituted counterpart exhibited a relative lack of discrimination between respective enantiomers for interaction with the three transporters.

Model of Interaction. On the basis of our current results and the results from our previous publication,[29] we propose a model for the interaction of these pyran derivatives with monoamine transporter targets. This is shown in Figure 3. The biphenyl moiety in this model may represent a common pharmacophoric element that is important for all three transporters. In both disubstituted and trisubstituted compounds, the substituents on the phenyl moiety dictate selectivity and potency mainly for the SERT and NET. Increasing interaction with the NET was observed when H-bonding substitution was introduced. In the trisubstituted compounds, the stereoselective orientation of the hydroxyl group is important for interaction with both SERT and NET, more so with NET. The interaction of the same hydroxyl group with the DAT appears to be unfavorable.

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]
GBR 12909	0.12	0.10	0.89
(+)-4a	0.03	0.96	27
(−)-4a	0.72	17	23
(+)-4b	0.82	14	17
(−)-4b	7.8	56.	7.2
(+)-9a	0.36	1.6	4.6
(−)-9a	2.2	17	7.4
(+)-9b	12.	9.1.	0.75
(−)-9b	15	33	2.2.
(+)-9c	0.92	0.73	0.79
(−)-9c	1.7.	0.63	0.36
(+)-9d	0.96	1.7.	1.8
(−)-9d	3.9	5.0	1.3

[a] Ratio of K_i values.

Conclusion

In this report, we describe the successful completion of the asymmetric synthesis of both disubstituted and trisubstituted pyran derivatives. In vitro binding results indicate that the presence of H bond forming moieties increases the potencies of these molecules for the SERT and the NET, especially for the NET. Several compounds from this latest series, for example, (−)-**4b**, (−)-**9a**, (+)-**9b**, (−)-**9b**, and (+)-**9d**, can be considered as dual acting SNRIs because they exhibited appreciable potencies at both the SERT and NET (Table 1 and Table 2). Compound (−)-**4a** exhibited the highest selectivity for the NET in the current series (Table 2). However, compound (−)-**9d** was triple acting because it was active at all three transporters. On the basis of the information available so far on this novel class of molecules, we propose a preliminary model for the interaction with the three monoamine transporters. This model will be refined further in the future when more SAR results become available. These compounds will have strong potential to act as antidepressants.

Experimental Details

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. The dry solvent

was obtained according to the standard procedure.[32] All reactions were performed under inert atmosphere (N_2) unless otherwise noted. Analytical silica gel-coated TLC plates (Si 250F) 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 mM. ^{1}H NMR spectra were routinely obtained using a Varian 400 MHz FT NMR spectrometer. The NMR solvent used was $CDCl_3$ as indicated. TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc. and were within ± 0.4% of the theoretical value.

[^{3}H]WIN 35,428 (87.0 Ci/mmol), [^{3}H]dopamine (59.4 Ci/mmol), [3H]serotonin (30.0 Ci/mmol), and [^{3}H]norepinephrine (52.0 Ci/mmol) were obtained from Dupont-New England Nuclear (Boston, MA). (−)-Cocaine hydrochloride, WIN 35,428 naphthalene sulfonate, and GBR 12909 dihydrochloride (1-[2-[bis(4-fluorophenyl)-methoxy]ethyl]-4-[3-phenylpropyl]piperazine) were purchased from SIGMA-Aldrich (St. Louis, MO).

Procedure A. Synthesis of (2*S*,4*R*,5*R*)-5-Azido-2-benzhydryl-tetrahydropyran-4-ol (2a). A solution of **1a** (0.05 g, 0.19 mmol) in an 8:1 MeOH/H_2O (2 mL) mixture was treated with NaN_3 (0.06 g, 0.94 mmol) and NH_4Cl (0.02 g, 0.41 mmol), and the resulting reaction mixture was stirred at 80 °C overnight. The reaction mixture was diluted with ether, and the organic layer was separated. The ether extract was washed with saturated aqueous $NaHCO_3$ and water and dried over Na_2SO_4. The ether was removed in vacuo to afford a crude solid product. Purification of the product by flash chromatography (hexane/ethyl acetate = 4:1) yielded **2a**: 0.05 g (95%, $[\alpha]_D$ (−)109.3, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.44 (m, 1H, H-3eq), 1.80 (ddd, *J* = 14 Hz, 11.2 Hz, 2.8 Hz, 1H, H-3ax), 1.91 (s, 1H, OH), 3.26 (m, 1H, H-5), 3.82−4.04 (m, 4H, H-4, H-6, Ph_2CH), 4.49 (dt, *J* = 2.4 Hz, 10.0 Hz, 1H, H-2), 7.00−7.40 (m, 10H, aromatic-CH).

