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Design, synthesis, and preliminary SAR study of 3- and 6-side-chain-extended tetrahydro-pyran analogues of *cis*- and *trans*-(6-benzhydryl-tetrahydropyran-3-yl)-benzylamine

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Abstract—In our effort to further understand interaction of novel pyran derivatives with monoamine transporters, we have designed, synthesized, and biologically characterized side-chain-extended derivatives of our earlier developed *cis*- and *trans*-(6-benzhydryl-tetrahydro-pyran-3-yl)-benzylamine derivatives. Both 3- and 6-position extensions were explored. 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. Compounds were also tested for their binding affinity at the DAT by their ability to inhibit binding of [^{3}H]WIN 35, 428. The results indicated that extension at the 3-position resulted in loss of activity compared to the original compound **I**. On the other hand, extension at the 6-position resulted in improvement of activity in the compound ***cis*-12** by 2-fold over the parent compound **I** indicating favorable interaction. In addition, two glycoside derivatives were designed, synthesized, and biologically characterized. The glycosidic *trans*-isomer **24** exhibited highest potency for the NET in the current series of compounds.
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1. Introduction

Monoamine transporters play vital roles in maintaining and terminating the action of biogenic amines including dopamine (DA), serotonin (5-HT), and norepinephrine (NE) in the synapse and are known as DAT, SERT, and NET, respectively.[1] Among these three transporters, it is widely believed that DAT mediates cocaine's reinforcing and addictive properties.[2–8] However, this does not rule out the involvement of non-dopaminergic systems in cocaine reinforcing effect. For example, the serotonergic system has been shown to modulate some of cocaine's effects.[9,10] Enormous efforts have been devoted toward developing selective DAT inhibitors as potential therapeutic agents to treat cocaine addiction. To date, several structurally diverse compounds have been synthesized and they can be classified in the following categories: tropine, benztropin, GBR 12909, methylphenidate, mazindol, and phencyclidine analogues (Fig. 1).[11–13] Recently, several review papers have been published summarizing most of this work.[12–14]

During the past 10 years, we have been focusing on developing selective DAT blocker based on piperidine derivatives,[15–21] and recently, we have embarked on the development of novel 3,6-disubstituted- and asymmetric (2,4,5)-trisubstituted-tetrahydro-pyran derivatives targeting monoamine transporter systems.[22–24] Results of our work from these two series of tetrahydro-pyran derivatives indicated that disubstituted and trisubstituted tetrahydro-pyran derivatives exhibited somewhat different activity profiles at the three monoamine transporters. In general, (−)-enantiomers of (2,4,5)-trisubstituted tetrahydro-pyran derivatives, such as compound (−)-**III**, turned out to be potent and selective at either NET or SERT or both,[24] while 3,6-disubstituted tetrahydro-pyran derivatives, such as compound **I**, exhibited potency and selectivity at either DAT or NET (Fig. 2).[22,23] On the other hand, we have observed that the requirement of *cis*-configuration between the benzhydryl substituent and the exocyclic N-substituent and their similar relative positions on the tetrahydro-pyran ring was maintained in these two different templates albeit **III** contained one additional hydroxyl substituent.

Keywords: Dopamine transporter; Serotonin transporter; Norepinephrine transporter; Cocaine.
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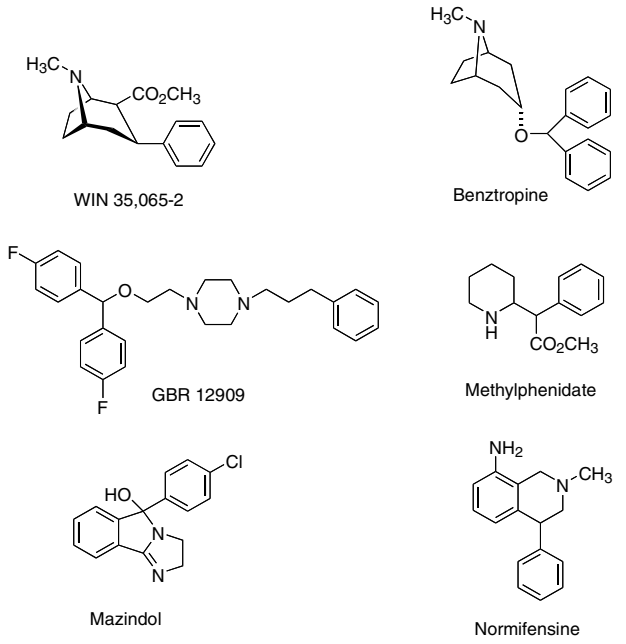


Figure 1. Different structures of DAT inhibitors.

However, series **III** molecules exhibited different activity profiles indicating the presence of an additional hydroxy substituent significantly altered interactions with the binding domains. This further has indicated that an optimal distance between aromatic rings in the benzhydryl moiety and the exocyclic N-atom is an important structural determinant for their affinities at monoamine transporters. Subtle change in this distance might lead to further optimization of binding and pharmacological properties. In our current study with disubstituted pyran derivatives, we wanted to explore the effects of change in distance between the exocyclic N-atom and the two aromatic rings in the benzhydryl moiety on their activities for monoamine transporter systems. The rationale behind our design is described below.

(a) Compounds **4** and **12** have been designed by extension of either the 3- or 6-position and compound **12** has been designed both in the *cis*- and *trans*-configurations, respectively (Fig. 3). Results from biological characterization of these derivatives will aid us to understand the importance of the distance between the exocyclic N-atom and the aromatic ring in the benzhydryl moiety in binding interaction. In addition, by designing ***cis***- and ***trans*-12**, we can further confirm whether the *cis*-stereochemistry is still required in these extended analogues for interaction with monoamine transporters.

(b) In our next design, we replaced the oxygen atom in the 6-position side chain in **12** by a bioisosteric more basic nitrogen atom as shown in compounds **17** and **18** (Fig. 3). The rationale behind this design was same as we described in our previous report.[22] The N- and O-atoms have different atom size, basicity, and hydrogen bonding capability. Therefore, this exchange might lead to new binding and pharmacological results due to different physicochemical and pharmacodynamic properties.

(c) Finally, we have designed two glycoside derivatives ***cis*-24** and ***trans*-24** (Fig. 4). The rationale behind this design was that diphenylmethoxy substitution will be in an α-position which corresponds to an axial position in a chair tetrahydro-pyran conformation in these two sugar-type molecules, and the results from these two compounds will help us to understand the importance of the relative positions of the diphenylmethoxy moiety and the exocyclic N-atom on the tetrahydro-pyran backbone. Furthermore, such sugar-type compounds were never explored for CNS activity including DAT blockade, and it would be interesting to examine binding affinities of these glycoside derivatives for monoamine transporter systems. This information will also shed more light on possible interaction mechanisms of this novel tetrahydro-pyran template.

2. Preliminary molecular modeling study of designed compounds

In order to demonstrate the different separation of distances between the exocyclic N-atom and the aromatic rings in benzhydryl moiety in our newly designed molecules, we have carried out a preliminary molecular modeling study using compounds **I**, **4**, and ***cis*-12**. The lowest energy conformations for these three compounds were established using the same procedure as we described in our earlier publication.[21,23] Briefly, compounds were minimized first with the SYBYL molecular modeling program (version 6.9, 2002, Tripos Associates, Inc., St. Louis, MO). Minimized molecules obtained from this operation were next subjected to a grid search protocol to search for the lowest energy conformer. Grid search operation was carried out with the change of torsional angle from 0° to 360° with an increment of 10°. The distances between the exocyclic N-atom and the two aromatic rings in benzhydryl moiety in each molecule were measured, and the results are shown in Figure 5.

3. Chemistry

The synthesis of final compound **4** with extended side chain at the 3-position is shown in Scheme 1. Briefly,

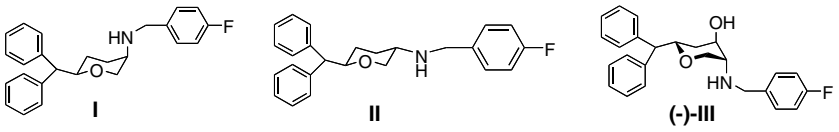


Figure 2. Di- and tri-substituted tetrahydro-pyran compounds.

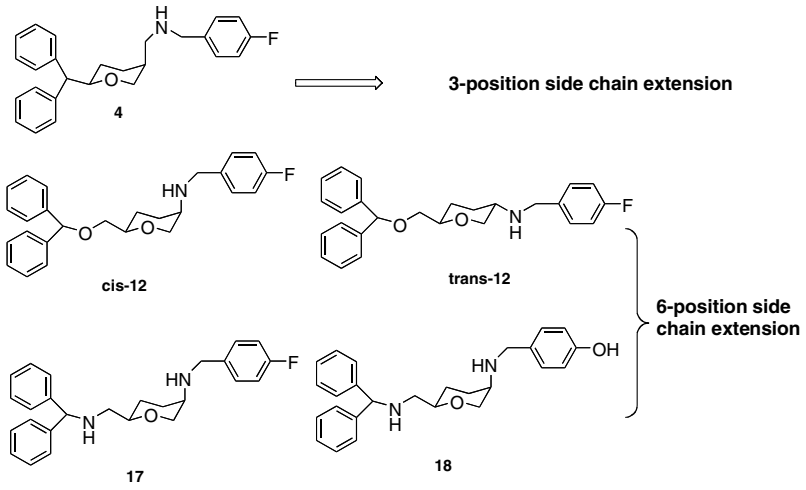


Figure 3. The design of side-chain-extended tetrahydro-pyran compounds at either 3- or 6-position.

