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Structural requirements for 2,4- and 3,6-disubstituted pyran biomimetics of *cis*-(6-benzhydryl-piperidin-3-yl)-benzylamine compounds to interact with monoamine transporters

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Abstract—In our effort to delineate novel pharmacophoric configuration of bioisosteric pyran versions of *cis*-(6-benzhydryl-piperidin-3-yl)-benzylamine derivatives in interacting with the monoamine transporter, further structure–activity relationship study was carried out. Both *cis* and *trans* 2,4- and 3,6-disubstituted derivatives were synthesized to determine the positional importance of N-substitution on affinity for monoamine transporters, that is the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET) in rat brain. For that purpose, the potency of compounds was determined in competing for the binding of [^{3}H]WIN 35,428, [^{3}H]citalopram, and [^{3}H]nisoxetine, respectively. Selected compounds were also evaluated for their activity in inhibiting the uptake of [^{3}H]DA by DAT. Our binding results demonstrated potency in 3,6-disubstituted derivatives while 2,4-disubstituted derivatives failed to exhibit any appreciable binding affinity. Further structural exploration of the exocyclic N-atom in 3,6-disubstituted derivatives produced compounds potent at both DAT and NET. Compounds **16h** and **16o** with hydroxyl and amino groups in the phenyl moiety of the benzyl group produced the highest activity for the NET. In this regard, compound **16e** with a methoxy substituent produced weak affinity at NET, which upon conversion into a hydroxyl functionality as in **16h** produced potent affinity for the NET. Various indole derivatives displayed different interactions; the 5-substituted indole derivative **16n** exerted potent affinity for NET, confirming the bioisosteric equivalence between this indole moiety and the phenyl-4-hydroxy group in **16h**.
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1. Introduction

Cocaine, a naturally occurring alkaloid, is well known for its powerful abuse and addiction potential. Cocaine dependence is a major problem in our society today, inflicting severe medical, social, judicial, and financial costs.[1,2] Currently, no effective medication is available for the treatment of cocaine addiction and there is an urgent need to develop a suitable medication to treat this chronic disorder.[3]

Extensive studies have been conducted so far to understand the mechanism of action of cocaine, which might eventually lead to the development of a much needed medication for cocaine dependence. Cocaine binds to all three monoamine transporter systems in the brain but its central reinforcing action is thought to be derived mainly from binding to the dopamine transporter (DAT).[4–7] Such a role for DAT is strongly supported by various experimental evidences.[8–10] However, this does not rule out the involvement of nondopaminergic systems in cocaine reward, and for example, the serotonergic system has been shown to modulate some of cocaine's effects.[11,12]

Many efforts have been directed toward the development of molecules targeting DAT and a great number of structurally diverse compounds have already been synthesized with an aim to develop effective pharmacotherapies for cocaine addiction. These compounds include tropane, benztropine, mazindol, or methylphenidate derivatives, and also piperazine or piperidine derivatives of GBR 12935. Detailed description of SAR studies on these compounds is provided in recent review papers.[13–15] The existence of this wide variety of molecular structures might indicate the existence of flexible binding pockets in the DAT, which can accommodate

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different molecular templates. Our efforts to develop molecules targeting DAT started with piperidine analogs of GBR 12909. A large number of potent and selective piperidine analogs have been synthesized and biologically characterized.[16–19] Most of these molecules possess a high degree of structural flexibility, and consequently, it was difficult to elucidate their biologically active conformation for interacting with DAT. Recently, we converted one of our lead piperidine analogs into structurally constrained 3,6-disubstituted piperidine derivatives possessing *cis*- and *trans*-structures.[20] The results demonstrated that preferential affinity for the DAT lied with the *cis*-structure compared to the *trans*-structure (Fig. 1). Further SAR study on the *cis*-template produced derivatives with higher affinity for the DAT confirming the *cis*-structure as a novel template for the DAT.[21]

In a recent preliminary study, we demonstrated that the piperidine ring in our structurally constrained 3,6-disubstituted piperidine derivatives can be replaced by a pyran moiety while preserving DAT activity in the same stereochemical *cis*-structural preference (Fig. 2).[22] However, the relative activity was some what greater in the piperidine derivatives, for example the IC_{50} for, inhibiting radioligand binding to DAT for **1a** was 31.5 nM versus 52.6 nM for **16c**, indicating the potential importance of the more basic N-atom in interacting with DAT. Our earlier study reported the synthesis and biological characterization of a *trans*-3,6-disubstituted pyran derivative and a limited number of *cis*-3,6-disubstituted pyran derivatives. The result demonstrated that the *cis* derivative was approximately two times as potent as the *trans* compound. In previous studies with tropane and benztropine analogs, transformation of certain DAT selective 3-aryltropane and benztropine analogs into oxy-3-aryltropane and oxy-benztropine analogs was carried out, which resulted in divergent results.[23,24] Thus transformation of tropane to oxy-3-aryltropane had a minimal influence on activity at DAT compared to its parent bioisosteric N-analog.[23] On the other hand, similar transformation of benztropine to oxy-benztropine analogs resulted in loss of potency for the DAT.[24] Both oxy-3-aryltropane and oxy-benztropine have a constrained tetrahydro-pyran moiety albeit oxy-3-aryltropane analogs contain additional substitutions. These results point to the N-atom in benztropine as a critical requirement for binding to the DAT, whereas the N-atom in 3-aryltropane analogs may not be so critical, consonant with the existence of flexible binding pockets in the DAT. These results also indicate that a structurally constrained pyran moiety requires more molecular specificity for exhibiting activity at DAT compared to a structurally constrained piperidine motif. These differences in activity at the DAT might be due to the fact that several changes can occur in the pharmacodynamic properties upon the replacement of an N-atom by a less basic O-atom. Consequently, different modes of interaction with DAT could occur for pyran and their bioisosteric piperidine counterparts. These two types of compounds may also produce different pharmacokinetic properties.

In our current study we wanted to explore further substitution on the exocyclic N-atom in 3,6-disubstituted derivatives to gain more insight in the molecular deter-

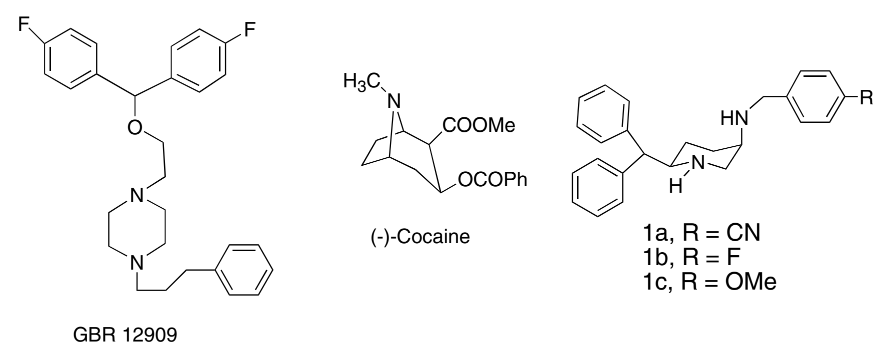


Figure 1. Molecular structure of dopamine transporter blockers.

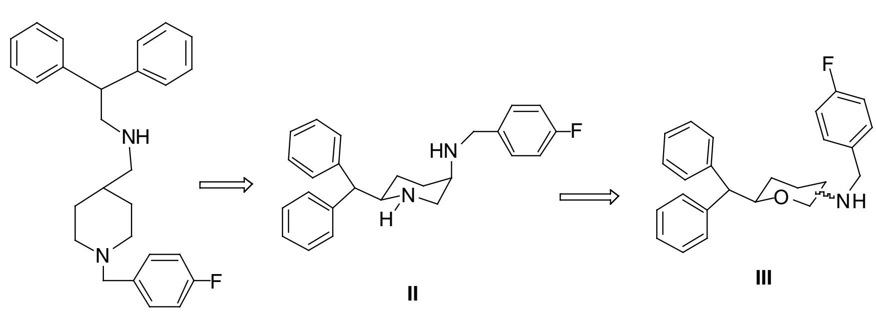


Figure 2. Rational modification of flexible piperidine molecules into constrained structures.

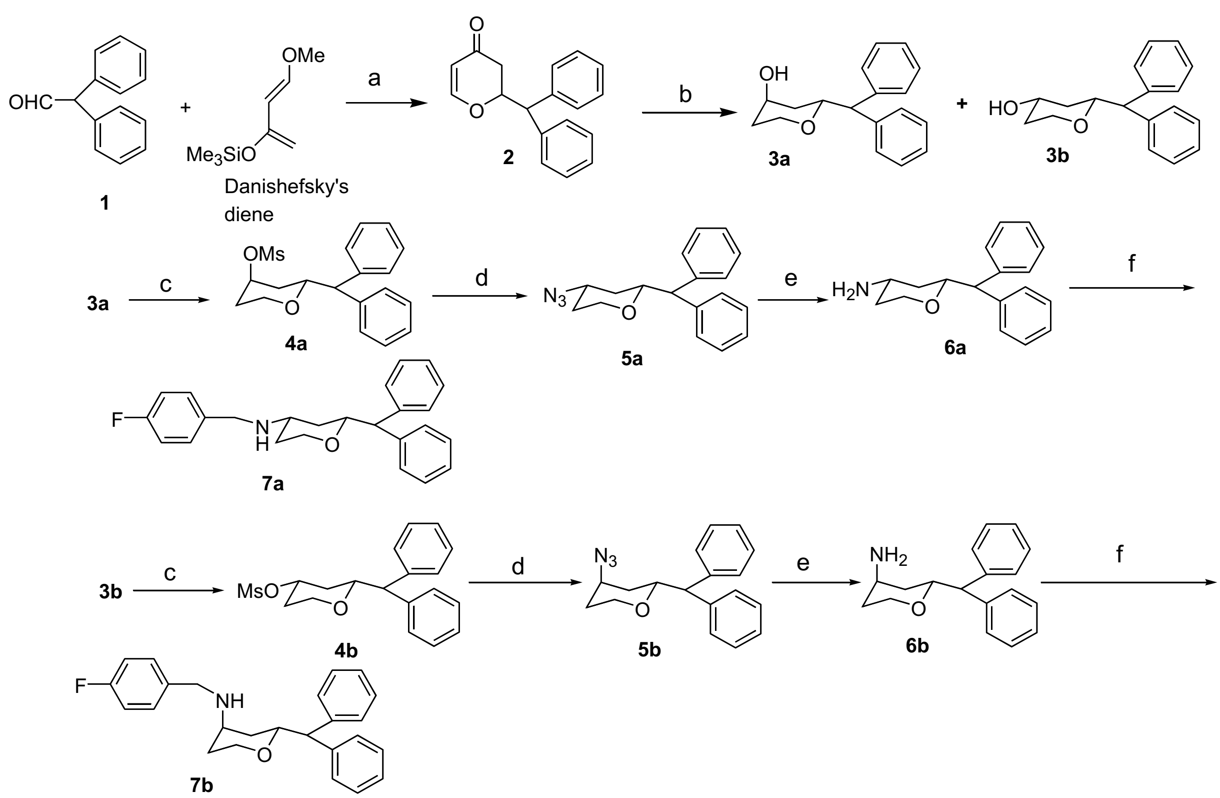
minants required for activity. In addition, we wanted to map out the positional requirement of the amino moiety on the pyran ring for interaction with the DAT by varying its location. For this purpose, we have designed, in addition to 3,6-disubstituted derivatives, 2,4-disubstituted pyran derivatives in their *cis*- and *trans*-isomeric forms. The results from these studies should shed more light on the dynamics of molecular interactions of these novel pyran derivatives with monoamine transporters.