Synthesis of (2*R*,4*S*,5*S*)-5-Azido-2-benzhydryl-tetrahydropyran-4-ol (2b). Compound **1b** (0.04 g, 0.15 mmol) was treated with NaN_3 (0.05 g, 0.75 mmol) and NH_4Cl (0.02 g, 0.33 mmol) (Procedure A) to yield **2b**: 0.04 g (95%, $[\alpha]_D$ (+)108, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.45 (m, 1H, H-3eq), 1.80 (ddd, *J* = 14 Hz, 11.2 Hz, 2.8 Hz, 1H, H-3ax), 2.0 (bs, 1H, OH), 3.27 (m, 1H, H-5), 3.84−4.05 (m, 4H, H-4, H-6, Ph_2CH), 4.50 (dt, *J* = 2.4 Hz, 10.0 Hz, 1H, H-2), 7.00−7.40 (m, 10H, aromatic-CH).

Procedure B. Synthesis of (2*S*,4*R*,5*R*)-5-Amino-2-benzhydryl-tetrahydropyran-4-ol (3a). Compound **2a** (0.05 g, 0.18 mmol), dissolved in methanol (20 mL), was hydrogenated in the presence of 10% Pd/C (0.01 g). The mixture was filtered through a short bed of cellite, and the evaporation of the solvent gave **3a**: 0.05 g (97%, $[\alpha]_D$ (−)66, *c*=1, MeOH), which was pure enough for the next reaction.

^{1}HNMR ($CDCl_3$, 400 MHz): 1.40 (m, 1H, H-3), 1.70 (m, 1H, H-3), 2.73 (s, 1H, H-5), 3.20 (m, 3H, NH, OH), 3.60 (m, 1H, H-6), 3.80−4.00 (m, 3H, H-4, H-6, Ph_2CH), 4.46 (t, *J* = 10.0 Hz, 1H, H-2), 7.00−7.40(m, 10H, aromatic-CH).

Synthesis of (2*R*,4*S*,5*S*)-5-Amino-2-benzhydryl-tetrahydropyran-4-ol (3b). Compound **2b** (0.05 g, 0.14 mmol) was hydrogenated (Procedure B) to yield **3b**: 0.04 g (97%, $[\alpha]_D$ (+)66.2, *c*=1, MeOH).

^{1}HNMR (CD_3OD, 400 MHz): 1.43 (m, 1H, H-3), 1.72 (m, 1H, H-3), 2.65 (m, 1H, H-5), 3.57 (m, 1H, H-6), 3.82 (m, 1H, H-4), 3.92−4.00 (m, 2H, H-6, Ph_2CH), 4.52 (dt, *J* = 2.0 Hz, 10.4 Hz, 1H, H-2), 7.00−7.40 (m, 10H, aromatic-CH).

Procedure C. Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydropyran-4-ol ((−)-4a). Into a solution of **3a** (0.02 g, 0.09 mmol), 4-hydroxybenzaldehyde (0.01 g, 0.09 mmol) and glacial acetic acid (0.01 g, 0.09 mmol) in 1,2-dichloroethane (5 mL) was added portionwise $NaCNBH_3$ (0.01 g, 0.11 mmol) followed by methanol (1 mL). The reaction was continued for 4 h. Water was added to quench the reaction, and the mixture was stirred for 30 min at 0 °C. The reaction mixture was stirred with saturated aqueous $NaHCO_3$, and the product was extracted with methylene chloride (3 × 10 mL). The combined organic phase was washed with brine and water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexane/ethyl acetate/triethylamine, 3:2:0.2) to give, (−)-**4a**: 0.03 g (80%, $[\alpha]_D$ (−)72.6, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.40 (m, 1H, H-3eq), 1.66 (dt, *J* = 2.8 Hz, 14.0 Hz, 1H, H-3ax), 2.45 (m, 1H, H-5), 3.23 (bs, NH, OH), 3.58 (d, *J* = 12.4 Hz, 1H, (OH)$PhCH_2$), 3.70−3.80 (m, 2H, H-6, (OH)$PhCH_2$), 3.84−4.00 (m, 3H, H-4, H-6, Ph_2CH), 4.49 (dt, *J* = 2.0 Hz, 10.0 Hz, 1H, H-2), 6.57, 7.03, 7.10−7.36 (m, 14H, aromatic-CH).