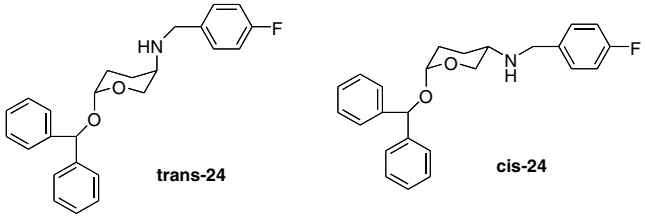


Figure 4. The design of glycoside-type derivatives.

starting intermediate alcohol *trans*-6-benzhydryl-tetrahydro-pyran-3-ol **1** which was synthesized by us earlier,[22,23] was converted into *cis*-6-benzhydryl-tetrahydro-pyran-3-carbonitrile **2** by two-step reactions. Thus, mesylation with methanesulfonyl chloride in dichloromethane produced methanesulfonic acid 6-benzhydryl-tetrahydro-pyran-3-ol ester which on S_N2 substitution reaction with NaCN in dimethylformamide (DMF) at 100 °C yielded **2**. Raney-Ni catalyzed reduction gave amine precursor *cis*-(6-benzhydryl-tetrahydro-pyran-3-yl)-methylamine **3** which on reductive amination with 4-fluorobenzaldehyde, as we described in our earlier publication,[19] gave the final product (6-benzhydryl-tetrahydro-pyran-3-ylmethyl)-(4-fluorobenzyl)-amine **4**.

Scheme 2 describes the synthesis of ***trans*-12** and ***cis*-12**. 3,4-Dihydro-2*H*-pyran-2-carbaldehyde **5** was reduced by $NaBH_4$ in ethanol to give alcohol intermediate (3,4-dihydro-2*H*-pyran-2-yl)-methanol **6** in 85% yield.[25] Protection of compound **6** with *tert*-butyl-(3,4-dihydro-2*H*-pyran-2-yl-methoxy)-diphenyl-silane (TBDPS), followed by hydroboration and oxidation, gave the *trans*-product 6-(*tert*-butyl-diphenyl-silanyloxylmethyl)-tetrahydro-pyran-3-ol **8** as a major product.[26] Compound **8** was subjected to Swern oxidation to give compound

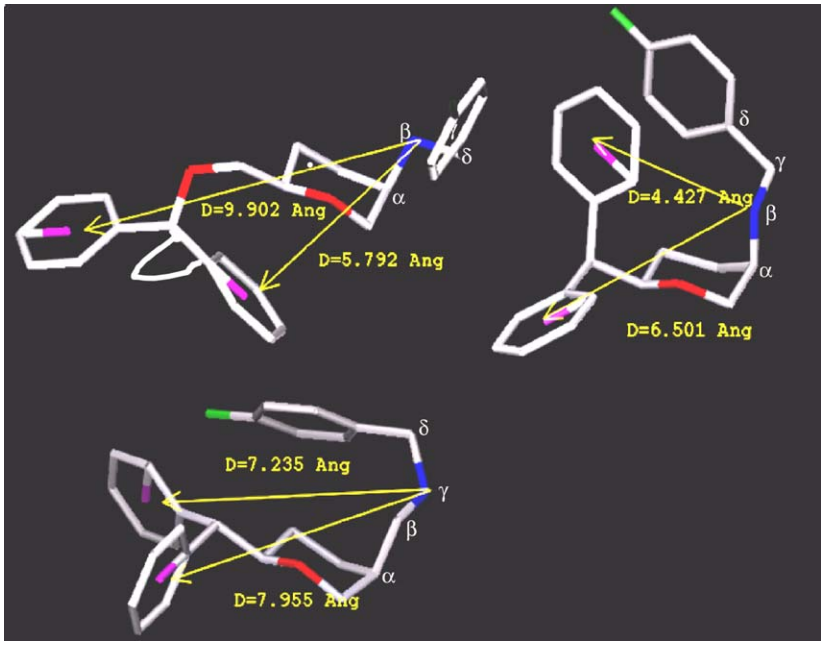
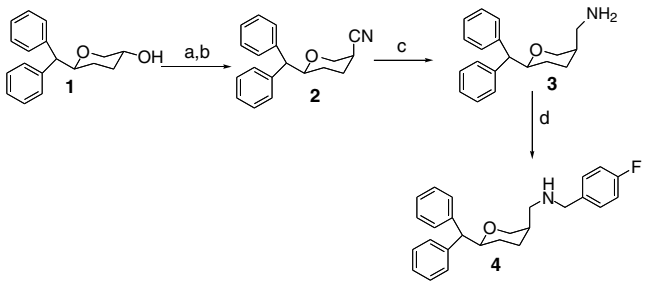


Figure 5. Preliminary modeling study of different substituted tetrahydro-pyran derivatives.

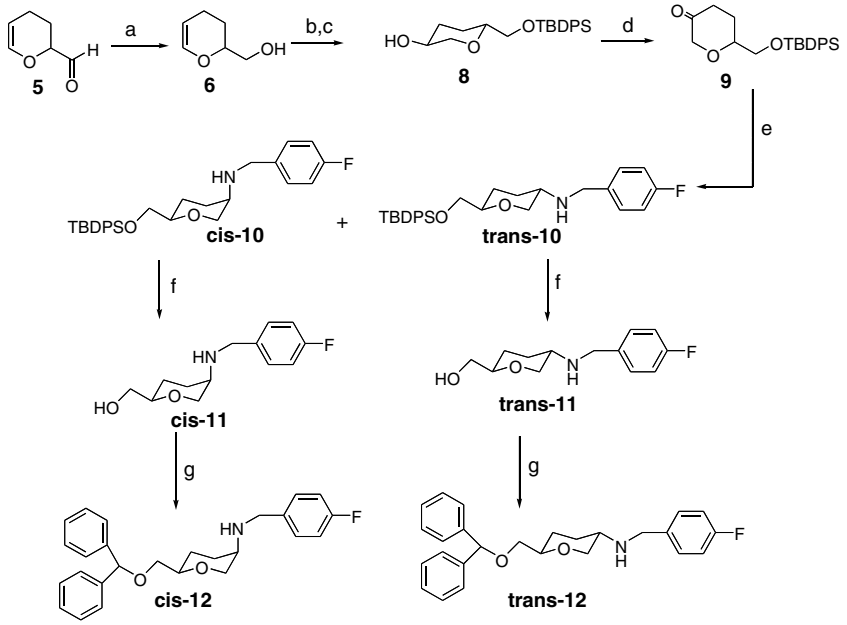


Scheme 1. Reagents and conditions: (a) CH_3SO_2Cl, Et_3N/CH_2Cl_2, room temperature, 4 h, 77.8%; (b) NaCN/DMF, 100 °C, 85%; (c) Raney-Ni; (d) 4-fluorobenzaldehyde, AcOH, $NaCNBH_3$/$ClCH_2CH_2Cl$, room temperature, 65%.

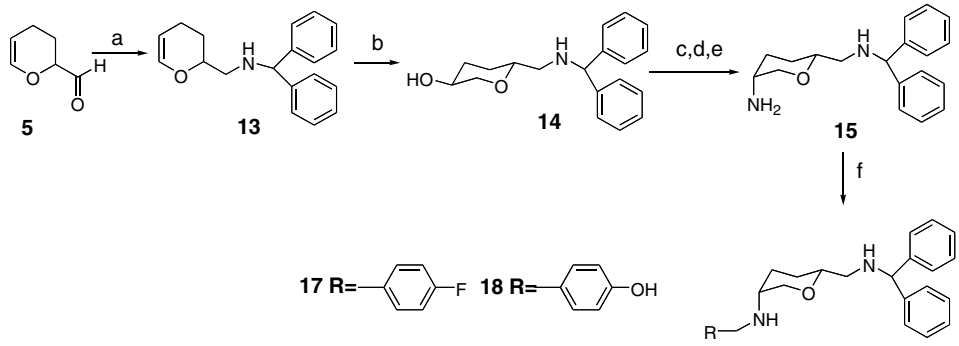
6-(*tert*-butyl-diphenyl-silanyloxylmethyl)-dihydro-pyran-3-one **9**. Reductive amination of compound **9** with 4-fluorobenzylamine gave *trans*-[6-(*tert*-butyl-diphenyl-silanyloxylmethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine and *cis*-[6-(*tert*-butyl-diphenyl-silanyloxylmethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine **10**, respectively, which were carefully separated by chromatography in 55% and 40% yield, respectively. Deprotection of ***trans*-10** with tetra-*n*-butylammonium fluoride (TBAF) in THF gave *trans*-[5-(4-fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol **11** in 70% yield, and the same procedure starting from ***cis*-10** afforded *cis*-[5-(4-fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol ***cis*-11** in 75% yield. Williamson condensation with benzhydrol starting from ***trans*-11** and ***cis*-11**, respectively, gave the final products *trans*-(6-benzhydryloxymethyl-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine, ***trans*-12**, and *cis*-(6-benzhydryloxymethyl-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)- amine, ***cis*-12**, in 70% and 65% yield, respectively.