2. Chemistry

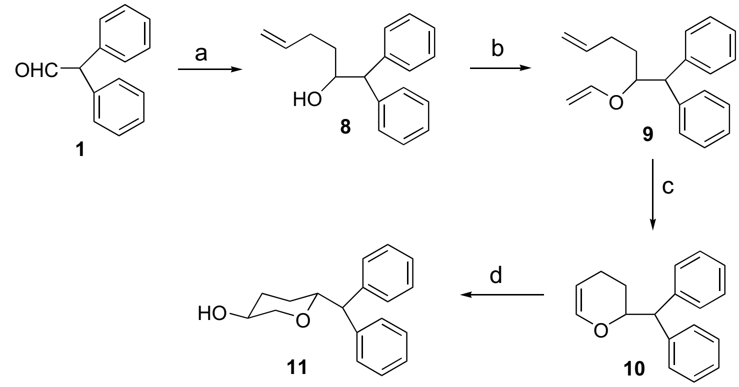
Target compounds **7a**,**b** and **16a**–**p** were synthesized by following the synthetic procedures shown in Schemes 1–5.

Synthesis of the target compounds **7a** and **7b**, shown in Scheme 1, was accomplished in high yields by following efficient synthetic routes. The basic pyranose ring structure in compound **2** was achieved by [4+2] hetero-Diels–Alder cycloaddition between Danishefsky's diene and aldehyde **1** in the presence of $BF_3{\cdot}Et_2O$, which produced **2** in 80% yield.[25,26] Reduction of **2** with $NaCNBH_3$ in presence of $BF_3{\cdot}Et_2O$ in THF produced racemic *cis*- and *trans*-mixture of **3a** and **3b** (2.5:1) in 96% yield. The two isomers were separated by careful flash chromatography, and their structures were assigned by NMR and NOE (see Supplementary data). Compounds **6a** and **6b** were synthesized from **3a** and **3b**, respectively, in high yields by three steps that involved first mesylation with methanesulfonyl chloride in dry dichloromethane to produce **4a** and **4b**, which were then treated with sodium azide in DMF to produce azides **5a** and **5b** with inversion of configuration.[27] This azido displacement reaction resulted in production of the *cis*-isomer **5a** from *trans*-**4a** and the *trans*-isomer **5b** from *cis*-**4b**. Finally, catalytic hydrogenation of the azides **5a** and **5b** with Pd/C produced the amine precursors **6a** and **6b** in good yield. Reductive amination of **6a** and **6b** by following a procedure described by us earlier furnished **7a** and **7b**, respectively, in 72.6% and 54% yield.

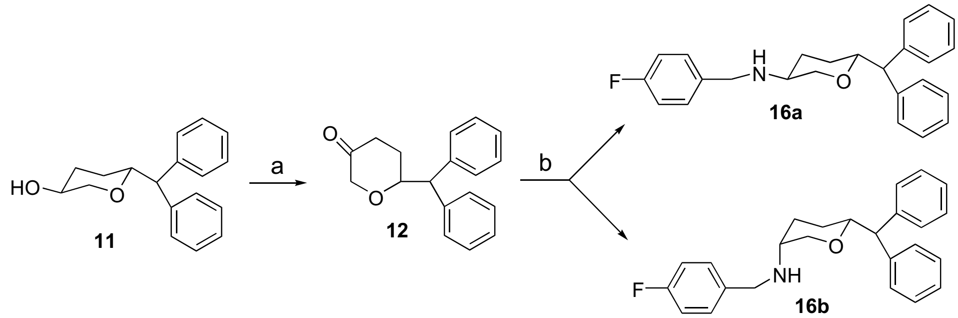
Scheme 2 delineates the preparation of the key pyran 3,6-disubstituted intermediate **11** with *trans*-stereochemistry. Briefly, aldehyde **1** was converted into **8** by reacting with the in situ prepared Grignard reagent 4-bromomagnesium-1-butene, prepared from 4-bromo-1-butene and magnesium in dry ether in 91% yield. O-vinyllation of **8** with ethyl vinyl ether in the presence of $Hg(OCOCF_3)_2$ at room temperature produced **9** in 66% yield.[28] Ring closing metathesis of **9** in presence of a Grubb's catalyst in refluxing benzene afforded olefin **10** in 92.6% yield.[29] Hydroboration of **10** with 9-BBN in THF, followed by oxidation gave exclusively *trans*-isomer **11** in 93.5% yield.[30] Compound **11** was used next as a starting precursor for the synthesis of various derivatives with different substitutions at the exocyclic



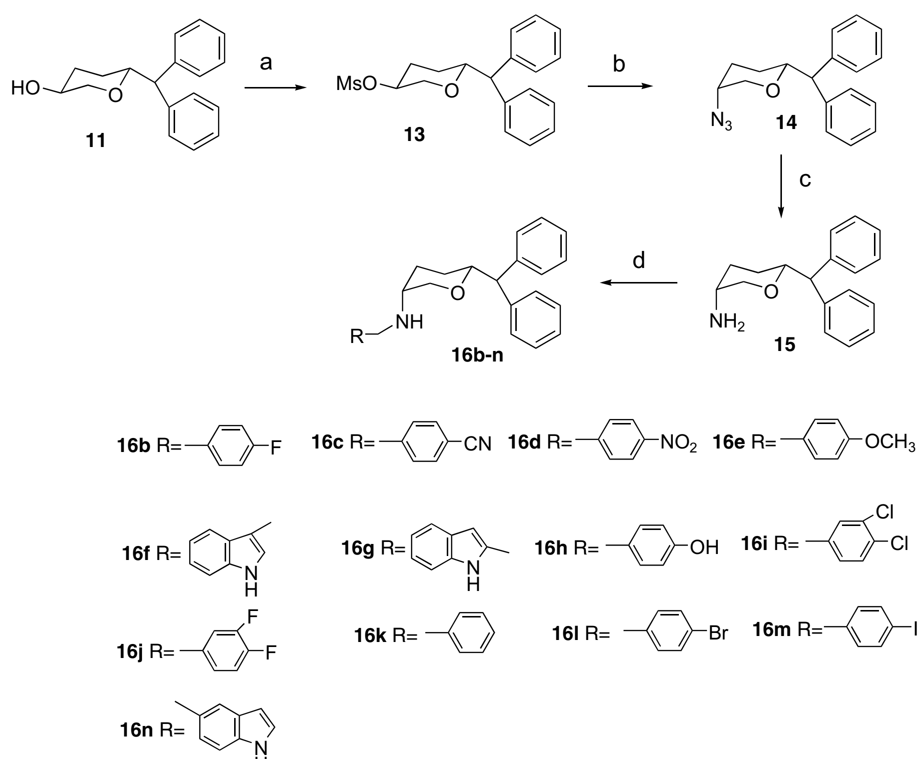
Scheme 1. Reagents and conditions: (a) Danishefsky's diene (*trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene), BF_3/Et_2O, dry ethyl ether, −78 to 0 °C, 4 h, 80.2%; (b) BF_3/Et_2O, $NaCNBH_3$, dry THF, −78 °C to room temperature, 2 h, 96%; (c) CH_3SO_2Cl, Et_3N, (d) NaN_3, DMF, 100 °C, 4 h, 82.7%; (e) H_2/Pd–C, MeOH, 60 psi, 4 h, quantitative yields; (f) 4-fluorobenzaldehyde, AcOH, $NaCNBH_3$, $ClCH_2CH_2Cl$, room temperature, 4 h, 54–72.6%.



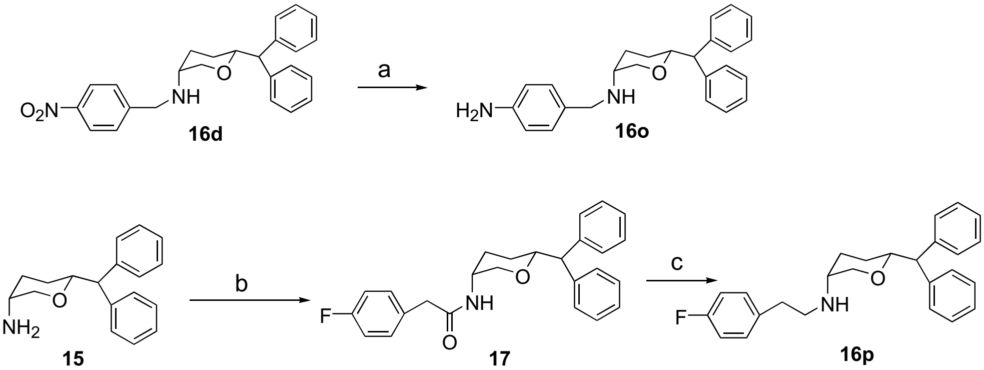
Scheme 2. Reagents and conditions: (a) 4-bromo-1-butene, Mg, Et_2O, $-78\,°C$ to room temperature, 4h, 91%; (b) ethyl vinyl ether, $Hg(OCOCF_3)_2$, room temperature, overnight, 66%; (c) Grubb's catalyst (benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium), benzene, 80 °C, 20h, 92.6%; (d) (i) 9-BBN, THF, room temperature, overnight; (ii) NaOH, H_2O_2, 55 °C, 1h, 93.5% overall yield.



Scheme 3. Reagents and conditions: (a) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, $-78\,°C$ to room temperature, 30 min, 91%; (b) 4-fluorobenzylamine, AcOH, $NaCNBH_3$, $ClCH_2CH_2Cl$, room temperature, 4h, 15–45%.