The free base was converted into oxalate: mp 202−205 °C. Anal. [$C_{25}H_{27}NO_3 \cdot (COOH)_2$ $0.4H_2O$] C, H, N.

Synthesis of (2*R*,4*S*, 5*S*)-2-Benzhydryl-5-(4-hydroxy-benzylamino)-tetrahydro-pyran-4-ol ((+)-4a). Compound **3b** (0.02 g, 0.07 mmol) was reacted with 4-hydroxybenzaldehyde (0.01 g, 0.07 mmol), glacial acetic acid (0.004 g, 0.07 mmol), and $NaCNBH_3$ (0.01 g, 0.09 mmol) (Procedure C) to give (+)-**4a**: 0.02 g (85%, $[\alpha]_D$ (+)72.4, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.42 (m, 1H, H-3eq) 1.68 (dt, *J* = 2.8 Hz, 12.0 Hz, 1H, H-3ax), 2.46 (m, 1H, H-5), 3.52 (bs, NH, OH), 3.60 (d, *J* = 12.8 Hz, 1H, (OH)$PhCH_2$), 3.72−3.82 (m, 2H, H-6, (OH)$PhCH_2$), 3.86−4.00 (m, 3H, H-4, H-6, Ph_2CH), 4.50 (dt, *J* = 2.4 Hz, 10.4 Hz, 1H, H-2), 6.58, 7.05, 7.10−7.36 (m, 14H, aromatic-CH).

The free base was converted into oxalate: mp 196−199 °C. Anal. [$C_{25}H_{27}NO_3 \cdot (COOH)_2$ $0.4H_2O$] C, H, N.

Synthesis of (2*S*,4*R*,5*R*)-2-Benzhydryl-5-[(1*H*-indol-5-yl-methyl)-amino]-tetrahydro-pyran-4-ol ((−)-4b). Compound **3a** (0.03 g, 0.11 mmol) was reacted with 1*H*-indol-5-carbaldehyde (0.02 g, 0.11 mmol), glacial acetic acid (0.01 g, 0.11 mmol), and $NaCNBH_3$ (0.01 g, 0.21 mmol) (Procedure C) to give **4b**: 0.04 g (92%, $[\alpha]_D$ (−)69.90, *c*=1, acetone).

^{1}HNMR (DMSO, 400 MHz): 1.24 (m, 1H, H-3eq), 1.63 (dt, *J* = 2.8 Hz, 12.0 Hz, 1H, H-3ax), 2.35 (m, 1H, H-5), 3.35 (bs, NH, OH), 3.61 (d, *J* = 10.4 Hz, 1H, H-6), 3.68−3.90 (m, 4H, H-4, H-6, indol-CH_2), 3.97(d, *J* = 10.0 Hz, 1H, Ph_2CH), 4.45 (dt, *J* = 2.0 Hz, 10.0 Hz, 1H, H-2), 6.40, 7.00−7.60 (m, 15H, aromatic-CH).

The free base was converted into oxalate: mp 221−224 °C. Anal. [$C_{27}H_{28}N_2O_2 \cdot (COOH)_2$ $0.5H_2O$] C, H, N.

Synthesis of (2*R*,4*S*,5*S*)-2-Benzhydryl-5-[(1*H*-indol-5-ylmethyl)-amino]-tetrahydro-pyran-4-ol ((+)-4b). Compound **3b** (0.05 g, 0.18 mmol) was reacted with 1*H*-indol-5-carbaldehyde (0.03 g, 0.18 mmol), glacial acetic acid (0.01 g, 0.18 mmol), and $NaCNBH_3$ (0.02 g, 0.35 mmol) (Procedure C) to give (+)-**4b**: 0.05 g (69%, $[\alpha]_D$ (+)70.9, *c*=1, acetone).

^{1}HNMR (acetone, 400 MHz): 1.27 (td, *J* = 2.8 Hz, 14.0 Hz, 1H, H-3eq), 1.61 (dt, *J* = 2.8 Hz, 14.0 Hz, 1H, H-3ax), 2.34 (m, 1H, H-5), 3.58 (d, *J* = 12.0 Hz, 1H, H-6), 3.68−3.90 (m, 5H, H-4, H-6, indol-CH_2, Ph_2CH), 4.41 (dt, *J* = 2.4 Hz, 10.0 Hz, 1H, H-2), 6.28, 6.94−7.44 (m, 15H, aromatic-CH).