The synthesis of the final products **17** and **18** is shown in Scheme 3. Starting with the same reagent 3,4-dihydro-2*H*-pyran-2-carbaldehyde **5**, as we used in Scheme 2, reductive amination with amino-diphenylmethane gave intermediate benzhydryl-(3,4-dihydro-2*H*-pyran-2-ylmethyl)-amine **13** in 85% yield.[19] Hydroboration with BH_3 in THF followed by oxidation with NaOH and H_2O_2 produced *trans*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-ol **14** as the major product in 55% yield.[26] This *trans*-alcohol intermediate **14** was converted into *cis*-amine precursor 6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-ylamine **15** through three reactions which involved first mesylation with methanesulfonyl chloride in dichloromethane followed by S_N2 substitution with NaN_3 in DMF, and finally reduction by lithium aluminum hydride (LAH) in tetrahydrofuran (THF). Reductive amination with 4-fluorobenzaldehyde and 4-hydroxy-benzaldehyde gave the final products *cis*-6-[(benzhydryl-amino)-methyl-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine **17** and *cis*-6-[(benzhydryl-amino)-methyl-tetrahydro-pyran-3-yl]-(4-hydroxy-benzyl)-amine **18**, both in 85% yield, respectively.

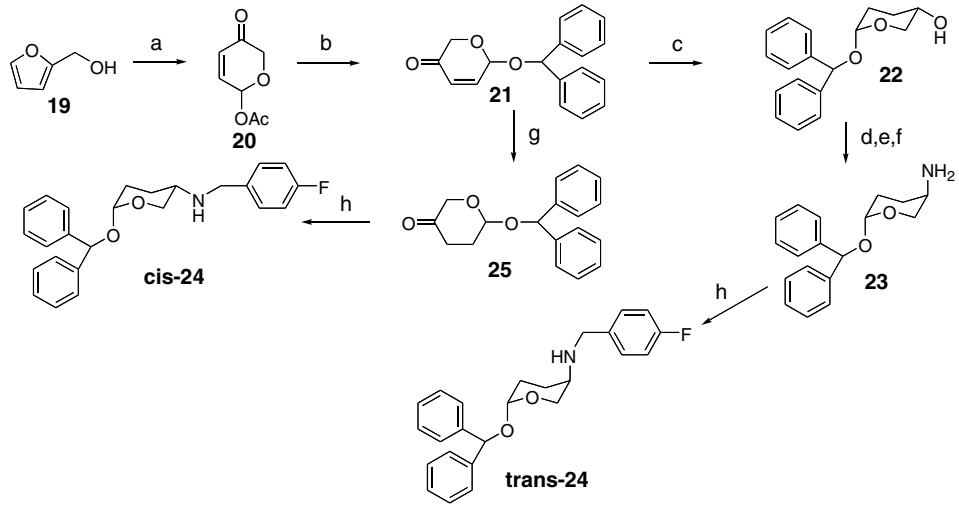
Lastly, the synthesis of sugar-type derivatives *cis*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **24** and *trans*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **24** is shown in Scheme 4. Starting from commercially available furfuryl alcohol **19**, reaction in the presence of *N*-bromosuccinimide (NBS), $NaHCO_3$, and NaOAc followed by the addition of acetic anhydride gave acetic acid 5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester **20** in 64% yield. This ester **20** was reacted with benzhydrol in the presence of $SnCl_4$ to produce 6-benzhydryloxy-6*H*-pyran-3-one **21** in 90%



Scheme 2. Reagents and conditions: (a) $NaBH_4$/EtOH, −78 °C to room temperature, 4 h, 85%; (b) TBDPSCI, imidazole/DMF, room temperature, quantitative yield; (c) i—BH_3/THF; ii—NaOH, H_2O_2, 92.4%; (d) oxalyl chloride, DMSO, Et_3N/CH_2Cl_2, −78 °C to room temperature, 30 min, 81%; (e) 4-fluorobenzylamine, AcOH, $NaCNBH_3/ClCH_2CH_2Cl$, room temperature, 55% and 40%; (f) TBAF/THF, 0 °C to room temperature, 70–75%; (g) benzhydrol, TsOH/benzene, azotropic distillation, 65–70%.



Scheme 3. Reagents and condition: (a) benzhydrylamine, AcOH, $NaCNBH_3/ClCH_2CH_2Cl$; (b) i—BH_3/THF; ii—NaOH, H_2O_2; (c) CH_3SO_2Cl, Et_3N/CH_2Cl_2; (d) NaN_3/DMF; (e) LAH/THF; (f) aldehyde, AcOH, $NaCNBH_3/ClCH_2CH_2Cl$.



Scheme 4. Reagents and conditions: (a) i—NBS, $NaHCO_3$, NaOAc/MeOH/H_2O; ii—AC_2O; (b) $SnCl_4$, benzhydrol/CH_2Cl_2; (c) BF_3/Et_2O, $NaCNBH_3$/THF; (d) CH_3SO_2Cl, Et_3N/CH_2Cl_2; (e) NaN_3/DMF; (f) LAH/THF; (g) L-selectride/THF; (h) aldehyde or amine, AcOH, $NaCNBH_3/ClCH_2CH_2Cl$.

yield.[27] Starting from this enone intermediate **21**, two different methods have been employed to synthesize ***cis*-24** and ***trans*-24**. Reduction of this enone **21** under the same condition as we used in our previous reported method, gave predominantly *cis*-6-benzhydryloxy-tetrahydro-pyran-3-ol **22** in 70% yield.[22] The conversion of ***cis*-22** into *trans*-6-benzhydryloxy-tetrahydro-pyran-3-yl-amine **23** was achieved under the same set of reaction conditions as we employed for the conversion of ***trans*-14** into ***cis*-15** shown in Scheme 3. Thus, mesylation with methanesulfonyl chloride in dichloromethane followed by S_N2 substitution with NaN_3 in DMF and reduction with LAH in THF yielded **23**. Reductive amination of ***trans*-23** with 4-fluorobenzaldehyde produced the final compound *trans*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **24** in 81% yield. For the synthesis of ***cis*-24**, 6-benzhydryloxy-6*H*-pyran-3-one **21** was reduced to 6-benzhydryloxy-dihydro-pyran-3-one **25** with L-selectride in THF in 80% yield. Reductive amination of this keto compound **25** with 4-fluorobenzylamine gave only the final product *cis*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **24** in 80% yield.

All the synthesized compounds were characterized by ^1H NMR and ^{13}C NMR, and their elemental analysis results are shown in Table 4 of the supplemental section.

3.1. In vitro characterization

All the synthesized molecules were tested for their in vitro binding affinity at rat DAT by measuring their ability to compete for the high-affinity binding of the radioligand [^{3}H]WIN35,428 and the uptake of dopamine, serotonin, and norepinephrine as we described in our earlier report. The results are shown in Table 1.

4. Discussion

In our earlier reports, we have established two different types of substituted tetrahydro-pyran pharmacophoric structures with different potency and selectivity at monoamine transporter systems.[22–24] Even though the 3,6-disubstituted tetrahydro-pyran derivatives exhibited preferential potency and selectivity at DAT or NET, while the (2,4,5)-trisubstituted tetrahydro-pyran deriva-

Table 1. Affinity of drugs at dopamine, serotonin, and norepinephrine transporters in rat striatum

Compound	DAT binding, IC_{50}, nM, [^{3}H]WIN 35, 428[a]	DAT uptake, IC_{50}, nM, [^{3}H]DA[a]	SERT uptake, IC_{50}, nM, [^{3}H]5-HT[a]	NET uptake, IC_{50}, nM [^{3}H]NE[a]
Cocaine	266 ± 37		737 ± 160[a]	3130 ± 550[b]
GBR 12909	10.6 ± 1.9	14.2 ± 2.9	101.4 ± 14.2	114 ± 36
II	313 ± 71[b]			
I	163 ± 29[b]	156 ± 36		
III	308 ± 25[c]	169 ± 20	676 ± 33	13.3 ± 1.0
4	398 ± 33	215 ± 14	4400	3432 ± 1752
***cis*-12**	80.4 ± 17.4	104 ± 49	>10,000	1328 ± 592
***trans*-12**	162 ± 19	165 ± 17	>10,000	1435
17	110 ± 6	168 ± 9	3570 ± 664	1489 ± 133
18	247 ± 23	239 ± 9	1477 ± 224	536 ± 45
***cis*-24**	520 ± 47	213 ± 38	1660 ± 150	1689 ± 503
***trans*-24**	366 ± 52	309 ± 16	2977 ± 229	290 ± 59

[a] For binding, the DAT was labeled with [^{3}H]WIN 35, 428. For uptake by DAT, SERT and NET, [^{3}H]DA, [^{3}H]5-HT and [^{3}H]NE accumulation were measured. Results are averages ± SEM of three to eight independent experiments assayed in triplicate.
[b] Results are from Ref. 23.
[c] Results are from Ref. 24.

tives exhibited potency and selectivity at either NET or SERT, still an overall *cis*-stereochemistry between the benzhydryl substituent and the exocyclic N-substituent in tetrahydro-pyran ring was maintained in these two series of derivatives.[24] These results indicated that the distance between these two groups and their orientation which is controlled by their positions in tetrahydro-pyran ring are important structural determinants required for their affinities at monoamine transporter systems. To further explore the effects of the change in distance between these two groups on their potency and selectivity for monoamine transporter systems, we have designed and biologically characterized various side-chain-extended analogues at either 3- or 6-positions on the tetrahydro-pyran ring (Table 1).