Scheme 4. Reagents and conditions: (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, room temperature, 4h, 77.8%; (b) NaN_3, DMF, 100 °C, 4h, 92%; (c) H_2, Pd–C, MeOH, 60 psi, 4h, 78% (d) aldehyde, AcOH, $ClCH_2CH_2Cl$, $NaCNBH_3$, MeOH, room temperature, 4h, 82%.



Scheme 5. Reagents and conditions: (a) $SnCl_2{\cdot}2H_2O$, EtOH/EtOAc (7:3), reflux, 1.5h, 60%; (b) 4-fluorophenylacetyl chloride, Et_3N, CH_2Cl_2, room temperature, 80%; (c) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, reflux, overnight, 81%.

N-atom as shown in Schemes 3 and 4. First, compound **11** was subjected to Swern oxidation reaction condition, which produced ketone **12** in 91% yield. Reductive amination of **12** with 4-fluorobenzylamine produced **16a** as a major product in 45% yield (Scheme 3). As described in the synthesis of compound **6a–b** in Scheme 1, compound **11** was next converted into a *cis*-amine intermediate **15** via three steps consisting of first mesylation with methanesulfonyl chloride in dry dichloromethane followed by displacement with sodium azide in DMF and finally, catalytic hydrogenation with Pd–C in methanol (Scheme 4). Reductive amination of **15** with various aldehydes furnished target compounds **16b–n** in good yield (Scheme 4).

The synthesis of compounds **16o** and **16p** is described in Scheme 5. The compound **16o** was synthesized by the reduction of **16d** with tin(II) chloride dihydrate in ethanol and ethyl acetate in 60% yield. Amide intermediate **17** was obtained from the reaction of amino-compound **15** with 4-fluorophenylacetyl chloride. Reduction of **17** with freshly generated borohydrate gave the target compound **16p**.

3. Results and discussions

As an extension of our studies on structurally constrained piperidine derivatives, we have developed novel 3,6-disubstituted pyran molecules as potential blockers of monoamine transporters. Preliminary binding results of the compounds at monoamine transporters indicated a positive correlation with the results from our structurally constrained 3,6-disubstituted piperidine template including the *cis*-isomeric preference for higher activity. However, in comparison to their piperidine counterparts, these compounds were somewhat less potent at DAT. This might indicate that even though the N- and O-atoms in the piperidine and pyran rings are bioisosteres, the existence of different interaction modes with the monoamine transporter systems can not be ruled out as the physical properties such as basicity of these two atoms are quite different. Consequently, in our current SAR study we wanted to examine additional derivatives. These derivatives were synthesized by functionalizing the exocyclic N-atom with various bioisosteric heterocyclic moieties and other substituted benzyl derivatives. Results from these derivatives will allow us to compare any similarity or dissimilarity in molecular interaction between the piperidine and pyran series of compounds, which in turn could provide a unique pharmacophoric models for pyran derivatives.

Additionally, we wanted to investigate the positional importance of the exocyclic N-substituted moiety on the pyran ring. This exploration was thought to be necessary since any loss in potency from transforming the piperidine to a pyran moiety might lead to a less than optimal interaction at the 3-amino substituent site on the pyran ring. This could potentially arise as the O-atom in the pyran ring, being less basic than the piperidine N-atom, may interact with (a) different residue (s) of the DAT. A shift of the N-substituent to the adjacent position could be thought to compensate for this, leading to enhanced interaction. Moreover, testing the effect of a positional shift of the amino substituent will answer the question of whether the 3,6-disubstituted configuration is required as an optimal pharmacophore configuration for binding interaction. In an attempt to address these questions, 2,4-disubstituted derivatives in their *cis*- and *trans*-forms were designed and synthesized.

Following synthesis of the 2,4-disubstituted *cis* and *trans* compounds **7a** and **7b**, their potencies were determined in binding assays for the three monoamine transporters (Table 1). The results indicated that the positional change from 3,6-disubstitution to 2,4-disubstitution adversely affected the binding activity of these two molecules. It is interesting to note that even though the activity was low in the 2,4-disubstituted compounds, the preferential affinity for DAT was still exhibited in the *cis* version. These results confirmed that the *cis*-form of the 3,6-disubstituted pyran template contributes to the basic pharmacophore for interacting with DAT.

In the 3,6-disubstituted version, as we reported in our preliminary communication,[22] replacement of the fluoro substituent by electron withdrawing substituents resulted in more potent compounds for the DAT as illustrated in the cyano-substituted molecule **16c** and the nitro-substituted molecule **16d**. Nitro-substitution produced the most potent compound among these

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

Compd	Inhibition of [^{3}H]Win 35, 428 binding to DAT, IC_{50} (nM)[a]	Inhibition of [^{3}H]citalopram binding to SERT, IC_{50} (nM)[a]	Inhibition of [^{3}H]nisoxetine binding to NET, IC_{50} (nM)[a]	Inhibition of [^{3}H]DA[a] uptake by DAT, IC_{50} (nM)
Cocaine	266 ± 37	737 ± 160	3130 ± 550	
GBR 12909	10.6 ± 1.9	132 ± 0	496 ± 22	
I	32.5 ± 12.6	2220 ± 590	1020 ± 72	45.7 ± 5.1
7a	1302 ± 68	3313 ± 170	5101 ± 1037	
7b	1581 ± 283	4778 ± 1808	17,543 ± 2153	
16a[b]	313 ± 71	8410 ± 163	12,700 ± 3180	
16b[b]	163 ± 29	1860 ± 22	232 ± 46	156 ± 36
16c[b]	52.6 ± 5.9	863 ± 52	1580 ± 89	58.6 ± 13.2
16d[b]	38.3 ± 3.9	738 ± 164	968 ± 98	102 ± 7
16e	84 ± 6.5	1180 ± 269	1550 ± 682	59.5 ± 11.6
16f	794 ± 111	2590 ± 1410	1860 ± 847	
16g	227 ± 67	1640 ± 448	401 ± 96	135.2 ± 47.5
16h	78.4 ± 9	398 ± 22	22.6 ± 1.4	
16i	400 ± 31	780 ± 84	144 ± 25	880 ± 136
16j	368 ± 85	3520 ± 831	695 ± 142	
16k	303 ± 14	1577 ± 97	274 ± 29	242 ± 39
16l	202 ± 13	2363 ± 92	592 ± 12	251 ± 14
16m	319 ± 21	2477 ± 145	234 ± 17	500 ± 34
16n	587 ± 66	325 ± 20	56 ± 6	
160	151 ± 13	1690 ± 169	123 ± 10	155 ± 14
16p	129 ± 58	3950 ± 660	5210 ± 678	
15	777 ± 41			251 ± 31

[a] For binding, the DAT was labeled with [^{3}H]WIN 35,428, the SERT with [^{3}H]citalopram and the NET with [3H]nisoxetine. For uptake by DAT, [3H]DA accumulation was measured. Results are average ± SEM of three to eight independent experiments assayed in triplicate.
[b] See Ref. 22.

synthesized analogs for the DAT (IC_{50} = 38.3 nM). This trend agrees with our previous data for the piperidine counterparts. On the other hand, the electron donating methoxy substituent in **16e** produced comparable potency at the DAT (IC_{50} = 84 nM).[22] Similar relative differences in potency were observed for piperidine derivatives.[21] Introduction of 3,4-difluoro substituents in **16j** reduced potency at all three transporters compared to the 4-fluoro compound **16b**. For the dichloro-substituted compound **16i**, no improvement in potency at DAT was observed compared to the unsubstituted **16k**, suggesting a different mode of binding interaction compared to tropane- and methylphenidate-type of compounds.[31,32] As far as other halogen derivatives are concerned, the bromo compound **16l** exhibited somewhat higher activity at DAT compared to unsubstituted **16k** whereas the iodo compound **16m** displayed comparable potency.

Compared to the methoxy substituted compound **16e**, the hydroxy substituted compound **16h** retained potency at DAT (IC_{50} = 78.4 nM for **16h** and IC_{50} = 84 nM for **16e**), but its selectivity was shifted in favor of norepinephrine transporter (NET) shown by the much higher activity at NET (IC_{50} = 22.6 nM for the NET, NET/DAT = 0.29) (Table 2). The amino-substituted compound **16o** also exhibited high potency at NET. Hydroxy or amino substituents can act as both hydrogen-bond donor or acceptor sites, although in different capacity. The appreciable shift toward potency and selectivity at NET caused by these two polar substituents might indicate a critical involvement of hydrogen bonding in interacting with NET. However, similar results were not observed in the structurally constrained piperidine analogs, reflecting the existence of different interaction modes between these two templates.[21] Since a high degree of homogeneity has been demonstrated

Table 2. Selectivity of various drugs for their activity at monoamine transporters

Compound	SERT binding/ DAT binding	NET binding/ DAT binding	[3H]DA uptake/ DAT binding
Cocaine	2.8	11.8	
GBR 12909	12.5	46.8	
I	68.3	31.4	1.4
7a	2.5	3.9	
7b	3	11.1	
16a	26.9	40.6	
16b	11.4	1.4	0.96
16c	16.4	30	1.1
16d	19.3	25.3	2.7
16e	14	18.5	0.71
16f	3.3	2.3	
16g	7.2	1.8	0.60
16h	5.1	0.29	
16i	1.9	0.36	
16j	9.6	1.9	
16k	5.20	0.90	0.79
16l	11.69	2.93	1.24
16m	7.76	0.73	1.56
16n	0.55	0.09	
16o	11.19	0.81	1.02
16p	30.6	40.4	
15			0.32

between the DAT and NET structural sequence, it is of interest to observe that a subtle change in pyran structure can induce differential interactions in favor of the NET.[33,34]

In order to gain further insight into the hydrophobic nature of the interaction between the aromatic moiety and monoamine transporters, we decided to replace the phenyl aromatic moiety in the benzyl group by bioisosteric indole moieties. Thus, replacement with 2- and 3-indole moieties as illustrated in compounds **16g** and **16f**, led to moderate to diminished potency at DAT. Interestingly, as was seen with our piperidine derivative counterparts, the 2-indole substituted derivative **16g** was 3.5-fold more active at DAT compared to the 3-substituted **16f** (227 vs 794 nM) and was also more active than the unsubstituted derivative **16k**. A similar increase in affinity for the NET was also observed for the 2-substituted indole compared to the 3-substituted compound (401 vs 1860 nM). In our further attempt to test the importance of the position of the indole N-atom along with its hydrophobicity, the 5-substituted indole derivative **16n** was designed and synthesized. In this regard, 5-substitution was chosen as a bioisosteric configuration of the *p*-hydroxy-phenyl moiety of **16h**. The binding results for **16n** indicated high affinity, similar to **16h**, for the NET, indicating the involvement of H-bonding with the indole amino moiety. This result further demonstrates the existence of a H-bond donor or acceptor site in the NET, which when oriented correctly with respect to ligand's H-bond forming functionality, can provide potent interaction.