The free base was converted into oxalate: mp 224−228 °C. Anal. [$C_{27}H_{28}N_2O_2 \cdot (COOH)_2$] C, H, N.

Procedure D. Synthesis of (3*R*,6*S*)-6-Benzhydryl-tetrahydropyran-3-ol (5a). To compound **1a** (0.3 g, 1.13 mmol) in hexane (20 mL) and ether (0.2 mL) was added $LiAlH_4$ (0.21 g, 5.64 mmol). The resulting reaction mixture was stirred under N_2 for 20 h at room temperature. The reaction was next quenched with 10% NaOH and diluted with ethyl acetate (30 mL), and the precipitate was removed by filtration. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The removal of the solvent gave a crude product mixture (1:1.3) of **5a** and *trans*-4-hydroxy isomer **5c** (0.24 g).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.29−1.46 (m, 2H, H-5), 1.50−1.60 (m, 1H, H-4), 2.00−2.12 (m, 1H, H-4), 3.08−3.18 (t, *J* = 10.4 Hz, 1H, H-2), 3.64−3.74 (m, 1H, H-3ax), 3.83−3.92 (d, *J* = 9.2 Hz, 1H, Ph_2CH), 3.92−4.04 (m, 2H, H-2, H-6), 7.10−7.40 (aromatic-CH).

Synthesis of (3*S*,6*R*)-6-Benzhydryl-tetrahydro-pyran-3-ol (5b). Compound **1b** (0.30 g, 1.1 mmol) was reduced by $LiAlH_4$ (0.22 g, 5.5 mmol) (Procedure D) in 1% ether−hexanes to yield a mixture (1:1.3) of **5b** and *trans*-4-hydroxy isomer **5d** (0.25 g).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.34−1.43 (m, 2H, H-5), 1.54−1.62 (m, 1H, H-4), 2.03−2.12 (m, 1H, H-4), 3.10−3.19 (t, J = 10.4 Hz, 1H, H-2), 3.62−3.73 (m, 1H, H-3ax), 3.87−3.93 (d, J = 9.2 Hz, 1H, Ph_2CH), 3.94−4.04 (m, 2H, H-2, H-6), 7.10−7.40 (aromatic-CH).

Procedure E. Synthesis of Methanesulfonic Acid *trans*-(3*R*,6*S*)-6-Benzhydryl-tetra-hydropyran-3-yl Ester (6a). To a mixture of **5a**, *trans*-4-hydroxy isomer **5c** (0.23 g, 0.85 mmol), and triethylamine (0.13 g, 1.3 mmol) in dry methylene chloride (10 mL) was added methanesulfonyl chloride (0.15 g, 1.3 mmol). The reaction mixture was stirred under N_2 at room temperature overnight and then diluted with ethyl ether (50 mL). The organic phase was washed in turn with saturated $NaHCO_3$, brine, and water and then dried over anhydrous Na_2SO_4. The removal of the solvent and purification by chromatography (hexane/ethyl acetate: 4:1) gave **6a** (eluting first) as a white solid (0.12 g) ([α]$_D$ (−)54, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.38−1.53 (m, 1H, H-5), 1.60−1.78 (m, 2H, H-5, H-4), 2.16−2.30 (m, 1H, H-4), 2.93 (s, 3H, CH_3-SO_2), 3.28−3.42 ((t, J = 10.4 Hz, 1H, H-2ax), 3.84−3.94 (d, J = 8.8 Hz, 1H, Ph_2H), 3.94−4.07 (dt, J = 2.0 Hz, 9.6 Hz, 1H− H-6), 4.06−4.19 (m, 1H, H-2eq), 4.52−4.68 (m, 1H, H-3ax), 7.16−7.38 (m, 10H, aromatic-CH).

Synthesis of Methanesulfonic Acid *trans*-(3*S*,6*R*)-6-Benzhydryl-tetra-hydropyran-3-yl Ester (6b). A mixture of compound **5b** and *trans*-4-hydroxy isomer **5d** (0.25 g, 0.93 mmol) was reacted with methanesulfonyl chloride (0.15 g, 1.3 mmol) (Procedure E) to yield **6b** (0.13 g) ([α]$_D$ (+)54.8, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.38−1.52 (m, 1H, H-5), 1.62−1.78 (m, 2H, H-5, H-4), 2.20−2.29 (m, 1H, H-4), 2.96 (s, 3H, CH_3-SO_2), 3.32−3.40 ((t, J = 10.4 Hz, 1H, H-2ax), 3.88−3.92 (d, J = 8.8 Hz, 1H, Ph_2H), 3.97−4.06 (dt, J = 2.0 Hz, 9.6 Hz, 1H− H-6), 4.10−4.18 (m, 1H, H-2eq), 4.55−4.66 (m, 1H, H-3ax), 7.16−7.38 (m, 10H, aromatic).