Compound **4** exhibited decreased activities compared to its parent compound **I** at all three transporters including DAT (Table 1, DAT; IC_{50}, 215 vs 156 nM). Results from compound **4** indicated that side-chain extension at the 3-position of tetrahydro-pyran ring adversely affected the binding activity of this molecule and that the direct linkage between the exocyclic N-substituent and the tetrahydro-pyran ring is important for interaction with monoamine transporters. On the other hand, compounds ***trans*-12** and ***cis*-12** both exhibited increased activity at DAT compared to their parent compounds **II** and **I**, respectively, and the increase in DAT binding activity was 2-fold for both the compounds (162 and 80.4 vs 313 and 163 nM). It is also interesting to note that the *cis*-stereochemical preference for DAT activity was still maintained in these side-chain-extended derivatives as *cis*-isomer of **12** was two times more active at the DAT compared to its *trans*-version. The increase in DAT activity in this 6-position side-chain-extended template might be caused by conformational changes due to the introduction of more flexible side chain, or additional hydrogen bonding interaction with the newly incorporated side-chain oxygen-atom. These results also indicated that side-chain modification at the 6-position on this new *cis*-tetrahydro-pyran template might lead to development of more potent and selective molecules at the DAT.

Following the above results, compounds **17** and **18** were designed to investigate whether the replacement of the O-atom by a bioisosteric NH will alter interaction with monoamine transporters especially with DAT. In these N-version analogues, we also wanted to examine introduction of *p*-hydroxy-benzyl substitution as shown in compound **18**. In this regard, in our previous study, we found that introduction of a hydroxyl substitution in the *para*-position of the *N*-benzyl moiety in *cis*-3,6-disubstituted pyran derivatives could shift potency selectivity in favor of NET.[23] Results from compound **17** indicated that replacement of the oxygen-atom by a more basic NH moiety in 6-position side chain marginally decreased its activity at the DAT, and this compound exhibited little or no activity at SERT and NET. This slight loss in DAT activity compared to compound ***cis*-12** might be caused by the subtle change in interactions caused by replacement of the O-atom by a more basic N-atom. However, the binding activity of this compound is still greater than its parent compound **I** which further indicated that 6-position-side-chain modification might lead to more potent and selective molecules at DAT. Interestingly, compound **18** exhibited 3-fold decrease in DAT binding activity when compared with compound ***cis*-12** while its NET activity was increased by 2.5 times as found in our earlier work.[23] However, the selectivity of compound **18** was exhibited still in favor of DAT in spite of its increase in NET activity. These results indicated that even though hydroxyl substitution in the *para*-position of benzyl phenyl ring could decrease DAT activity and increase NET activity, it could not reverse the selectivity as shown in our previous 3,6-disubstituted compound. This further indicated the existence of different interaction modes between these side-chain derivatives and our first-generation *cis*-3,6-disubstituted tetrahydro-pyran derivatives. More work will be needed to map out the molecular determinant requirements in this new side-chain-extended tetrahydro-pyran template.

Glycoside derivatives ***cis*-24** and ***trans*-24** exhibited interesting results. ***cis*-24** exhibited weak activity at DAT and no activity at SERT and NET; however, a separation in DAT binding and dopamine uptake activity in this compound was noticed, and the selectivity was reversed in favor of uptake inhibition. On the other hand, ***trans*-24** exhibited relatively higher activity at both DAT and NET. The activity for NET in ***trans*-24** was substantially higher compared to that in ***cis*-24** (290 vs 1689 nM). It is interesting to note that even though the activity of these two compounds was low, stereochemical preference for the overall monoamine transporter activity was found in the *trans*-version.

5. Conclusion

In our current study, the effects of the change in distance between the exocyclic N-atom and the benzhydryl moiety on activity at monoamine transporters were explored, and results from this study indicated that side-chain extension at 6-position of tetrahydro-pyran ring could lead to increase in DAT activity as shown in compound ***cis*-12**, while 3-position extension adversely affected activity at all three transporters. In two glycoside derivatives, ***cis*-24** exhibited weak activity at DAT, while ***trans*-24** exhibited dual weak activity at both DAT and NET. In general, *cis*-stereochemistry between two substituents on the tetrahydro-pyran ring is a preferential pharmacophoric requirement for interacting with DAT.

6. Experimental details

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Dry solvent was obtained according to the standard procedure as in Vogel's. All reactions were performed under inert atmosphere (N_2) unless otherwise noted. Analytical silica gel-coated TLC plates (Si250F) were purchased from Baker, Inc. and were visualized with UV light or by treatment with phosphomolybdic acid (PMA) and ninhydrin solution. Flash chromatography was carried out on Baker silica gel 40 mm. ^{1}H NMR and ^{13}C NMR spectra were routinely obtained at GE-300 MHz FT NMR, Varian Unity-300/500, and Varian Mercury-400 NMR. The NMR solvents used were $CDCl_3$, CD_3OD, or deuterium-acetone 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 values. Yield is of purified product.

[^{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, USA). (−)-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).

6.1. Synthesis of 6-benzhydryl-tetrahydro-pyran-3-carbonitrile (2)

6.1.1. Procedure A. Synthesis of methanesulfonic acid *trans*-6-benzhydryl-tetra-hydropyran-3-yl ester. Methanesulfonyl chloride (0.62 g, 5.41 mmol) dissolved in dry methylene chloride (10 ml) was added dropwise to a mixture of *trans*-6-benzhydryl-tetrahydro-pyran-3-ol **1** (0.73 g, 2.71 mmol), triethylamine (0.41 g, 4.06 mmol) in methylene chloride (10 ml) and was cooled to 0 °C. After 1 h, the reaction was brought to room temperature over a period of 4 h. Additional methylene chloride (20 ml) was added to the reaction mixture, and the mixture was washed in turn with saturated aqueous sodium bicarbonate, brine, and water, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and purification by flash chromatography gave methanesulfonic acid *trans*-6-benzhydryl-tetrahydro-pyran-3-yl ester (0.94 g, quantitative yield).

^{1}H NMR (300 Hz, $CDCl_3$): 1.50 (m, 1H, H-5), 1.60–1.80 (m, 2H, H-4, H-5), 2.26 (m, 1H, H-4), 2.98 (s, 3H, CH_3SO_2), 3.38 (t, J = 10.50 Hz, 1H, H-2ax), 3.91 (d, J = 9.30 Hz, 1H, Ph_2CH), 4.03 (dt, J = 1.80 Hz, 9.50 Hz, 1H, H-6), 4.15 (m, 1H, H-2eq), 4.63 (m, 1H, H-3), 7.16–7.38 (m, 10H, aromatic-CH).

^{13}C NMR (75 MHz, $CDCl_3$): 29.51, 30.59, 38.69, 57.11, 69.87, 75.25, 79.04, 126.71, 126.95, 128.57, 128.62, 128.66, 128.92, 141.62, 141.77.

6.1.2. Procedure B. Synthesis of 6-benzhydryl-tetrahydro-pyran-3-carbonitrile (2). Into a solution of methanesulfonic acid *trans*-6-benzhydryl-tetrahydropyran-3-yl ester (0.1 g, 0.29 mmol) in dry DMF was added NaCN (0.03 g, 0.58 mmol). The mixture was heated at 100 °C overnight. The mixture was diluted with ethyl ether (50 ml), and was washed in turn with water, saturated $NaHCO_3$, and brine, and then was dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (hexane/ethyl acetate 7:3) gave *cis*-6-benzhydryl-tetrahydropyran-3-carbonitrile **2** (0.07 g, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 1.50 (m, 1H, H-5), 1.62–1.84 (m, 2H, H-4, H-5), 2.08 (m, 1H, H-4), 2.71 (m, 1H, H-3), 3.55 (dd, J = 1.80 Hz, 11.70 Hz, 1H, H-2), 4.00–4.20 (m, 3H, H-2, H-6, Ph_2CH), 7.06–7.40 (m, 10H, aromatic-CH).

6.1.3. Synthesis of *cis*-(6-benzhydryl-tetrahydro-pyran-3-yl)-methylamine (3). *cis*-6-Benzhydryl-tetrahydropyran-3-carbonitrile **2** (0.6 g, 0.22 mmol) dissolved in ethanol was hydrogenated in the presence of Raney-Ni (70 mg, wet weight) overnight (60 psi pressure) to give *cis*-(6-benzhydryl-tetrahydro-pyran-3-yl)-methylamine **3** (0.5 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (m, 1H, H-5), 1.37 (m, 1H, H-5), 1.58–1.76 (m, 3H, H-4, H-3), 2.59 (m, 1H, CH_2NH_2), 2.73 (m, 1H, CH_2NH_2), 3.60 (m, 1H, H-2), 3.80 (d, J = 12.00 Hz, H-2), 3.92 (m, 1H,

Ph_2CH), 4.11 (m, 1H, H-6), 7.00–7.40 (m, 10 H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 25.66, 25.79, 33.56, 47.13, 57.32, 69.38, 79.51, 125.95, 126.26, 127.98, 128.33, 128.42, 128.69, 141.90.

6.1.4. Procedure C. Synthesis of (6-benzhydryl-tetrahydro-pyran-3-ylmethyl)-(4-fluorobenzyl)-amine (4). A solution of *cis*-(6-benzhydryl-tetrahydro-pyran-3-yl)-methylamine **3** (0.04 g, 0.14 mmol), 4-fluorobenzaldehyde (0.02 g, 0.14 mmol), and glacial acetic acid (0.01 g, 0.14 mmol) in dry CH_2Cl_2 (20 ml) was stirred at room temperature for 2 h. $NaCNBH_3$ (0.01 g, 0.21 mmol) in methanol (5 ml) was added into above solution, and the mixture was stirred at room temperature for 4 h. Water was added to quench the reaction and the mixture was stirred for 30 min at 0 °C. Then the mixture was basified with saturated aqueous $NaHCO_3$ and extracted thrice with CH_2Cl_2 (3× 30 ml). The combined organic phase was washed with brine, water and dried over anhydrous Na_2SO_4. Solvent was removed to collect the crude residue. The residue was purified by flash chromatography (hexane/ethyl acetate/triethylamine 3:2:0.2) to give (6-benzhydryl-tetrahydro-pyran-3-ylmethyl)-(4-fluorobenzyl)-amine **4** (0.03 g, 65% yield).