In compound **16p**, the fluorobenzyl moiety was replaced by a 4-fluorophenylethyl moiety which did not result, surprisingly, in decreased activity at DAT compared to **16b**. This result was in contrast to the results observed in the constrained piperidine counterpart where a drop in DAT activity resulted from such modification.[21] This result likely indicates that a different pharmacophoric optimization is required, probably via a distance geometry approach, to produce optimum activity in the pyran template. As we expected, the exocyclic-N-substitution with an aromatic moiety is necessary in pyran derivatives for their activity at monoamine transporter systems, as compound **15** exhibited little or no activity.

Selected compounds with relatively higher affinity for DAT were tested in the DA uptake assay. For the most part no differential uptake and binding activity was observed with the exception of compound **16d**, which showed a 3-fold higher potency in inhibiting binding than uptake.

4. Molecular modeling

In order to test for a difference in spatial distribution in the lowest energy conformers between 3,6-disubstituted and 2,4-disubstituted pyran derivatives, we have carried out a preliminary molecular modeling study. 2,4-Disubstituted compound **7a** 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 Figures 3A and B for both **7a** and **16b**. This operation resulted in the generation of 3.16 kcal/mol lowest energy for **7a** with a corresponding torsional angle of 77.8° and 5.61 kcal/mol for **16b** with a torsional angle of 300°. In the final step, the two minimized structures were overlapped with the alignment program (see Fig. 3C). It was quite evident that the exocyclic amino substituents in the two compounds were oriented very differently in the two different directions.

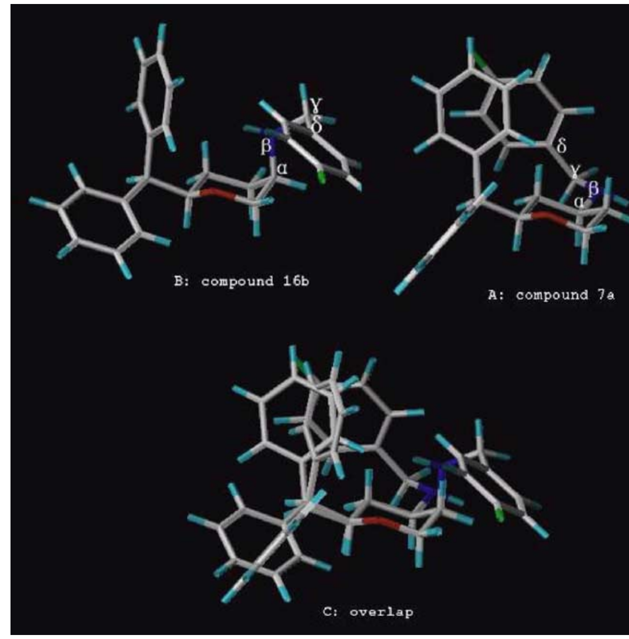


Figure 3. Three-dimensional orientation of the lowest energy conformers and the overlapped ligands: (A) lowest energy conformer from compound **7a**; (B) lowest conformer from compound **16b**; (C) overlapped ligands based on two conformers A and B.

5. Conclusion

In this report, we have outlined the *cis*-3,6-disubstituted tetrahydro-pyran template as a pharmacophore for activity at the monoamine transporter systems. The SAR exploration with this template with various substituents on the exocyclic N-atom produced potencies at both DAT and NET. Compound **16d** with the electron withdrawing nitro-substituent turned out to be the most potent for the DAT. Interestingly, the compounds **16h** and the **16o** with *para*-hydroxy and *para*-amino substituents exhibited high potency for the NET, indicating formation of H-bonding. This was further confirmed by the bioisosteric version **16n**, which exhibited strong selective potency at NET. The SAR results for the current pyran molecules do not correspond with those for the piperidine derivatives, indicating differential interaction modes with monoamine transporters. Our ongoing studies at different molecular centers on this pyran ring to probe and identify optimum pharmacophoric structure will shed more light on their nature of interaction with monoamine transporters.

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 described in Vogel's book. 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 at Varian 400 MHz FT NMR. 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 (86.0 Ci/mmol), [^{3}H]nisoxetine (80.0 Ci/mmol), and [3H]dopamine (48.2 Ci/mmol) were obtained from Dupont-New England Nuclear (Boston, MA, USA). [3H]citalopram (85.0 Ci/mmol) was from Amersham Pharmacia Biotech Inc. (Piscataway, NJ, USA). Cocaine hydrochloride was purchased from Mallinckrodt Chemical Corp. (St. Louis, MO, USA.). WIN 35,428 napthalene sulfonate was purchased from Research Biochemicals, Inc. (Natick, MA, USA). (−)-Cocaine HCl was obtained from the National Institute on Drug Abuse. GBR 12909 Dihydrochloride (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]-piperazine) was purchased from SIGMA-ALDRICH (#D-052; St. Louis, MO).

6.1. Molecular modeling

Molecular modeling investigation was performed by using the SYBYL molecular modeling package (version 6.9, 2002, Tripos Associates, Inc., St. Louis, MO). Modeling was carried out on Silicon Graphics Octane IRIX 6.5 workstation. The compounds were sketched in appropriate stereochemistry.

First, each structure was fully minimized using standard Tripos force field with a distance-dependent dielectric function, a 0.05 kcal/mol Å energy gradient convergence criterion was used and the six-membered pyran ring was treated as an aggregate. The Powell method was used during minimization, and charges were computed using the Gasteiger–Huckel method within SYBYL 6.9. The number of iteration was 1000. After minimization the energy for 2,4-disubstituted molecule **7a** was 5.85 kcal/mol and the energy for 3,6-disubstituted molecule **16b** was 5.63 kcal/mol.

In the next step, using the grid search protocol, a conformational search on each minimized molecule was performed by rotating the torsion angle of compounds **7a** and **16b** formed by atoms α–β–γ–δ (see Fig. 3) from 0° to 360° by 10° increments. This method was used to perform a simple systematic search such that each specified torsion angle is varied over a grid of equally space value. While searching for the lowest energy conformer, a cutoff value of 8 kcal/mol was specified relative to the lowest conformer, and charges were computed using the Gasteiger–Huckel method. Also, the six-membered pyran ring was treated as an aggregate. For compound **7a**, a conformer with torsional angle 77.8° was found to have lowest energy 3.16 kcal/mol, whereas compound **16b** produced lowest energy 5.61 kcal/mol with a torsion angle 300° (see Supplementary data for detail energy distribution). These two lowest energy conformers were used next for overlapping.

During overlapping, the alignment program within SYBYL 6.9 was employed, and the approach used was the common structure method. The compound **16b** was used as a template molecule and the six-membered pyran ring was used as a common substructure for overlapping.

6.1.1. Synthesis of 2-benzhydryl-2,3-dihydro-4*H*-pyran-4-one (2). A solution of boron trifluoride diethyl etherate (7.80 g, 55 mmol) in dry ether (50 mL) was added to a stirred mixture of *E*-1-methoxy-3-trimethylsilyloxy-buta-1,3-diene (Danishefsky's Diene) (8.30 g, 48 mmol), diphenylacetaldehyde **1** (11.40 g, 58 mmol), and dry ether (300 mL) cooled to −78 °C. After 1 h, the mixture was allowed to reach 0 °C for 3 h. The deep red reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the mixture was allowed to come to room temperature. The organic phase was separated and the aqueous phase was extracted with ether (3 × 70 mL). Combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the crude product by chromatography (hexane/ethyl acetate 8:2) gave 2-benzhydryl-2,3-dihydro-4*H*-pyran-4-one **2** (10.20 g, 80.2%, yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): 2.38 (dd, $J = 3.20$, 16.80 Hz, 1H, H-3), 2.51 (m, 1H, H-3), 4.23 (d, $J = 9.20$ Hz, 1H, $(Ph)_2CH$), 5.15 (dt, $J = 3.20$, 8.80 Hz, 1H, H-2), 5.44 (d, $J = 6.40$ Hz, 1H, H-5), 7.16–7.38 (m, 11H, H-6, aromatic-CH).

6.1.2. Synthesis of *cis*- and *trans*-2-benzhydryl-tetrahydropyran-4-ol (3a) and (3b). $NaCNBH_3$ (0.75 g, 12 mmol) was added portionwise to a mixture of 2-diphenylmethyl-2,3-dihydro-4*H*-pyran-4-one **2** (1.05 g, 4 mmol) and boron trifluoride etherate (1.99 g, 14 mmol) in dry THF (50 mL) cooled to −78 °C. The reaction mixture was allowed to reach room temperature and 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 organic phase was combined and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure, and purification by flash chromatography (hexane/ethyl acetate 7:3) first afforded *trans*-2-benzhydryl-tetrahydropyran-4-ol **3a** (0.73 g, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.50–1.58 (m, 4H, H-3, H-5eq, OH), 1.84 (m, 1H, H-5ax), 3.79 (m, 1H, H-6eq), 3.88 (d, $J = 8.80$ Hz, $(Ph)_2CH$), 3.91 (dt, $J = 3.20$, 11.20 Hz, 1H, H-6ax), 4.18 (m, 1H, H-4eq), 4.52 (dt, $J = 4.00$, 8.80 Hz, 1H, H-2), 7.16–7.38 (m, 10H, aromatic-CH).

Eluted second was *cis*-2-benzhydryl-tetrahydropyran-4-ol, **3b** (0.30 g, 28.1% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (q, $J = 12.00$ Hz, 1H, H-3ax), 1.46 (dq, $J = 4.80$, 12.00 Hz, 1H, H-5ax), 1.74–1.86 (m, 2H, H-3eq, H-5eq), 3.40 (dt, $J = 2.00$, 12.00 Hz, 1H, H-6ax), 3.71 (m, 1H, H-4), 3.94–4.04 (m, 2H, H-6eq, $(Ph)_2CH$), 7.15–7.4 (m, 10H, aromatic-CH).