Procedure F. Synthesis of *cis*-(3*S*,6*S*)-3-Azido-6-benzhydryl-tetrahydropyran (7a). NaN_3 (0.13 g, 2.03 mmol) was added into a mixture of **6a** (0.23 g, 0.68 mmol) in dry DMF (10 mL). The reaction was stirred under N_2 at 100°C overnight. Ethyl ether (50 mL) was added, and the organic phase was washed in turn with saturated $NaHCO_3$, brine, and water and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified on silica gel using hexanes−ethyl acetate (7:3) to give, **7a**: 0.17 g (86%, [α]$_D$ (−)78.2, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.34−1.42 (m, 1H, H-5), 1.60−1.84 (m, 2H, H-5, H-4), 1.94−2.03 (m, 1H, H-4), 3.52−3.58 (m, 1H, H-3), 3.60−3.67 (dd, J = 2.0 Hz, 12.4 Hz, 1H, H-2), 3.98−4.12 (m, 3H, H-2, H-6, Ph_2CH), 7.15−7.45 (m, 10H, aromatic-CH).

Synthesis of *cis*-(3*R*,6*R*)-3-Azido-6-benzhydryl-tetrahydropyran (7b). Compound **6b** (0.03 g, 0.08 mmol) was reacted with NaN_3 (0.016 g, 0.25 mmol) (Procedure F) to yield c*is*-azide **7b**: 0.02 g (quantitative yield, [α]$_D$ (+)77.6, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.30−1.40 (m, 1H, H-5), 1.52−1.85 (m, 2H, H-5, H-4), 1.92−2.02 (m, 1H, H-4), 3.52−3.58 (m, 1H, H-3), 3.59−3.67 (dd, J = 2.4 Hz, 17.2, Hz, 1H, H-2), 3.94−4.10 (m, 3H, H-2, H-6, Ph_2CH), 7.14−7.42 (m, 10H, aromatic-CH).

Procedure G. Synthesis of *cis*-(3*S*,6*S*)-(6-Benzhydryl-tetrahydropyran-3-yl)-amine (8a). Compound **7a** (0.17 g, 0.58 mmol) in methanol (25 mL) was hydrogenated under a 10% Pd-C (0.02 g, 10wt %) catalyst for 4 h to give *cis*-amine **8a**: 0.12 g (78%, [α]$_D$ (−)74.3, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.22−1.36 (m, 1H, H-5), 1.45−1.59 (m, 1H, H-5), 1.62−1.84 (m, 2H, H-4), 2.78 (bs, 1H, H-3), 3.56−3.70 (m, 2H, H-2), 3.92−3.99 (d, J = 8.8 Hz, 1H, Ph_2CH), 4.06−4.13 (m, 1H, H-6), 7.04−7.40 (m, 10H, aromatic-CH).

Synthesis of *cis*-(3*R*,6*R*)-(6-Benzhydryl-tetrahydropyran-3-yl)-amine (8b). Compound **7b** (0.02 g, 0.08 mmol) was hydrogenated under a 10% Pd−C (0.002 g, 10wt %) catalyst (Procedure G) to yield c*is*-amine **8b**: 0.02 g (92%, [α]$_D$ (+)74.0, *c*=1, MeOH).

^{1}HNMR ($CDCl_3$, 400 MHz): 1.25−1.36 (m, 1H, H-5), 1.47−1.61 (m, 1H, H-5), 1.68−1.88 (m, 2H, H-4), 2.90 (bs, 1H, H-3), 3.62−3.74 (m, 2H, H-2), 3.93−3.99 (d, J = 9.2 Hz, 1H, Ph_2CH), 4.05−4.19 (m, 1H, H-6), 7.02−7.40 (m, 10H, aromatic-CH).