^1H NMR (400 MHz, $CDCl_3$): 1.20–1.46 (m, 2H, H-5), 1.60–1.82 (m, 3H, H-3, H-4), 2.66 (m, 1H, $–CH_2NH–$), 2.81 (m, 1H, $–CH_2NH–$), 3.61 (dd, $J = 2.80$ Hz, 11.60 Hz, 1 H, H-2), 3.73 (m, 2H, (F)$PhCH_2$), 3.92 (m, 2H, Ph_2CH, H-2), 4.03 (dt, $J = 2.00$ Hz, 9.60 Hz, 1H, H-6), 6.80–7.40 (m, 14H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 26.00, 26.08, 34.00, 49.79, 53.59, 57.49, 70.13, 79.57, 115.22, 115.43, 126.43, 126.61, 128.54, 128.71, 129.77, 129.85.

Free base was converted into oxalate in ethanol: mp 136–138 °C. Anal. [$C_{25}H_{27}NO_2 \cdot (COOH)_2 0.4H_2O$] C, H, N.

6.2. Synthesis of 3,4-dihydro-2*H*-pyran-2-yl-methanol (6)

Into a solution of 3,4-dihydro-2*H*-pyran-2-carbaldehyde **5** (1 g, 8.93 mmol) in ethanol (25 ml) at −78 °C was added $NaBH_4$ (1.01 g, 26.8 mmol) in portionwise manner. After 1 h, the mixture was brought to room temperature over a period of 4 h. Saturated $NaHCO_3$ was added and the resulting solution was concentrated under reduced pressure. The aqueous phase was extracted with ethyl acetate (3× 30 ml), and the combined organic phase was dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (hexane/ethyl acetate 7:3) gave pure product 0.87 g (85% yield).

^1H NMR (400 MHz, $CDCl_3$): 1.61 (m, 1H, H-3), 1.72 (m, 1H, H-3), 1.90 (m, 1H, H-4), 2.03 (m, 1H, H-4), 2.95 (s, 1H, OH), 3.59 (m, 2H, CH_2OH), 3.83 (m, 1H, H-2), 4.62 (M, 1H, H-5), 6.30 (d, $J = 5.6$ Hz, 1H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): 19.57, 24.07, 65.37, 75.81, 100.97, 143.48.

6.3. Synthesis of *trans*-6-(*tert*-butyl-diphenyl-silanyl-oxymethyl)-tetrahydro-pyran-3-ol (8)

6.3.1. (a) Synthesis of *tert*-butyl-(3,4-dihydro-2*H*-pyran-2-yl-methoxy)-diphenyl-silane. Into a solution of 3,4-dihydyo-2*H*-pyran-2-yl-methanol **6** (1 g, 8.8 mmol) and imidazole (1.32 g, 19.36 mmol) in dry DMF (50 ml) was added *tert*-butyl-diphenylsilylchloride (2.65 g, 9.6 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and was continued for 2 h. Removal of the solvent and purification by flash chromatography (hexane/ether 20:1) gave pure product *tert*-butyl-(3,4-dihydro-2*H*-pyran-2-yl-methoxy)-diphenyl-silane 3.09 g (quantitative yield).

^1H NMR (400 MHz, $CDCl_3$): 1.47 (s, 9H, $3CH_3$), 1.79 (m, 1H, H-3), 2.00 (m, 2H, H-3, H-4), 2.11 (m, 1H, H-4), 3.76 (m, 1H, CH_2OH), 3.87 (m, 1H, CH_2OH), 4.71 (m, 1H, H-5), 6.44 (d, $J = 5.60$ Hz, 1H, H-6), 7.20–7.80 (m, 10H, aromatic-CH).

6.3.2. (b) Procedure D. Synthesis of *trans*-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-ol (8). Into a solution of *tert*-butyl-(3,4-dihydro-2*H*-pyran-2-yl-methoxy)-diphenyl-silane (0.31 g, 0.88 mmol) in dry THF was added BH_3/THF drop by drop (4.4 ml of 1.0 M BH_3/THF, 4.4 mmol) at 0 °C. After addition, the mixture was brought to room temperature and the reaction was continued at room temperature overnight. The reaction mixture was then oxidized by adding NaOH (1.76 ml of 3 N NaOH, 5.28 mmol) and H_2O_2 (0.24 g, 7.04 mmol), and the reaction was kept at 55 °C for 1 h. K_2CO_3 was added at 0 °C and the mixture was stirred for 30 min. The reaction mixture was extracted with ethyl acetate (3× 30 ml). The combined organic phase was dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (hexane/ethyl acetate 1:1) gave pure *trans*-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-ol **8** (0.3 g, 92.4% yield).

^1H NMR (300 MHz, $CDCl_3$): 1.06 (s, 9H, 3CH3), 1.39 (m, 1H, H-5), 1.83 (m, 2H, H-5, H-4), 2.13 (m, 1H, H-4), 3.10 (t, $J = 10.50$ Hz, 1H, H-2), 3.37 (m, 1H, H-6), 3.54 (m, 1H, $CH_2OTBDPS$), 3.62–3.78 (m, 2H, $CH_2OTBDPS$, H-3), 3.99 (m, 1H, H-2), 7.20–7.80 (m, 10H, aromatic-CH).

^{13}C NMR (75 MHz, $CDCl_3$): 27.10, 27.42, 32.72, 66.63, 66.88, 72.77, 77.71, 127.88, 129.88, 133.81, 133.84, 135.85.

6.4. Synthesis of 6-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-one (9)

Into a solution of dimethylsulfoxide (DMSO) (0.15 g, 1.94 mmol) in dry CH_2Cl_2 (20 ml) at −78 °C was added oxylyl chloride (0.13 g, 0.97 mmol) in dry CH_2Cl_2 in a dropwise manner. *trans*-6-(*tert*-Butyl-diphenyl-silanyl-oxymethyl)-tetrahydro-pyran-3-ol **8** (0.32 g, 0.88 mmol) in dry CH_2Cl_2 (10 ml) was then added via syringe. After 15 min, Et_3N (0.44 g, 4.4 mmol) was added drop by drop. After 5 min at −78 °C, the reaction mixture was

brought to room temperature over a period of 30 min. The mixture was washed in turn with saturated $NaHCO_3$, brine, and water, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by chromatography (hexane/ethyl acetate 7:3) gave pure 6-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-one **9** (0.26 g, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 1.09 (s, 9H, $3CH_3$), 1.96 (m, 1H, H-5), 2.12 (m, 1H, H-5), 2.47 (m, 1H, H-4), 2.62 (m, 1H, H-4), 3.71 (m, 1H, H-6), 3.82 (m, 2H, CH_2OTBDPS), 3.96 (m, 1H, H-2), 4.15 (m, 1H, H-2), 7.20–7.80 (m, 10H, aromatic-CH).

6.5. Synthesis of *trans*-[6-(*tert*-butyl-diphenyl-silanyl-oxymethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine (10) and *cis*-[6-(*tert*-butyl-diphenyl-silanyloxy-methyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine (10)

6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-one **9** (0.26 g, 0.7 mmol) was reacted with 4-fluorobenzylamine (0.09 g, 0.7 mmol) in the presence of glacial acetic acid (0.04 g, 0.7 mmol) in 1,2-dichloroethane (10 ml) and then reduced by $NaCNBH_3$ (0.05 g, 0.84 mmol) in methanol (5 ml) (Procedure B) to give a mixture of *cis*-[6-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine and *trans*-[6-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine.

cis-[6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine was eluted first (0.13 g, 40% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 1.05 (s, 9H, $3CH_3$), 1.27 (m, 1H, H-5), 1.50–1.70 (m, 2H, H-4, H-5), 1.98 (m, 1H, H-4), 2.64 (m, 1H, H-3), 3.40–3.80 (m, 6H, H-2, H-6, CH_2OTBDPS, $PhCH_2$), 3.97 (m, 1H, H-2), 6.90–7.80 (m, 14H, aromatic-CH).

Eluted second was *trans*-[6-(*tert*-butyl-diphenyl-silanyl-oxymethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine (0.19 g, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 1.08 (s, 9H, $3CH_3$), 1.24–1.42 (m, 2H, H-5), 1.81 (m, 1H, H-4), 2.07 (m, 1H, H-4), 2.66 (m, 1H, H-3), 3.06 (t, J = 10.50 Hz, 1H, H-2), 3.39 (m, 1H, H-6), 3.55 (m, 1H, CH_2OTBDPS), 3.70–3.82 (m, 3H, CH_2OTBDPS, $PhCH_2$), 4.06 (M, 1H, H-2), 6.90–7.80 (m, 14H, aromatic-CH).