6.1.3. Procedure A. Synthesis of methanesulfonic acid *trans*-2-benzhydryl-tetrahydro-pyran-4-yl ester (4a). Methanesulfonyl chloride (0.62 g, 5.41 mmol) in dry methylene chloride (10 mL) was added dropwise to a mixture of *trans*-2-benzhydryl-tetrahydropyran-4-ol **3a** (0.73 g, 2.70 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 gradually allowed to reach 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, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and purification by flash chromatography gave compound **4a** (0.93 g, 99.9% yield) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): 1.61 (m, 1H, H-3ax), 1.80–1.96 (m, 4H, –OH, H-3eq, H-5), 2.96 (s, 3H, CH_3SO_2), 3.80–3.94 (m, 3H, H-6, $(Ph)_2CH$), 4.46 (dt, $J = 2.00$, 10.00 Hz, 1H, H-2), 5.10 (m, 1H, H-4), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.4. Synthesis of methanesulfonic acid *cis*-2-benzhydryl-tetrahydro-pyran-4-yl ester (4b). *cis*-2-Benzhydryltetrahydro-pyran-4-ol **3b** (0.30 g, 1.12 mmol) was reacted with methanesulfonyl chloride (0.26 g, 2.24 mmol) (Procedure A) to give compound **4b** (0.38 g, 98%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): 1.54 (m, 1H, H-3ax), 1.82 (m, 1H, H-5ax), 1.95 (m, 1H, H-3eq), 2.10 (m,1H, H-5eq), 2.95 (s, 3H, CH_3SO_2), 3.46 (dt, 1H, H-6ax), 3.96 (d, 1H, $(Ph)_2CH$), 4.10 (m, 2H, H-2, H-6eq), 4.83 (m, 1H, H-4), 7.15–7.38 (m, 10H, aromatic-CH).

6.1.5. Procedure B. Synthesis of *cis*-4-azido-2-benzhydryl-tetrahydropyran (5a). Into a solution of methanesulfonic acid *trans*-2-diphenylmethylpyran-4-yl ester **4a** (0.33 g, 0.95 mmol) in dry DMF (40 mL) was added sodium azide (0.18 g, 2.85 mmol). The mixture was heated to 100 °C and stirred for 4 h. The mixture was diluted with ethyl ether, washed with 2 M aqueous $NaHCO_3$ and brine, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (hexane/ethyl acetate 9:1) afforded compound **5a** (0.23 g, 82.7% yield) as a liquid.

^{1}H NMR (500 MHz, $CDCl_3$): 1.32 (q, $J = 11.00$ Hz, 1H, H-3ax), 1.61 (dq, $J = 5.50$, 13.00 Hz, 1H, H-5ax), 1.82 (m, 1H, H-3eq), 1.90 (m, 1H, H-5eq), 3.44–3.50 (m, 2H, H-4, H-6ax), 3.96 (d, $J = 8.50$ Hz, 1H, $(Ph)_2CH$), 4.03 (dt, $J = 2.00$, 9.00 Hz, 1H, H-2), 4.08 (ddd, $J = 2.00$, 5.50, 12.50 Hz, 1H, H-6eq), 7.16–7.38 (m,10H, aromatic-CH).

6.1.6. Synthesis of *trans*-4-azido-2-benzhydryl-tetrahydropyran (5b). Methanesulfonic acid *cis*-2-benzhydryl-tetrahydro-pyran-4-yl ester **4b** (0.38 g, 1.10 mmol) was reacted with sodium azide (0.29 g, 4.4 mmol) in dry DMF (Procedure B) to yield compound **5b** (0.26 g, 80%) as a liquid.

^{1}H NMR (400 MHz, $CDCl_3$): 1.50–1.68 (m, 3H, H-3, H-5eq), 1.86 (m, 1H, H-5ax), 3.74–3.86 (m, 2H, H-6), 3.87 (d, $J = 9.20$ Hz, 1H, $(Ph)_2CH$), 4.02 (m, 1H, H-4), 4.39 (dt, $J = 3.20$, 13.00 Hz, 1H, H-2), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.7. Procedure C. Synthesis of *cis*-(2-benzhydryl-tetrahydropyran-4-yl)-amine (6a). *cis*-4-Azido-2-benzhydryl-tetrahydropyran **5a** (0.23 g, 0.78 mmol) was hydrogenated (60 psi) in the presence of 10% Pd–C (0.02 g, 10%wt) for 4 h. Reaction mixture was filtered through a short bed of Celite and removal of the solvent afforded 0.21 g (quantitative yield) product. This product was pure enough for continuation to the next reaction step.

^{1}H NMR (400 MHz, $CDCl_3$): 1.15–1.25 (m, 1H, H-3), 1.40–1.52 (m, 1H, H-3), 1.70–1.88 (m, 2H, H-5), 2.99 (m, 1H, H-4), 3.41 (dt, $J = 2.00$, 12.40 Hz, 1H, H-6ax), 3.90–4.06 (m, 3H, H-2, H-6ax, $(Ph)_2CH$), 4.70 (br s, 2H, NH_2), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.8. Synthesis of *trans*-(2-benzhydryl-tetrahydropyran-4-yl)-amine (6b). *trans*-4-Azido-2-benzhydryl-tetrahydropyran **5b** (0.26 g, 0.89 mmol) was hydrogenated (Procedure C) to yield compound **6b** (0.24 g, quantitative).

^{1}H NMR (300 MHz, $CDCl_3$): 1.21–1.40 (m, 4H, H-3, NH_2), 1.59 (m, 1H, H-5ax), 1.87 (m, 1H, H-5eq), 3.37 (m, 1H, H-4), 3.77 (m, 1H, H-6eq), 3.91 (dt, $J = 2.40$, 11.70 Hz, 1H, H-6ax), 3.94 (d, $J = 9.30$ Hz, 1H, $(Ph)_2CH$), 4.56 (dt, $J = 2.40$, 10.20 Hz, 1H, H-2), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.9. Procedure D. Synthesis of *cis*-(2-benzhydryl-tetrahydropyran-4-yl)-(4-fluorobenzyl)-amine (7a). Into a solution of *cis*-(2-benzhydryl-tetrahydro-pyran-4-yl)-amine **6a** (0.20 g, 0.75 mmol), 4-fluorobenzaldehyde (0.83 g, 0.67 mmol), and glacial acetic acid (0.45 g, 0.75 mmol) in 1,2-dichloroethane (20 mL) was added portion wise $NaCNBH_3$ (0.57 g, 0.90 mmol) dissolved in methanol (5 mL). After 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 methylene chloride (3 × 30 mL). The combined organic phase was washed with brine, water and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo to collect the crude residue. The residue was purified by flash chromatography (hexane/ethyl acetate/triethylamine 3:2:0.2) to give *cis*-(2-benzhydryl-tetrahydro-pyran-4-yl)-(4-fluorobenzylamino)-tetrahydropyran **7a** (0.20 g, 72.6%) as a liquid.

^{1}H NMR (500 MHz, $CDCl_3$): 1.13 (q, $J = 10.50$ Hz, 1H, H-3ax), 1.32 (broad, NH), 1.38 (dq, $J = 5.00$, 12.50 Hz, 1H, H-5ax), 1.74 (m, 1H, H-3eq), 1.87 (m, 1H, H-5eq), 2.72 (tt, $J = 4.00$, 11.50 Hz, 1H, H-4), 3.44 (dt, $J = 2.00$, 12.00 Hz, 1H, H-6ax), 3.68 (d, $J = 13.50$ Hz, 1H, (F)Ph–CH), 3.75 (d, $J = 13.00$ Hz, 1H, (F)Ph–CH), 3.94 (d, $J = 9.00$ Hz, 1H, $(Ph)_2CH$), 4.00–4.08 (m, 2H, H-2, H-6eq), 6.90–7.38 (m, 14H, aromatic-CH).

Free base was converted into its oxalate salt: mp 177–181 °C, Anal. [$C_{25}H_{26}NOF{\cdot}(COOH)_2$] C, H, N.

6.1.10. Synthesis of *trans*-(2-benzhydryl-tetrahydropyran-4-yl)-(4-fluorobenzyl)-amine (7b). *trans*-(2-Benzhydryl-tetrahydro-pyran-4-yl)-amine **6b** (0.24 g, 0.90 mmol) was reacted with 4-fluorobenzaldehyde (0.11 g, 0.90 mmol) in presence of acetic acid (0.05 g, 0.90 mmol), and then reduced with $NaCNBH_3$ (0.07 g, 1.08 mmol) to yield compound **7b** (0.18 g, 54%) (Procedure D).

^{1}H NMR (400 MHz, $CDCl_3$): 1.24 (br s, 1H, –NH), 1.28 (m, 1H, H-3), 1.45–1.58 (m, 2H, H-3, H-5eq), 1.83 (tt, $J = 4.00$, 13.00 Hz, 1H, H-5ax), 3.07 (m, 1H, H-4), 3.65 (s, 2H, (F)Ph–CH_2), 3.75 (m, 1H, H-6eq), 3.91 (d, $J = 9.60$ Hz, 1H, $(Ph)_2CH$), 3.94 (dt, $J = 2.40$, 12.00 Hz, 1H, H-6ax), 4.59 (dt, $J = 3.20$, 9.60 Hz, 1H, H-2), 6.90–7.40 (m, 14H, aromatic-CH).

Free base was converted into its oxalate salt: mp 185–187 °C, Anal. [$C_{25}H_{26}NOF{\cdot}(COOH)_2$] C, H, N.

6.1.11. Synthesis of 1,1-diphenyl-hex-5-en-2-ol (8). A dry three-neck, round-bottom flask fitted with a reflux condenser, air-balance drop funnel and nitrogen inlet was charged with Mg (0.11 g, 4.44 mmol) and a crystal of I_2. The flask was warmed (heat gun) to volatilize the I_2 under vacuum, and was allowed to cool. Dry ethyl ether (10 mL) was added next followed by introduction of catalytic neat 4-bromo-1-butene (0.02 g). The reaction was initiated by brief warming and then the rest of total amount of bromide (0.40 g, 2.96 mmol) in dry ethyl ether (5 mL) was added dropwise over 5 min. The mixture was refluxed for 30 min and then was allowed to reach 0 °C. Into the stirred Grignard reagent solution was added dropwise a solution of diphenylacetaldehyde **1** (0.64 g, 3.26 mmol) in dry ethyl ether (5 mL), and the reaction mixture was stirred for an additional 3.5 h at room temperature. Saturated aqueous $NaHCO_3$ was added to the reaction mixture at 0 °C, organic phase was separated and the aqueous phase was extracted thrice with ethyl ether (3 × 20 mL). Combined organic phase was washed with brine and water, then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and flash chromatography of the crude residue (SiO2, hexane/ethyl acetate 9:1) gave 1,1-diphenyl-hex-5-en-2-ol **8** (0.68 g, 91%) as a liquid.