Syntheis of *cis*-(3*S*,6*S*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(4-hydroxy-benzyl)-amine ((−)-9a). Compound **8a** (0.02 g, 0.07 mmol) was reacted with 4-hydroxybenzaldehyde (0.01 g, 0.07 mmol) in the presence of glacial acetic acid (0.005 g, 0.075 mmol) in 1,2-dichloroethane (10 mL), followed by treatment with $NaCNBH_3$ (0.006 g, 0.09 mmol) (Procedure C) to give (−)**-9a**: 0.02 g (72%, [α]$_D$ (−) 38.3, *c*=1, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): 1.36 (m, 1H, H-5), 1.51 (m, 1H, H-5), 1.68 (m, 1H, H-4), 2.00 (m, 1H, H-4), 2.71 (s, 1H, H-3), 3.56 (dd, J = 1.6 Hz, 11.6 Hz, 1H, H-2), 3.64 (m, 2H, (HO)Ph-CH_2), 3.96 (d, J = 8.4 Hz, 1H, Ph_2CH), 4.02−4.16 (m, 2H, H-6, H-2), 6.52 (m, 2H, aromatic-CH), 6.98−7.38 (m, 12H, aromatic-CH).

The free base was converted into oxalate: mp 136−138 °C. Anal. [$C_{25}H_{27}NO_2$·$(COOH)_2$ 0.6H_2O] C, H, N.

Syntheis of *cis*-(3*R*,6*R*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(4-hydroxy-benzyl)-amine ((+)-9a). Compound **8b** (0.02 g, 0.09 mmol) was reacted with 4-hydroxybenzaldehyde (0.01 g, 0.09 mmol) in the presence of glacial acetic acid (0.005 g, 0.09 mmol) in 1,2-dichloroethane (10 mL), followed by reduction with $NaCNBH_3$ (0.012 g, 0.18 mmol) (Procedure C) to give (+)**-9a**: 0.024 g (71%, [α]$_D$ (+) 40.1, *c*=1, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (m, 1H, H-5), 1.51 (m, 1H, H-5), 1.65 (m, 1H, H-4), 1.96 (m, 1H, H-4), 2.67 (m, 1H, H-3), 3.56 (dd, J = 1.6 Hz, 11.6 Hz, 1H, H-2), 3.66 (m, 2H, (HO)Ph-CH_2), 3.96 (d, J = 8.8 Hz, 1H, Ph_2CH), 3.98−4.12 (m, 2H, H-6, H-2), 6.65 (m, 2H, aromatic-CH), 7.06−7.38(m, 12H, aromatic-CH).

The free base was converted into oxalate: mp 136−138 °C. Anal. [$C_{25}H_{27}NO_2$·$(COOH)_2$ 1.8H_2O] C, H, N.

Synthesis of *cis*-(3*S*-6*S*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(1*H*-indol-5-ylmethyl)amine ((−)-9b). Compound **8a** (0.05 g, 0.19 mmol) was reacted with indole-5-carboxaldehyde (0.03 g, 0.19 mmol) in the presence of glacial acetic acid (0.05 mL) in 1,2-dichloroethane (5 mL) for 1 h. $NaCNBH_3$ (0.02 g, 0.37 mmol) in MeOH (1 mL) was added, and the reaction mixture was stirred at room temperature for 4 h (Procedure C) to give (−)**9b**: 0.04 g (60%, [α]$_D$ (−) 70.7, *c*=1, acetone).

^{1}H NMR (300 MHz, $CDCl_3$): 1.28−1.33 (m, 1H), 1.48−1.68 (m, 2H), 1.90−1.98 (m, 2H), 2.69 (bs, 1H), 3.50−3.57 (dd, J = 1.6 Hz, 12.0 Hz, 1H), 3.92−4.14 (m, 5H), 6.48 (s, 1H), 7.08−7.38 (m, 13H), 7.54 (s, 1H), 8.34 (bs, 1H).

The free base was converted into oxalate. mp 201−205 °C. Anal. [$C_{27}H_{28}N_2O$ $(COOH)_2$ 0.7H_2O] C, H, N.

Synthesis of *cis*-(3*R*-6*R*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(1*H*-indol-5-ylmethyl)amine ((+)-9b). Compound **8b** (0.02 g, 0.07 mmol) was reacted with indole-5-carboxaldehyde (0.01 g, 0.07 mmol) in the presence of glacial acetic acid (0.05 mL) in 1,2-dichloroethane (5 mL) for 1 h. $NaCNBH_3$ (0.01 g, 0.14 mmol) in MeOH (1 mL) was added, and the reaction mixture was stirred at room temperature for 4 h (Procedure C) to give (+)**-9b**: 0.01 g (37%, [α]$_D$ (+) 72.0, *c*=1, acetone).