6.5.1. Procedure E. Synthesis of *trans*-[5-(4-fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol (*trans*-11).

Into a solution of *trans*-[6-(*tert*-butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine **10** (0.09 g, 0.19 mmol) in dry THF (10 ml) was added TBAF (0.1 g, 0.38 mmol) at 0 °C. The reaction mixture was brought to room temperature over a period of 2 h. Removal of the solvent and purification by chromatography (hexane/ethyl acetate/Et_3N 7:3:0.3) gave pure *trans*-[5-(4-fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol **11** (0.03 g, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 1.45 (m, 1H, H-3), 1.56–1.72 (m, 2H, H-3, H-4), 2.08 (m, 1H, H-4), 2.67 (m, 1H, H-5), 3.10 (t, J = 11.00 Hz, 1H, H-6), 3.36 (m, 1H, H-2), 3.49 (m, 1H, CH_2OH), 3.60 (m, 1H, CH_2OH), 3.78 (m, 2H, $PhCH_2$), 4.08 (m, 1H, H-6), 6.90–7.40 (m, 4H, aromatic-CH).

^{13}C NMR (125 MHz, $CDCl_3$): 27.76, 27.79, 49.87, 50.59, 57.57, 70.50, 79.54, 126.56, 126.73, 127.57, 128.59, 128.72, 128.77, 130.11, 130.45, 130.79, 132.54, 141.34, 142.33, 142.59.

6.6. Synthesis of *cis*-[5-(4-fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol (*cis*-11)

cis-[6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-tetrahydro-pyran-3-yl]-(4-fluorobenzyl)-amine (0.09 g, 0.19 mmol) was reacted with TBAF (0.1 g, 0.38 mmol) at 0 °C in dry THF (Procedure E) to give *cis*-[5-(4-fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol **11** (0.03 g, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.16–1.40 (m, 2H, H-3), 1.55 (m, 1H, H-4), 2.02 (m, 1H, H-4), 2.59 (m, 1H, H-5), 3.04 (t, J = 10.40 Hz, 1H, H-6), 3.26-3.54 (m, 3H, H-2, CH_2OH), 3.72 (m, 2H, $PhCH_2$), 4.01 (m, 1H, H-6), 6.90–7.40 (m, 4H, aromatic-CH).

6.6.1. Procedure F. Synthesis of *trans*-(6-benzhydryloxymethyl-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine (*trans*-12).

A mixture of *trans*-[5-(4-fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol **11** (0.16 g, 0.67 mmol), benzhydrol (0.12 g, 0.67 mmol), and *p*-toluenesulfanic acid (0.15 g, 0.8 mmol) in benzene was refluxed under azotropic distillation condition overnight. Removal of solvent and purification by chromatography (hexane/ethyl acetate/Et_3N 7:3:0.3) gave pure *trans*-(6-benzhydryloxymethyl-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **12** (0.19 g, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.32 (m, 1H, H-4), 1.47 (dq, 1H, J = 2.40 Hz and 12.0 Hz, H-5ax), 1.80 (m, 1H, H-5eq), 2.10 (m, 1H, H-4), 2.70 (tt, 1H, J = 4.0 Hz and 10.40 Hz, H-3), 3.12 (t, J = 10.40 Hz, 1H, H-2ax), 3.45 (m, 1H, CH_2OR), 3.52–3.62 (m, 2H, H-6, CH_2OR), 3.80 (m, 2H, $PhCH_2$), 4.13 (m, 1H, H-2eq), 5.44 (s, 1H, Ph_2CH), 6.90–7.42 (m, 14H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 28.12, 31.13, 50.86, 53.46, 72.44, 72.85, 76.97, 84.35, 115.39, 115.61, 127.34, 127.38, 127.72, 128.64, 129.79, 129.87, 142.41.

Free base was converted into oxalate salt from ethanol: mp 207–208 °C. Anal. [$C_{26}H_{28}NFO_2 \cdot (COOH)_2$] C, H, N.

6.7. Synthesis of *cis*-(6-benzhydryloxymethyl-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine (*cis*-12)

cis-[5-(4-Fluorobenzylamino)-tetrahydro-pyran-2-yl]-methanol (0.16 g, 0.67 mmol) was reacted with benzhydrol (0.12 g, 0.67 mmol) in the presence of *p*-toluenesulfonic acid (0.15 g, 0.8 mmol) in benzene (Procedure F) to give pure *cis*-(6-benzhydryloxymethyl-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **12** (0.18 g, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.50–1.62 (m, 2H, H-5), 1.68 (tt, 1H, J = 4.80 Hz and 12.80 Hz, H-4ax), 1.97 (m, 1H, H-4eq), 2.64 (m, 1H, H-3), 3.41 (m, 1H, CH_2OR), 3.50–3.58 (m, 2H, H-2, CH_2OR), 3.63 (m, 1H, H-6), 3.78 (m, 2H, $PhCH_2$), 4.00 (m, 1H, H-2), 5.44 (s, 1H, Ph_2CH), 6.90–7.42 (m, 14H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 23.67, 27.27, 50.31, 50.66, 70.26, 72.42, 84.28, 115.25, 115.46, 127.08, 127.20, 127.29, 127.67, 128.60, 129.76, 129.84, 142.42.

Free base was converted into oxalate salt from ethanol: mp 203–204 °C. Anal. [$C_{26}H_{28}NFO_2 \cdot (COOH)_2 0.7H_2O$] C, H, N.

6.8. Synthesis of benzhydryl-(3,4-dihydro-2*H*-pyran-2-yl-methyl)-amine (13)

3,4-Dihydro-2*H*-pyran-2-carbaldehyde **5** (1.5 g, 13.39 mmol) was reacted with benzhydrylamine (2.45 g, 13.39 mmol) in the presence of glacial acetic acid (0.8 g, 13.39 mmol) in 1,2-dichloroethane (50 ml) and then reduced by $NaCNBH_3$ (1.01 g, 16.1 mmol) in methanol (5 ml) (Procedure B) to give benzhydryl-(3,4-dihydro-2*H*-pyran-2-yl-methyl)-amine **13** (3.17 g, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.64–1.84 (m, 2H, H-3), 1.90–2.16 (m, 2H, H-4), 2.73 (m, 2H, CH_2NHR), 4.01 (m, 1H, H-2), 4.68 (m, 2H, H-5), 4.85 (s, 1H, Ph_2CH), 6.37 (d, J = 4.00 Hz, 1H, H-6), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 19.87, 26.14, 52.58, 67.69, 74.73, 100.84, 127.21, 127.24, 127.53, 127.57, 128.70, 128.73, 143.78, 144.29.

6.9. Synthesis of *trans*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-ol (14)

Benzhydryl-(3,4-dihydro-2*H*-pyran-2-yl-methyl)-amine **13** (0.6 g, 2.25 mmol) in dry THF was reacted with BH_3/THF (11.2 ml 1.0 M BH_3/THF, 11.2 mmol) at 0 °C, then followed by addition of NaOH (3.7 ml of 3 N NaOH, 11.2 mmol) and H_2O_2 (1.27 g, 11.2 mmol) to give pure *trans*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-ol **14** (0.35 g, 55% yield) (Procedure D).

^{1}H NMR (400 MHz, $CDCl_3$): 1.39 (m, 2H, H-5), 1.62 (m, 1H, H-4), 1.92 (br s, 2H, NH, OH), 2.08 (m, 1H, H-4), 2.58 (m, 2H, CH_2NHR), 3.10 (t, J = 10.40 Hz, 1H, H-2), 3.43 (m, 1H, H-6), 3.64 (m, 1H, H-3), 3.96 (m, 1H, H-2), 4.78 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 28.57, 32.89, 53.06, 66.59, 67.86, 72.77, 127.19, 127.24, 127.53, 127.57, 128.68, 128.72, 144.31.

6.10. Synthesis of *cis*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-ylamine (15)

6.10.1. (1) Synthesis of *trans*-methanesulfonic acid 6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-yl ester. *trans*-6-[(Benzhydryl-amino)-methyl]-tetrahydro-pyran-3-ol (0.1 g, 0.35 mmol) was reacted with methanesulfonyl chloride (0.06 g, 0.53 mmol), triethylamine (0.04 g, 0.35 mmol) (Procedure A) to give methanesulfonic acid *trans*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-yl ester (0.11 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): 1.53 (m, 1H, H-5), 1.72 (m, 2H, H-4, H-5), 1.93 (br s, 1H, NH), 2.28 (m, 1H, H-4), 2.60 (m, 2H, CH_2NHR), 2.99 (s, 3H, CH_3SO_2), 3.33 (t, J = 10.40 Hz, 1H, H-2), 3.48 (m, 1H, H-6), 4.12 (m, 1H, H-2), 4.61 (m, 1H, H-3), 4.79 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 28.43, 30.31, 38.74, 52.60, 67.77, 69.55, 75.20, 127.26, 127.29, 127.48, 127.52, 128.72, 128.76, 144.04, 144.23.

6.10.2. (2) Synthesis of *cis*-(5-azido-tetrahydro-pyran-2-yl-methyl)-benzhydryl-amine. Methanesulfonic acid *trans*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-yl ester (0.25 g, 0.68 mmol) was reacted with sodium azide (0.13 g, 2.03 mmol) (Procedure B) to give *cis*-(5-azido-tetrahydro-pyran-2-yl-methyl)-benzhydryl-amine (0.19 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (m, 1H, H-3), 1.60–1.84 (m, 2H, H-3, H-4), 2.00 (m, 1H, H-4), 2.13 (br s, 1H, NH), 2.57–2.74 (m, 2H, CH_2NHR), 3.52–3.64 (m, 3H, H-2, H-5, H-6), 3.98 (m, 1H, H-6), 4.81 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 24.65, 27.29, 53.42, 55.83, 67.88, 69.48, 77.29, 127.20, 127.25, 127.54, 127.59, 128.70, 128.73, 144.08, 144.48.