^{1}H NMR (400 MHz, $CDCl_3$): 1.45–1.70 (m, 2H, H-3), 1.69 (br d, –OH), 2.10–2.40 (m, 2H, H-4), 3.91 (d, $J = 8.40$ Hz, 1H, H-1), 4.39 (m, 1H, H-2), 4.95–5.10 (m, 2H, H-6), 5.81 (m, 1H, H-5), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.12. Synthesis of 1,1-diphenyl-2-(1-ethenoxy)-hex-5-ene (9). Into a mixture of 1,1-diphenyl-hex-5-en-2-ol **8** (7.00 g, 27.78 mmol) in ethyl vinyl ether (250 mL) was added $Hg(OCOCF_3)_2$ (2.37 g, 5.56 mmol) and was stirred overnight at room temperature. The reaction mixture was neutralized by addition of saturated aqueous $NaHCO_3$. Organic phase was separated and the aqueous layer was extracted with ethyl ether, dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (hexane/ethyl acetate 20:1) gave 1,1-diphenyl-2-(1-ethenoxy)-hex-5-ene **9** (5.10 g, 66%) as a liquid.

^{1}H NMR (400 MHz, $CDCl_3$): 1.58–1.78 (m, 2H, H-3), 2.08–2.30 (m, 2H, H-4), 3.86 (dd, $J = 1.60$, 8.40 Hz, 1H, H-2′), 4.15 (d, $J = 8.00$ Hz, 1H, H-1), 4.25 (dd, $J = 1.60$, 14.00 Hz, 1H, H-2′), 4.50 (m, 1H, H-2), 5.00 (m, 2H, H-6), 5.77 (m, 1H, H-5), 6.15 (dd, $J = 6.80$, 14.80 Hz, 1H, H-1′), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.13. Synthesis of 2-benzhydryl-3,4-dihydro-2*H*-pyran (10). A solution of 1,1-diphenyl-2-(1-ethenoxy)-hex-5-ene **9** (5.10 g, 18.30 mmol) and Grubb's catalyst, benzylidene-bis(tricyclohexylphosphine)dichloro ruthenium (1.50 g, 1.83 mmol) in benzene (200 mL) was heated under reflux for 20 h. The solvent was removed under vacuo and the residue was chromatographed over silica gel (hexane/ethyl acetate 20:1) to give 2-benzhydryl-3,4-dihydro-2*H*-pyran **10** (4.25 g, 92.6%) as a liquid.

^{1}H NMR (400 MHz, $CDCl_3$): 1.52–1.66 (m, 1H, H-3), 1.76–1.84 (m, 1H, H-3), 1.92–2.14 (m, 2H, H-4), 4.08 (d, $J = 9.20$ Hz, 1H, Ph_2CH), 4.59 (dt, $J = 2.40$, 8.80 Hz, 1H, H-2), 4.72 (m, 1H, H-5), 6.38 (d, $J = 6.04$ Hz, 1H, H-6), 7.16–7.50 (m, 10H, aromatic-CH).

6.1.14. Synthesis of *trans*-6-benzhydryl-tetrahydropyran-3-ol (11). Into a solution of 0.5 M 9-BBN–THF complex (24 mL, 12 mmol) in dry THF (20 mL) was added in a drop wise manner 2-diphenyl-3,4-dihydro-2*H*-pyran **10** (1.00 g, 4 mmol) dissolved in dry THF (10 mL). The mixture was kept under stirring at room temperature. After the completion of initial addition reaction, the intermediate reaction mixture was oxidized with 5.3 mL 3 N sodium hydroxide and 3 mL of 30% hydrogen peroxide. The reaction was continued at 55 °C for 1 h to insure the completion of oxidation. After the mixture was diluted with satd aqueous $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined extract was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography (hexane/ethyl acetate 7:3) to furnish *trans*-6-benzhydryl-tetrahydropyran-3-ol **11** (1.00 g, 93.5%) as a liquid.

^{1}H NMR (300 MHz, $CDCl_3$): 1.32–1.44 (m, 2H, H-5), 1.54–1.64 (m, 1H, H-4), 1.75 (br s, 1H, OH), 2.02–2.14 (m, 1H, H-4), 3.14 (t, $J = 10.20$ Hz, 1H, H-2ax), 3.67 (m, 1H, H-3), 3.90 (d, $J = 9.30$ Hz, 1H, Ph_2CH), 3.95–4.04 (m, 2H, H-2eq, H-6), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.15. Synthesis of 6-benzhydryl-dihydro-pyran-3-one (12). Into a solution of DMSO (0.13 g, 1.64 mmol) in methylene chloride (5 mL) at −78 °C was added a solution of oxalyl chloride (0.11 g, 0.82 mmol) in methylene chloride (1 mL) in a drop wise manner. A solution of *trans*-2-diphenylmethyl-tetrahydropyran-5-ol **11** (0.20 g, 0.75 mmol) in methylene chloride (2 mL) was added next. The reaction was continued for 15 min, triethylamine (0.38 g, 3.73 mmol) was next added portion wise and the reaction mixture was allowed to come to room temperature for over a period of 30 min. Additional methylene chloride (10 mL) was added, and washed with satd aqueous $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. Removal of the solvent and purification by flash chromatography (SiO_2, hexane/ethyl acetate 8.5:1.5) gave 6-benzhydryl-dihydro-pyran-3-one **12** (0.18 g, 91%) as a liquid.

^{1}H NMR (300 MHz, $CDCl_3$): 1.90–1.98 (m, 2H, H-5), 2.38–2.62 (m, 2H, H-4), 4.00 (d, $J = 17.10$ Hz, 1H, H-2), 4.05 (d, $J = 9.00$ Hz, 1H, Ph_2CH), 4.17 (dd, $J = 1.80$, 16.20 Hz, 1H, H-2), 4.44 (dt, $J = 5.20$, 8.40 Hz, 1H, H-6), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.16. Synthesis of *trans*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-fluorobenzy)-amine (16a). 6-Benzhydryl-dihydro-pyran-3-one **12** (0.18 g, 0.68 mmol) was reacted with 4-fluorobenzylamine (0.08 g, 0.68 mmol) in the presence of glacial acetic acid (0.04 g, 0.68 mmol) in 1,2-dichloroethane (10 mL) at room temperature, and then reduced by $NaCNBH_3$ (0.05 g, 0.81 mmol) (Procedure D) to yield a mixture of **16a** and **16b**. *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-(4-fluorobenzyl)-amine **16b** was eluted first (0.04 g, 15%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (m, 1H, H-5), 1.46–1.72 (m, 2H, H-5, H-4), 1.94 (m, 1H, H-4), 2.03 (br m, 1H, NH), 2.64 (m, 1H, H-3), 3.57 (dd, $J = 1.80$, 11.40 Hz, 1H, H-2ax), 3.75 (m, 2H, (F)Ph–CH_2), 3.95–4.14 (m, 3H, H-6, H-2eq, Ph_2CH), 6.90–7.38 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 229–230 °C, Anal. [$C_{25}H_{26}NOF{\cdot}(COOH)_2$] C, H, N.

Eluted second was *trans*-(6-benzhydryl-tetrahydro-pyran-3-yl)-(4-fluorobenzyl)-amine **16a** (0.11 g, 45%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.24–1.44 (m, 2H, H-5), 1.55 (m, 1H, H-4), 1.75 (br m, NH), 2.02 (m, 1H, H-4), 2.68 (m, 1H, H-3), 3.11 (t, $J = 10.80$ Hz, 1H, H-2ax), 3.76 (s, 2H, (F)Ph–CH_2), 3.89 (d, $J = 9.00$ Hz, 1H, Ph_2CH), 3.99 (dt, $J = 3.00$, 8.70 Hz, 1H, H-6), 4.08 (m, 1H, H-2eq) 6.90–7.38 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 141–143 °C, Anal. [$C_{25}H_{26}NOF{\cdot}(COOH)_2 0.65H_2O$] C, H, N.

6.1.17. Synthesis of methanesulfonic acid *trans*-6-benzhydryl-tetra-hydropyran-3-yl ester (13). Methanesulfonyl chloride (0.33 g, 2.87 mmol) was reacted with *trans*-6-benzhydryl-tetrahydropyran-3-ol **11** (0.38 g, 1.43 mmol) in the presence of triethylamine (0.22 g, 2.15 mmol) in methylene chloride (10 mL) to give *trans*-6-benzhydryl-tetrahydropyran-3-yl methanesulfonate **13** (0.39 g, 77.8%) as an oil (Procedure A).

^{1}H NMR (400 MHz, $CDCl_3$): 1.47 (m, 1H, H-5), 1.62–1.78 (m, 2H, H-5, H-4), 2.25 (m, 1H, H-4), 2.96 (s, 3H, CH_3SO_2), 3.36 (t, $J = 10.40$ Hz, 1H, H-2ax), 3.89 (d, $J = 8.80$ Hz, 1H, Ph_2CH), 4.00 (dt, $J = 2.00$, 9.60 Hz, 1H, H-6), 4.14 (m, 1H, H-2eq), 4.61 (m, 1H, H-3), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.18. Synthesis of *cis*-3-azido-6-benzhydryl-tetrahydropyran (14). *trans*-6-Diphenylmethyl-tetrahydropyran-3-yl methanesulfonate **13** (0.39 g, 1.12 mmol) in dry DMF (50 mL) was reacted with sodium azide (0.22 g, 3.35 mmol) to yield *cis*-3-azido-6-diphenylmethyl-tetrahydropyran **14** (0.30 g, 92%) as an oil (Procedure B).

^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (m, 1H, H-5), 1.63 (m, 1H, H-5), 1.76 (m, 1H, H-4), 1.96 (m, 1H, H-4), 3.53 (m, 1H, H-3), 3.61 (dd, $J = 2.00$, 12.60 Hz, 1H, H-2), 3.95–4.10 (m, 3H, H-2, H-6, Ph_2CH), 7.16–7.38 (m, 10H, aromatic-CH).

6.1.19. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-amine (15). *cis*-5-Azido-2-diphenylmethyl-tetrahydropyran **14** (0.30 g, 1.02 mmol) in methanol (25 mL) was hydrogenated in presence of 10% Pd–C (0.03 g, 10% wt) for 4 h (Procedure C) to give *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.21 g, 78%) as an oil.