^{1}H NMR (300 MHz, $CDCl_3$): 1.28−1.33 (m, 1H), 1.48−1.68 (m, 2H), 1.90−1.98 (m, 2H), 2.69 (bs, 1H), 3.51−3.57 (dd, J = 2.0 Hz, 12.0 Hz, 1H), 3.94−4.16 (m, 5H), 6.50 (s, 1H), 7.12−7.38 (m, 13H), 7.55 (s, 1H), 8.18 (bs, 1H).

The free base was converted into oxalate. mp 206−211 °C. Anal. [$C_{27}H_{28}N_2O$ $(COOH)_2$ 0.5H_2O] C, H, N.

Synthesis of *cis*-(3*S*,6*S*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(4-nitrobenzyl)amine ((−)-9c). Compound **8a** (53.0 mg, 0.198 mmol) was reacted with 4-nitrobenzaldehyde (30.5 mg, 0.202 mmol) in the presence of glacial acetic acid (15 μL) in 1,2-dichloroethane (2 mL) for 1 h. $NaCNBH_3$ (20.5 mg, 0.31 mmol) in MeOH (0.5 mL) was added, and the reaction mixture was stirred at room temperature for 4 h (Procedure C) to give (−)**-9c**: 68.3 mg (86%, [α]$_D$ (−) 57.7, *c*=1.01, acetone).

^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (bd, 1H), 1.45−1.57 (m, 1H), 1.66 (tt, J = 13.6, 4.0 Hz, 1H), 1.80 (bs, 1H), 1.88−1.95 (m, 1H),

2.60 (s, 1H), 3.57 (dd, J = 11.6 Hz, 1.6 Hz, 1H), 3.80−4.10 (m, 5H), 7.14−7.36 (m, 10H), 7.49 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H).

The free base was converted into the oxalate salt: mp 218−220 °C. Anal. [$C_{25}H_{26}N_2O_3$ $(COOH)_2$] C, H, N.

Synthesis of *cis*-(3*R*,6*R*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(4-nitrobenzyl)amine ((+)-9c). Compound **8b** (77.8 mg, 0.275 mmol) was reacted with 4-nitrobenzaldehyde (42 mg, 0.28 mmol) in the presence of glacial acetic acid (20 μL) in 1,2-dichloroethane (2 mL) for 1 h. $NaCNBH_3$ (25 mg, 0.38 mmol) in MeOH (0.5 mL) was added, and the reaction mixture was stirred at room temperature for 4 h (Procedure C) to give (+)-**9c**: 90.3 mg (82%, $[\alpha]_D$ (+) 56.2, c=1.015, acetone).

The free base was converted into oxalate: mp 215−218 °C. Anal. [$C_{25}H_{26}N_2O_3$ $(COOH)_2$] C, H, N.

^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (bd, 1H), 1.45−1.57 (m, 1H), 1.66 (tt, J = 13.6, 4.0 Hz, 1H), 1.80 (bs, 1H), 1.88−1.95 (m, 1H), 2.60 (s, 1H), 3.57 (dd, J = 11.6 Hz, 1.6 Hz, 1H), 3.80−4.10 (m, 5H), 7.14−7.36 (m, 10H), 7.49 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H).

Procedure H. Synthesis of *cis*-(3*S*-6*S*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(4-aminobenzyl)amine ((−)-9d). A mixture of (−)-**9c** (0.10 g, 0.25 mmol) and $SnCl_2$ $2H_2O$ (0.22 g, 1.00 mmol) in EtOH/EtOAc (20 mL, 7:3) was heated to reflux for 1.5 h. After the removal of the solvent, the residue was diluted with 10% $NaHCO_3$ and EtOAc and stirred vigorously for 30 min. After filtration, the organic phase was separated, and the aqueous phase was extracted with EtOAc (20 mL ×2). The combined organic phase was dried over Na_2SO_4. The removal of the solvent and purification by flash chromatography (EtOAc/MeOH/triethylamine 95:4:1) gave (−)-**9d**: 0.05 g (52%, $[\alpha]_D$ (−) 47.3, c=1, acetone).

^{1}H NMR (300 MHz, $CDCl_3$): 1.22−1.34 (m, 1H), 1.44−1.67 (m, 2H), 1.86−1.96 (m, 2H), 2.16 (d, J = 5.2 Hz, 2H), 2.62 (s, 1H), 3.48−3.56 (dd, J = 11.6 Hz, 1.6 Hz, 1H), 3.58−3.70 (m, 2H), 3.92−4.18 (m, 3H), 6.55−6.65 (m, 2H), 7.05−7.37 (m, 12H).