6.10.3. (3) Procedure G. Synthesis of *cis*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-ylamine (15). Into a suspension of $LiAlH_4$ (0.06 g, 1.49 mmol) in dry ethyl ether (20 ml) was added a solution of *cis*-(5-azido-tetrahydro-pyran-2-yl-methyl)-benzhydryl-amine (0.12 g, 0.37 mmol) in dry ethyl ether (25 ml) at 0 °C under N_2. The reaction mixture was brought to room temperature over a period of 5 h. The reaction was quenched by the addition of 10% NaOH drop by drop. The mixture was dried over anhydrous Na_2SO_4. Removal of the solvent and purification by chromatography (ethyl acetate/methanol/triethylamine 8.8:1:0.2) gave *cis*-6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-yl-amine **15** (0.09 g, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (m, 1H, H-5), 1.56 (m, 1H, H-5), 1.66–1.84 (m, 2H, H-4), 2.48–2.66 (m, 2H, CH_2NHR), 2.82 (m, 1H, H-3), 3.51 (m, 1H, H-6), 3.60 (m, 1H, H-2), 3.73 (m, 1H, H-2), 4.81 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 23.85, 29.00, 45.38, 52.78, 67.88, 72.00, 76.89, 127.20, 127.25, 127.54, 127.59, 128.70, 128.73, 144.08, 144.48.

6.11. Synthesis of *cis*-{6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-yl}-(4-fluorobenzyl)-amine (17)

cis-6-[(Benzhydryl-amino)-methyl]tetrahydro-pyran-3-yl-amine **15** (0.27 g, 0.91 mmol) was reacted with 4-flu-

orobenzaldehyde (0.11 g, 0.91 mmol) in the presence of glacial acetic acid (0.05 g, 0.91 mmol) and then reduced by $NaCNBH_3$ (0.07 g, 1.1 mmol) in methanol (5 ml) (Procedure C) to give *cis*-{6-[(benzhydryl-amino)-methyl]tetrahydro-pyran-3-yl}-(4-fluorobenzyl)-amine **17** (0.32 g, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.37 (m, 1H, H-5eq), 1.56 (m, 1H, H-5ax), 1.65 (tt, 1H, J = 3.60 Hz and 12.80 Hz, H-4ax), 1.84–1.96 (m, 3H, H-4, NH), 2.53–2.67 (m, 3H, H-3, CH_2NHR), 3.48–3.58 (m, 2H, H-2, H-6), 3.75 (m, 2H, $PhCH_2$), 3.93 (m, 1H, H-2), 4.78 (s, 1H, Ph_2CH), 6.90–7.60 (m, 14H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 24.70, 27.27, 50.31, 50.72, 53.52, 67.89, 70.31, 115.21, 115.43, 127.15, 127.20, 127.54, 127.56, 128.66, 128.69, 129.73, 129.80, 126.47, 136.50, 144.17, 144.48, 160.87, 163.30.

Free base was converted into oxalate salt from ethanol: mp 171–175 °C. Anal. [$C_{26}H_{29}N_2FO\cdot(COOH)_2 0.7H_2O$] C, H, N.

6.12. Synthesis of *cis*-{6-[(benzhydryl-amino)-methyl]-tetrahydro-pyran-3-yl}-(4-hydroxy-benzyl)-amine (18)

cis-6-[(Benzhydryl-amino)-methyl]tetrahydro-pyran-3-yl-amine **15** (0.27 g, 0.91 mmol) was reacted with 4-hydroxy-benzaldehyde (0.11 g, 0.91 mmol) in the presence of glacial acetic acid (0.05 g, 0.91 mmol), and then reduced by $NaCNBH_3$ (0.07 g, 1.1 mmol) in methanol (5 ml) (Procedure C) to give *cis*-{6-[(benzhydryl-amino)-methyl]tetrahydro-pyran-3-yl}-(4-fluorobenzyl)-amine **18** (0.32 g, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.38 (m, 1H, H-5eq), 1.56 (dq, 1H, J = 3.60 Hz and 14.20 Hz, H-5ax), 1.65 (tt, 1H, J = 4.0 Hz and 14.20 Hz, H-4ax), 1.97 (m, 1H, H-4), 2.60 (m, 2H, CH_2NHR), 2.68 (m, 1H, H-3), 3.50 (m, 1H, H-2), 3.53 (m, 1H, H-6), 3.68 (m, 2H, $PhCH_2$), 3.95 (m, 1H, H-2), 4.78 (s, 1H, Ph_2CH), 6.50–7.60 (m, 14H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 24.62, 27.03, 50.51, 50.81, 53.37, 67.89, 69.90, 115.92, 127.19, 127.23, 127.54, 127.57, 128.69, 128.71, 129.82, 131.15, 143.98, 144.29, 155.71.

Free base was converted into oxalate salt from ethanol, mp 200–204 °C. Anal. [$C_{26}H_{30}N_2FO_2\cdot(COOH)_2 1.05H_2O$] C, H, N.

6.13. Synthesis of acetic acid 5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester (20)

Into a solution of furfuryl alcohol (6 g, 61.2 mmol) in THF/H_2O (4:1, 100 ml) was added portionwise finely mixed *N*-bromo succinimide (NBS) (11.43 g, 64.2 mmol), $NaHCO_3$ (10.3 g, 122.4 mmol), and NaOAc (5.02 g, 61.2 mmol) at 0 °C. After 10 min, acetic anhydride (18.74 g, 183.6 mmol) was added in a portionwise manner. The mixture was brought to room temperature gradually and stirred overnight at room temperature. The reaction mixture was neutralized by the addition of saturated $NaHCO_3$ and was extracted with ethyl acetate (3× 50 ml). The combined organic phase was washed in turn with brine and water, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by chromatography (hexane/ethyl acetate 1:1) gave pure product acetic acid 5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester **20** (6.1 g, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 2.12 (s, 3H, CH_3CO), 4.20 (d, J = 17.00 Hz, 1H, H-6), 4.48 (d, J = 17.00 Hz, 1H, H-6), 6.25 (d, J = 10.50 Hz, 1H, H-2), 6.46 (d, J = 3.00 Hz, 1H, H-4), 6.91 (dd, J = 3.50 Hz, 10.00 Hz, 1H, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): 21.11, 67.58, 86.81, 94.99, 128.98, 142.47.

6.14. Synthesis of 6-benzhydryloxy-6*H*-pyran-3-one (21)

A solution of $SnCl_4$ (0.51 g, 1.96 mmol) in CH_2Cl_2 (5 ml) was added slowly to a stirred solution of acetic acid 5-oxo-5,6-dihydro-2*H*-pyran-2-yl ester (6.1 g, 39.1 mmol) and benzhydrol (36 g, 195 mmol) in CH_2Cl_2 (100 ml). The reaction mixture was stirred at room temperature for 5 h, which was followed by quenching of the reaction with saturated $NaHCO_3$ solution (100 ml) and the resulting oil was extracted with ethyl acetate (3× 60 ml). The organic phase was washed in turn with saturated $NaHCO_3$, brine, and water, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by chromatography (hexane/ethyl acetate 4:1) gave pure 6-benzhydryloxy-6*H*-pyran-3-one **21** (9.8 g, 90% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 4.09 (d, J = 17.10 Hz, 1H, H-2), 4.47 (d, J = 16.50 Hz, 1H, H-2), 5.27 (d, J = 3.30 Hz, 1H, H-4), 5.89 (s, 1H, Ph_2CH), 6.17 (d, J = 10.50 Hz, 1H, H-6), 6.90 (dd, J = 3.60 Hz, 10.50 Hz, 1H, H-5), 7.20–7.46 (m, 10H, aromatic-CH).

6.15. Synthesis of 6-benzhydryloxy-tetrahydro-pyran-3-ol (22)

$NaCNBH_3$ (0.42 g, 6.64 mmol) was added portionwise to a mixture of 6-benzhydryloxy-6*H*-pyran-3-one (0.062 g, 2.2 mmol) and BF_3/Et_2O (1.11 g, 7.8 mmol) in dry THF (30 ml) cooled to −78 °C. The reaction mixture was allowed to come to room temperature over a period of 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 ml). The organic phase was separated, and the aqueous phase was extracted with ethyl ether (3× 20 ml). The combined organic phase was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure, and purification by flash chromatography (hexane/ethyl acetate 4:1) afforded pure product 6-benzhydryloxy-tetrahydro-pyran-3-ol **22** (0.44 g, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.68 (m, 1H, H-5), 1.76–1.94 (m, 3H, H-4, H-5), 2.03 (br s, 1H, OH), 3.58 (d, J = 6.40 Hz, 2H, H-2), 3.68 (m, 1H, H-3), 4.65 (m, 1H, H-6), 5.78 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 28.26, 28.57, 65.86, 66.18, 78.63, 94.38, 126.99, 127.43, 127.87, 127.96, 128.18, 128.76, 128.82, 141.58, 142.68.