^{1}H NMR (400 MHz, CD_3OD): 1.31 (m, 1H, H-5eq), 1.54 (m, 1H, H-5ax), 1.70–1.86 (m, 2H, H-4), 2.90 (br s, 1H, H-3), 3.66–3.84 (m, 2H, H-2), 3.98 (d, $J = 9.20$ Hz, 1H, Ph_2CH), 4.18 (dt, $J = 2.00$, 9.60 Hz, 1H, H-6), 7.10–7.40 (m, 10H, aromatic-CH).

Free base was converted to HCl salt: mp 260–261 °C, Anal. [$C_{18}H_{21}NO{\cdot}HCl{\cdot}0.2H_2O$] C, H, N.

6.1.20. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-fluorobenzyl)-amine (16b). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.21 g, 0.79 mmol) was reacted with 4-fluorobenzaldehyde (0.10 g, 0.79 mmol) in the presence of glacial acetic acid (0.05 g, 0.79 mmol) in 1,2-dichloroethane (20 mL), and then reduced by $NaCNBH_3$ (0.06 g, 0.95 mmol) in methanol (5 mL) (Procedure D) to give compound **16b** (0.24 g, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (m, 1H, H-5), 1.46–1.72 (m, 2H, H-5, H-4), 1.94 (m, 1H, H-4), 2.03 (br m, 1H, NH), 2.64 (m, 1H, H-3), 3.57 (dd, $J=1.80$, 11.40 Hz, 1H, H-2ax), 3.75 (m, 2H, (F)Ph–CH_2), 3.95–4.14 (m, 3H, H-6, H-2eq, Ph_2CH), 6.90–7.38 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 229–230 °C, Anal. $[C_{25}H_{26}NOF{\cdot}(COOH)_2]$ C, H, N.

6.1.21. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-cyano-benzyl)-amine (16c). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.15 g, 0.56 mmol) was reacted with 4-cyanobenzaldehyde (0.07 g, 0.56 mmol) in the presence of glacial acetic acid (0.03 g, 0.56 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.04 g, 0.67 mmol) in methanol (5 mL) (Procedure D) to give compound **16c** (0.17 g, 80%) as an oil.

^1H NMR (300 MHz, $CDCl_3$): 1.36 (m, 1H, H-5), 1.46–1.58 (m, 1H, H-5), 1.58–1.74 (m, 1H, H-4), 1.93 (m, 1H, H-4), 2.62 (br m, 1H, H-3), 3.59 (dd, $J=1.80$, 11.70 Hz, H-2ax), 3.83 (m, 2H, (CN)Ph–CH_2), 3.95–4.16 (m, 3H, H-6, H-2eq, Ph_2CH), 7.16–7.62 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 241–242 °C, Anal. $[C_{26}H_{26}N_2O{\cdot}(COOH)_2]$ C, H, N.

6.1.22. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-nitro-benzyl)-amine (16d). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.10 g, 0.38 mmol) was reacted with 4-nitrobenzaldehyde (0.06 g, 0.38 mmol) in the presence of glacial acetic acid (0.02 g, 0.38 mmol) in 1,2-dichloroethane (20 mL), and then reduced by $NaCNBH_3$ (0.03 g, 0.45 mmol) in methanol (5 mL) (Procedure D) to give compound **16d** (0.12 g, 80%) as an oil.

^1H NMR (300 MHz, $CDCl_3$): 1.35 (m, 1H, H-5), 1.53 (m, 1H, H-5), 1.67 (tt, $J=3.60$, 13.50 Hz, 1H, H-4), 1.91 (m, 2H, H-4, NH), 2.62 (m, 1H, H-3), 3.58 (dd, $J=1.80$, 9.60 Hz, 1H, H-2ax), 3.87 (m, 2H, (NO_2)Ph–CH_2), 3.92–4.14 (m, 3H, H-6, H-2eq, Ph_2CH), 7.14–7.54, 8.12–8.20 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 236–238 °C, Anal. $[C_{25}H_{26}N_2O_3{\cdot}(COOH)_2]$ C, H, N.

6.1.23. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-methoxy-benzyl)-amine (16e). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.15 g, 0.56 mmol) was reacted with 4-methoxybenzaldehyde (0.08 g, 0.56 mmol) in the presence of glacial acetic acid (0.03 g, 0.56 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.04 g, 0.67 mmol) in methanol (5 mL) (Procedure D) to give compound **16e** (0.17 g, 78%) as an oil.

^1H NMR (300 MHz, $CDCl_3$): 1.35 (m, 1H, H-5), 1.48–1.76 (m, 2H, H-5, H-4), 1.88–2.02 (m, 1H, H-4), 2.68 (br s, 1H, H-3), 3.59 (dd, $J=12.30$, 2.40 Hz,1H, H-2ax), 3.76 (d, $J=7.20$ Hz, 2H, (CH_3O)Ph–CH_2), 3.83 (s, 3H, CH_3O), 3.98–4.16 (m, 3H, H-6, H-2eq, Ph_2CH), 6.88–6.94, 7.18–7.44 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 215–217 °C, Anal. $[C_{26}H_{29}NO_2{\cdot}(COOH)_2]$ C, H, N.

6.1.24. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(3-indole-methyl)-amine (16f). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.12 g, 0.45 mmol) was reacted with 3-indole-carboxaldehyde (0.07 g, 0.45 mmol) in the presence of glacial acetic acid (0.03 g, 0.45 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.03 g, 0.54 mmol) in methanol (5 mL) (Procedure D) to give compound **16f** (0.15 g, 82%) as an oil.

^1H NMR (300 MHz, $CDCl_3$): 1.33 (m, 1H, H-5), 1.48–1.76 (m, 2H, H-5, H-4), 1.99 (m, 1H, H-4), 2.27 (br s, 1H, NH), 2.79 (m, 1H, H-3), 3.60 (dd, $J=1.80$, 12.30 Hz, 1H, H-2ax), 4.00 (s, 2H, indole-3-CH_2), 4.02–4.20 (m, 3H, H-6, H-2eq, Ph_2CH), 7.00–7.80 (m, 14H, aromatic-CH), 8.42 (s, 1H, indole-NH).

Free base was converted into oxalate: mp 177–179 °C, Anal. $[C_{27}H_{28}N_2O{\cdot}(COOH)_2 0.5H_2O]$ C, H, N.

6.1.25. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(2-indole-methyl)-amine (16g). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.07 g, 0.25 mmol) was reacted with 2-indole-carboxaldehyde (0.04 g, 0.25 mmol) in the presence of glacial acetic acid (0.02 g, 0.25 mmol) in 1,2-dichloroethane (20 mL), and then reduced by $NaCNBH_3$ (0.02 g, 0.3 mmol) in methanol (5 mL) (Procedure D) to give compound **16g** (0.08 g, 82%) as an oil.

^1H NMR (300 MHz, $CDCl_3$): 1.34 (m, 1H, H-5), 1.56 (m, 1H, H-5), 1.69 (tt, $J=3.60$, 13.50 Hz, 1H, H-4), 1.99 (m, 1H, H-4), 2.27 (br m, 1H, NH), 2.79 (br s, 1H, H-3), 3.60 (dd, $J=10.70$, 1.60 Hz, 1H, H-2ax), 3.96 (s, 2H, 2-indole-CH_2), 3.92–4.14 (m, 3H, H-6, H-2eq, Ph_2CH), 6.35 (s, 1H, indole-3-H), 7.05–7.60 (m, 14H, aromatic-CH), 9.1 (s, 1H, indole-NH).

Free base was converted into oxalate: mp 215–216 °C, Anal. $[C_{27}H_{28}N_2O{\cdot}(COOH)_2 0.5H_2O]$ C, H, N.

6.1.26. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-hydroxy-benzyl)-amine (16h). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.15 g, 0.56 mmol) was reacted with 4-hydroxybenzaldehyde (0.07 g, 0.56 mmol) in the presence of glacial acetic acid (0.03 g, 0.56 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.04 g, 0.67 mmol) in methanol (5 mL) (Procedure D) to give compound **16h** (0.17 g, 80%) as an oil.

^1H NMR (400 MHz, $CDCl_3$): 1.34 (m, 1H, H-5), 1.50 (m, 1H, H-5), 1.67 (tt, $J=4.00$, 13.60 Hz, 1H, H-4), 2.02 (m, 1H, H-4), 2.71 (m, 1H, H-3), 3.56 (dd, $J=1.60$, 11.60 Hz, 1H, H-2ax), 3.64 (m, 2H, (HO)Ph–CH_2), 3.95 (d, $J=8.00$ Hz, 1H, Ph_2CH), 4.02–4.14 (m, 2H, H-6, H-2eq), 6.52 (m, 2H, aromatic-CH), 6.90–7.38 (m, 12H, aromatic-CH).

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

6.1.27. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(3,4-dichloro-benzyl)-amine (16i). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.10g, 0.38 mmol) was reacted with 3,4-dichlorobenzaldehyde (0.07 g, 0.38 mmol) in the presence of glacial acetic acid (0.02 g, 0.38 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.03 g, 0.45 mmol) in methanol (5 mL) (Procedure D) to give compound **16i** (0.12 g, 75%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): 1.34 (m, 1H, H-5), 1.52 (m, 1H, H-5), 1.66 (m, 1H, H-4), 1.79 (br s, 1H, NH), 1.91 (m, 1H, H-4), 2.61 (m, 1H, H-3), 3.57 (dd, $J = 1.50$, 11.50 Hz, 1H, H-2ax), 3.72 (m, 2H, (Cl,Cl)Ph–CH_2), 3.94–4.05 (m, 2H, H-2eq, Ph_2CH), 4.08 (dt, $J = 2.00$, 8.50 Hz, 1H, H-6), 7.10–7.50 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 251–252 °C, Anal. [$C_{25}H_{25}NOCl_2$·$(COOH)_2$] C, H, N.

6.1.28. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(3,4-difluorobenzyl)-amine (16j). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.10 g, 0.38 mmol) was reacted with 3,4-difluorobenzaldehyde (0.06 g, 0.38 mol) in the presence of glacial acetic acid (0.02 g, 0.38 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.03 g, 0.45 mmol) in methanol (5 mL) (Procedure D) to give compound **16j** (0.12 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.34 (m, 1H, H-5), 1.52 (m, 1H, H-5), 1.66 (tt, $J = 3.60$, 13.50 Hz, 1H, H-4), 1.76 (br s, 1H, NH), 1.92 (m, 1H, H-4), 2.61 (m, 1H, H-3), 3.57 (dd, $J = 1.80$, 11.40 Hz, 1H, H-2ax), 3.72 (m, 2H, (F,F)Ph–CH_2), 3.94–4.14 (m, 3H, H-6, H-2eq, Ph_2CH), 6.90–7.38 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 234–235 °C, Anal. [$C_{25}H_{25}NOF_2$·$(COOH)_2$] C, H, N.