The free base was converted into oxalate salt: mp 184−186 °C. Anal. [$C_{25}H_{28}N_2O$ $2(COOH)_2$] C, H, N.

Synthesis of *cis*-(3*R*-6*R*)-(6-Benzhydryl-tetrahydropyran-3-yl)-(4-aminobenzyl)amine ((+)-9d). A mixture of (+)-**9c** (0.02 g, 0.05 mmol) and $SnCl_2$ $2H_2O$ (0.04 g, 0.20 mmol) in EtOH/EtOAc (10 mL, 7:3) was heated to reflux for 1.5 h (Procedure H) to give (+)-**9d**: 0.01 g (54%, $[\alpha]_D$ (+) 47.5, c=1, acetone).

^{1}H NMR (300 MHz, $CDCl_3$): 1.22−1.34 (m, 1H), 1.44−1.67 (m, 2H), 1.86−1.96 (m, 2H), 2.17 (d, J = 4.8 Hz, 2H), 2.63 (s, 1H), 3.48−3.56 (dd, J = 12.0 Hz, 2.0 Hz, 1H), 3.59−3.72 (m, 2H), 3.92−4.18 (m, 3H), 6.55−6.68 (m, 2H), 7.06−7.38 (m, 12H).

The free base was converted into oxalate: mp 175−178 °C. Anal. [$C_{25}H_{28}N_2O$ $2(COOH)_2$] C, H, N.

Biology. The affinity of test compounds in binding to rat DAT and in inhibiting monoamine uptake was monitored exactly as previously described.[29] Briefly, rat striatum was used for measuring the binding of [^{3}H]WIN 35,428 by the DAT and the uptake of [^{3}H]-DA by the DAT. Rat cerebral cortex was used for assessing the uptake of [^{3}H]serotonin by the SERT and the uptake of [^{3}H]NE by the NET. Nonspecific binding at the DAT was defined with 100 mM cocaine; nonspecific uptake at the DAT, SERT, and NET with 100 mM cocaine, 10 mM citalopram, and 10 mM desipramine, respectively. The test compounds were dissolved in dimethyl sulfoxide (DMSO), diluted out in 10% (v/v) DMSO, and added to the assays resulting in a final DMSO concentration of 0.5%, which by itself did not interfere with the assays. At lease five triplicate concentrations of each test compound were studied, spaced evenly around the IC50 value. The latter was estimated by nonlinear computer curve-fitting procedures and converted to K_i with the Cheng-Prusoff equation as described previously.[29]

Single-Crystal X-ray Diffraction Analysis of 2. $C_{26}H_{32}BrNO_4$, FW = 502.44, monoclinic space group $P21$, a = 10.964(4) Å, b = 7.327(3) Å, c = 15.442(6) Å, and β = 106.72(1)°; V = 1188.1(7) Å^3; Z = 2; density (calcd) = 1.404 Mg/m^3; λ (MoKα) = 0.71073 Å; μ = 1.762 mm^{-1}; F(000)) 524; T = 294°K. A clear colorless 0.34 × 0.28 × 0.12 mm^3 crystal was used for data collection with a Bruker SMART 1000 CCD detector on a four-circle goniometer using SMART (1a). Lattice parameters were determined using SAINT(2b) from 5058 reflections within 1.38 < 2θ < 27.10. Data were collected to 2θ = 27.10°. A set of 9111 reflections was collected using a combination of ϕ and 2θ/ω scans. There were 5058 unique reflections. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL (3a) and refined with the aid of the SHELX system of programs. The full-matrix least-squares refinement on F2 used four restraints and varied 297 parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms on carbon atoms were included using a riding model (coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96−0.93 Å, H angles idealized, Uiso-(H) were set to 1.2 to 1.5 Ueq(C)). Final residuals were R1 = 0.0460 for the 3978 observed data with $Fo > 4\sigma(Fo)$ and 0.0663 for all data. Final difference Fourier excursions were 0.533 and −0.322 eÅ^{-3}. The absolute configuration was determined using anomalous diffraction (absolute structure parameter = 0.078(10)). The asymmetric unit contains one molecule of the title compound, plus a bromine counterion and one water molecule. Tables of coordinates, bond distances and bond angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge, CB2, and 1EW, England.

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Supporting Information Available: Crystal structure, additional ^{1}H NMR, elemental analysis, and molecular modeling data. This material is available free of charge via the Internet at http://pubs.acs.org.

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