6.16. Synthesis of *trans*-6-benzhydryloxy-tetrahydro-pyran-3-yl-amine (23)

6.16.1. (1) Synthesis of methanesulfonic acid *cis*-6-benzhydryloxy-tetrahydro-pyran-3-yl ester. *cis*-6-Benzhydryloxy-tetrahydro-pyran-3-ol **22** (0.09 g, 0.31 mmol) was reacted with methanesulfonyl chloride (0.07 g, 0.61 mmol) in the presence of triethylamine (0.05 g, 0.45 mmol) (Procedure A) to give methanesulfonic acid *cis*-6-benzhydryloxy-tetrahydro-pyran-3-yl ester (0.1 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): 1.77 (m, 1H, H-5), 1.92–2.10 (m, 2H, H-4, H-5), 2.19 (m, 1H, H-4), 2.99 (s, 3H, CH_3SO_2), 3.70–3.85 (m, 2H, H-2), 4.65–4.73 (m, 2H, H-3, H-6), 5.75 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 25.94, 28.67, 38.89, 52.76, 62.69, 74.68, 78.92, 93.88, 126.91, 127.56, 127.80, 128.10, 128.57, 128.85, 128.91, 141.33, 142.46.

6.16.2. (2) Synthesis of *trans*-5-azido-2-benzhydryloxy-tetrahydro-pyran. Methanesulfonic acid *cis*-6-benzhydryloxy-tetrahydro-pyran-3-yl ester (0.12 g, 0.33 mmol) was reacted with sodium azide (0.09 g, 1.33 mmol) (Procedure B) to give *cis*-(5-azido-2-benzhydryloxy-tetrahydro-pyran (0.09 g, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.69 (m, 2H, H-3), 2.00 (m, 1H, H-4), 2.22 (m, 1H, H-4), 3.47–3.60 (m, 2H, H-5, H-6), 3.96 (dd, J = 2.40 Hz, 12.00 Hz, 1H, H-6), 4.76 (m, 1H, H-2), 5.77 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 23.34, 26.06, 55.83, 62.64, 78.93, 94.96, 126.94, 127.50, 127.81, 128.03, 128.54, 128.80, 141.49, 142.70.

6.16.3. (3) Synthesis of *trans*-6-benzhydryloxy-tetrahydro-pyran-3-yl-amine (23). *trans*-(5-Azido-2-benzhydryloxy-tetrahydro-pyran (0.08 g, 0.27 mmol) was reduced by $LiAlH_4$ (0.04 g, 1.07 mmol) in dry ethyl ether (5 ml) to give *trans*-6-[(benzhydryloxy-tetrahydro-pyran-3-yl-amine **23** (0.072 g, 95%) (Procedure G).

^{1}H NMR (400 MHz, CD_3OD): 1.47 (m, 1H, H-5), 1.64 (m, 1H, H-5), 1.92 (m, 1H, H-4), 2.12 (m, 1H, H-4), 2.91 (m, 1H, H-3), 3.25 (m, 1H, H-2), 3.96 (m, 1H, H-2), 4.62 (m, 1H, H-6), 4.79 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, CD_3OD): 26.32, 26.51, 45.92, 66.22, 79.20, 96.22, 126.63, 127.05, 127.41, 127.64, 128.03, 128.40, 141.67, 142.79.

6.17. Synthesis of *trans*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine (*trans*-24)

trans-6-Benzhydryloxy-tetrahydro-pyran-3-yl-amine **23** (0.04 g, 0.15 mmol) was reacted with 4-fluorobenzaldehyde (0.02 g, 0.15 mmol) in the presence of glacial acetic acid (0.009 g, 0.15 mmol) and then reduced by $NaCNBH_3$ (0.02 g, 0.30 mmol) in methanol (1 ml) (Procedure C) to give *trans*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **24** (0.05 g, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.53 (m, 2H, H-5, NH), 1.65 (m, 1H, H-5), 1.92 (m, 1H, H-4), 2.09 (m, 1H, H-4), 2.71 (m, 1H, H-3), 3.70 (dd, J = 4.80 Hz and 11.20 Hz, 1H, H-2ax), 3.76 (s, 2H, $PhCH_2$), 3.99 (m, 1H, H-2eq), 4.65 (t, 1H, J = 3.60 Hz, H-6), 5.82 (s, 1H, Ph_2CH), 6.80–7.50 (m, 14H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 25.33, 27.21, 50.73, 51.51, 65.42, 78.87, 96.23, 115.30, 115.51, 127.01, 127.38, 127.87, 127.92, 127.45, 127.74, 129.73, 129.82, 141.64, 142.77.

Free base was converted into oxalate salt from ethanol: mp 178–180 °C Anal. [$C_{25}H_{26}NFO_2 \cdot (COOH)_2 0.3H_2O$] C, H, N.

6.18. Synthesis of 6-benzhydryloxy-dihydro-pyran-3-one (25)

Into a solution of 6-benzhydryloxy-6*H*-pyran-3-one **21** (0.15 g, 0.53 mmol) in dry THF (20 ml) was added L-selectride (0.53 ml of 1.0 M solution in THF, 0.53 mmol) drop by drop at −78 °C. After 20 min, the reaction was quenched with saturated NH_4Cl. The mixture was extracted by ethyl acetate (3× 20 ml). The combined organic phase was washed with brine and water, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by chromatography (hexane/ethyl acetate 4:1) gave pure 6-benzhydryloxy-dihydro-pyran-3-one **25** (0.12 g, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 2.14 (m, 1H, H-5), 2.26 (m, 1H, H-5), 2.48 (m, 1H, H-4), 2.67 (m, 1H, H-4), 3.91 (d, J = 16.80 Hz, 1H, H-2), 4.17 (d, J = 16.80 Hz, 1H, H-2), 5.06 (m, 1H, H-6), 5.82 (s, 1H, Ph_2CH), 7.10–7.60 (m, 10H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 28.44, 34.03, 67.79, 79.44, 93.86, 126.85, 127.67, 127.74, 128.16, 128.61, 128.88, 141.19, 142.25.

6.19. Synthesis of *cis*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine (*cis*-24)

6-Benzhydryloxy-dihydro-pyran-3-one **25** (0.05 g, 0.16 mmol) was reacted with 4-fluorobenzylamine (0.02 g, 0.16 mmol) in the presence of glacial acetic acid (0.009 g, 0.16 mmol) and then reduced by $NaCNBH_3$ (0.01 g, 0.21 mmol) in methanol (1 ml) (Procedure C) to give *cis*-(6-benzhydryloxy-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **24** (0.05 g, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.62–1.92 (m, 4H, H-4, H-5), 2.72 (tt, 1H, J = 4.0 Hz and 9.60 Hz, H-3), 3.54 (t, J = 10.40 Hz, 1H, H-2ax), 3.65 (m, 1H, H-2eq), 3.77

(m, 2H, $PhCH_2$), 4.74 (t, 1H, $J = 2.40$ Hz, H-6), 5.76 (s, 1H, Ph_2CH), 6.80–7.50(m, 14H, aromatic-CH).

^{13}C NMR (100 MHz, $CDCl_3$): 26.15, 29.39, 50.56, 52.91, 65.02, 78.32, 94.01, 115.31, 115.53, 126.98, 127.32, 127.88, 128.45, 128.71, 129.70, 129.79, 141.75, 142.87.

Free base was converted into oxalate salt from ethanol. Anal. [$C_{25}H_{26}NFO_2 \cdot (COOH)_2 0.5H_2O$] C, H, N.

6.20. Molecular modeling

In order to demonstrate the difference in distances between the exocylic N-atom in benzyl substitution and the two phenyl rings of benzhydryl substituion, we have carried out a preliminary molecular modeling study. Side-chain-extended derivatives at 3- and 6-position **4** and ***cis*-12**, and the 3,6-disubstituted compound **16b** were chosen for this study. Compounds were minimized first with the SYBYL molecular modeling program (version 6.9, 2002, Tripos Associates, Inc., St. Louis, MO). Minimized molecules obtained from this operation were next subjected to a grid search protocol to search for the lowest-energy conformer. Grid search operation was carried out with the change of torsional angle from 0° to 360° with an increment of 10° comprising of atoms α–β–γ–δ as shown in Figure 5 for all three compounds. This operation resulted in the generation of lowest energy with a corresponding torsional angle for each of these three compounds. In the final step, the distance between the exocyclic N atom and two phenyl rings in benzhydryl moiety was measured and the value is shown in Figure 5. It was quite evident that the measured distances in three compounds were quite different.

6.21. Biological experiment

All transporter assays were performed exactly as we described previously.[24] Briefly, binding of [^{3}H]WIN 35,428 was measured in rat striatal membrane preparations with [Na^+] at 30 mM at 0–4 °C for a period of 2 h; nonspecific binding was defined with 100 μM cocaine. Rat striatal synaptosomes were used for measuring uptake of [^{3}H]DA; incubation with test compounds for 5 min was followed by the additional presence of [^{3}H]DA for 4 min at 25 °C. Nonspecific uptake was defined with 100 μM cocaine. For uptake assays with [^{3}H]serotonin and [^{3}H]NE, synaptosomes were prepared from rat cerebral cortex, with nonspecific uptake defined by 10 μM citalopram and 10 μM desipramine, respectively. Test compounds were dissolved in dimethylsulfoxide (DMSO) and diluted out in 10% (v/v) DMSO. Additions from the latter stocks resulted in a final concentration of DMSO of 0.5%, which by itself did not interfere with transporter measures. At least five triplicate concentrations of each test compound were studied, spaced evenly around the IC_{50} value. The latter was estimated by nonlinear computer curve-fitting procedures as we detailed previously.[24] The radioligand concentrations used were well below respective K_d or K_m values in the protocols used.[24]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2006.01.051.

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