6.1.29. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-benzyl-amine (16k). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.03 g, 0.11 mmol) was reacted with benzaldehyde (0.01 g, 0.11 mmol) in the presence of glacial acetic acid (0.01 g, 0.11 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.01 g, 0.14 mmol) in methanol (5 mL) (Procedure D) to give compound **16k** (0.03 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.30 (m, 1H, H-5), 1.44–1.70 (m, 2H, H-5, H-4), 1.80 (br s, 1H, NH), 1.92 (m, 1H, H-4), 2.64 (m, 1H, H-3), 3.55 (dd, $J = 1.80$, 11.70 Hz, 1H, H-2ax), 3.77 (m, 2H, Ph–CH_2), 3.92–4.10 (m, 3H, Ph_2CH, H-6, H-2eq), 7.00–7.38 (m, 15H, aromatic-CH).

Free base was converted into oxalate: mp 208–210 °C, Anal. [$C_{25}H_{27}NO$·$(COOH)_2$] C, H, N.

6.1.30. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-bromo-benzyl)-amine (16l). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.04 g, 0.15 mmol) was reacted with 4-bromobenzaldehyde (0.03 g, 0.15 mmol) in the presence of glacial acetic acid (0.01 g, 0.15 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.01 g, 0.18 mmol) in methanol (5 mL) (Procedure D) to give compound **16l** (0.05 g, 80%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): 1.31 (m, 1H, H-5), 1.50 (m, 1H, H-5), 1.64 (m, 1H, H-4), 1.80 (br s, 1H, NH), 1.90 (m, 1H, H-4), 2.61 (m, 1H, H-3), 3.56 (dd, $J = 1.60$, 11.60 Hz, 1H, H-2ax), 3.72 (m, 2H, (Br)Ph–CH_2), 3.94–4.30 (m, 2H, Ph_2CH, H-2eq), 4.07 (dt, $J = 1.60$, $J = 9.60$ Hz, 1H, H-6), 7.00–7.42 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 250–252 °C, Anal. [$C_{25}H_{26}BrNO$·$(COOH)_2$] C, H, N.

6.1.31. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-iodo-benzyl)-amine (16m). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.04 g, 0.15 mmol) was reacted with 4-iodobenzaldehyde (0.05 g, 0.15 mmol) in the presence of glacial acetic acid (0.01 g, 0.15 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.01 g, 0.18 mmol) in methanol (5 mL) (Procedure D) to give compound **16m** (0.06 g, 81%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): 1.28 (m, 1H, H-5), 1.50 (m, 1H, H-5), 1.64 (m, 1H, H-4), 1.72 (br s, 1H, NH), 1.90 (m, 1H, H-4), 2.60 (m, 1H, H-3), 3.56 (dd, $J = 1.60$, 12.40 Hz, 1H, H-2ax), 3.71 (m, 2H, (I)Ph–CH_2), 3.92–4.02 (m, 2H, Ph_2CH, H-2eq), 4.06 (dt, $J = 1.60$, 9.20 Hz, 1H, H-6), 7.00–7.70 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 243–244 °C, Anal. [$C_{25}H_{26}INO$·$(COOH)_2$] C, H, N.

6.1.32. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(1*H*-iodo-5-ylmethyl)-amine (16n). *cis*-(6-Benzhydryl-tetrahydropyran-3-yl)-amine **15** (0.05 g, 0.19 mmol) was reacted with 5-indole-carboxaldehyde (0.03 g, 0.19 mmol) in the presence of glacial acetic acid (0.01 g, 0.19 mmol) in 1,2-dichloroethane (20 mL), and $NaCNBH_3$ (0.02 g, 0.37 mmol) in methanol (5 mL) (Procedure D) to give compound **16n** (0.06 g, 82%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): 1.32 (m, 1H, H-5), 1.50–1.70 (m, 2H, H-5, H-4), 1.95 (m, 2H, H-4, NH), 2.71 (br s, 1H, H-3), 3.57 (dd, $J = 2.00$, 12.00 Hz, 1H, H-2ax), 3.88 (m, 2H, indole-CH_2), 3.96–4.12 (m, 3H, Ph_2CH, H-2eq, H-6), 6.51, 7.10–7.40, 7.57 (m, 15H, aromatic-CH), 8.36 (br s, 1H, NH).

Free base was converted into oxalate: mp 128–130 °C, Anal. [$C_{27}H_{28}N_2O$·$(COOH)_2 0.5H_2O$] C, H, N.

6.1.33. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-amino-benzyl)-amine (16o). A mixture of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-nitro-benzyl)-amine (**16f**) (0.16 g, 0.39 mmol) and $SnCl_2/2H_2O$ (0.35 g, 1.55 mmol) in EtOH/EtOAc (20 mL, 7:3) was heated to reflux for 1.5 h (monitored by TLC, Hex/EtOAc/Et_3N 5:5:0.4). After 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. After removal of the solvent, flash chromatography gave **16o**, *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-(4-amino-benzyl)-amine (0.09 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): 1.30 (m, 1H, H-5), 1.47 (m, 1H, H-5), 1.64 (tt, J = 4.00, 12.80 Hz, 1H, H-4), 1.90 (m, 1H, H-4), 2.53–2.70 (m, 3H, H-3, (NH_2)–$PhCH_2$), 3.54 (dd, J = 1.60, 11.20 Hz, 1H, H-2ax), 3.92–4.00 (m, 2H, Ph_2CH, H-2eq), 4.06 (dt, J = 2.40, 9.60 Hz, 1H, H-6), 7.06–7.38 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 151–153 °C, Anal. [$C_{25}H_{28}N_2O\cdot 2(COOH)_2 0.3H_2O$] C, H, N.

6.1.34. Synthesis of *cis*-*N*-(6-benzhydryl-tetrahydropyran-3-yl)-2-(4-fluorophenyl)-acetamide (17). Into a solution of 4-fluorophenylacetic acid (0.23 g, 1.46 mmol) in dichloromethane (25 mL) was added oxalyl chloride (0.22 g, 1.76 mmol) dissolved in dichloromethane (5 mL) at 0 °C, which was followed by addition of one drop of DMF. The reaction mixture was allowed to reach at room temperature over a period of 2 h. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane (5 mL) and was added into a solution of *cis*-(6-benzhydryl-tetrahydropyran-3-yl)-amine (0.26 g, 0.96 mmol) and triethylamine (0.31 g, 1.46 mmol) in dichloromethane (25 mL) at 0 °C. After 20 min the reaction mixture was allowed to come to room temperature. After 3 h, more dichloromethane was added and the mixture was washed in turn with 1 M $NaHCO_3$, H_2O, and brine, then dried over anhydrous Na_2SO_4. The solvent was removed under vacuo, and the residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to give *cis*-*N*-(6-benzhydryl-tetrahydropyran-3-yl)-2-(4-fluorophenyl)-acetamide **17** (0.31 g, yield 80%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): 1.10–1.40 (m, 2H, H-5), 1.60–1.93 (m, 2H, H-4), 3.49 (s, 2H, Ph–CH_2CO), 3.63 (dd, J = 1.80, 11.70 Hz, 1H, H-2ax), 3.70–3.85 (m, 2H, Ph_2CH, H-3), 3.90–4.08 (m, 2H, H-6, H-2eq), 6.90–7.40 (m, 14H, aromatic-CH).

6.1.35. Synthesis of *cis*-(6-benzhydryl-tetrahydropyran-3yl)-[2-(4-fluorophenyl)-ethyl]-amine (16p). Into a suspension of $NaBH_4$ (0.21 g, 3.33 mmol) in dry THF (20 mL) was added $BF_3\cdot Et_2O$ drop wise at 0 °C. The mixture was stirred for 1.5 h at room temperature and cooled to 0 °C. A solution of *cis*-*N*-(6-benzhydryl-tetrahydropyran-3-yl)-2-(4-fluorophenyl)-acetamide (0.17 g, 0.42 mmol) in dry THF (10 mL) was added drop wise into the solution. The mixture was refluxed overnight and cooled to room temperature. Methanol was added to quench the reaction followed by removal of solvent in vacuo. Into the residue was added 20 mL 10% HCl/MeOH and refluxed for 1 h. The reaction mixture was cooled down to room temperature and solid $NaHCO_3$ was added at 0 °C to pH 9. The aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. Flash chromatography gave **16p** *cis*-(6-benzhydryl-tetrahydropyran-3yl)-[2-(4-fluorophenyl)-ethyl]-amine (0.13 g, yield 81%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.20–1.42 (m, 2H, H-5, NH), 1.61 (m, 1H, H-5), 1.88 (m, 2H, H-4), 2.64 (m, 1H, H-3), 2.72–2.82 (m, 4H, Ph–CH_2CH_2), 3.55 (dd, J = 1.80, 11.70 Hz, 1H, H-2ax), 3.86–3.98 (m, 2H, Ph_2CH, H-2eq), 4.03 (dt, J = 3.00, 10.00 Hz, 1H, H-6), 6.90–7.40 (m, 14H, aromatic-CH).

Free base was converted into oxalate: mp 240–242 °C, Anal. [$C_{26}H_{28}NOF\cdot(COOH)_2$] C, H, N.

6.2. Biology

The affinity of test compounds in binding to rat DAT, SERT, and NET was assessed by measuring inhibition of binding of 5.0 nM [^{3}H]WIN 35,428, 3.5 nM [^{3}H]citalopram, and 1.1 nM [^{3}H]nisoxetine, respectively, exactly as described by us previously. Briefly, rat striatum was the source for DAT, and cerebral cortex for SERT and NET. Final [Na^+] was 30 mM for DAT and SERT assays, and 152 mM for NET assays. All binding assays were conducted at 0–4 °C, for a period of 2 h for [^{3}H]WIN 35,428 and [^{3}H]citalopram binding, and 3h for [^{3}H]nisoxetine binding. Nonspecific binding of [^{3}H]WIN 35,428 and [^{3}H]citalopram binding was defined with 100 μM cocaine, and that of [^{3}H]nisoxetine binding with 1 μM desipramine. Radioligand K_d values were 2.1, 3.2, and 2.2 nM, respectively. Test compounds were dissolved in dimethyl sulfoxide (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 radioligand binding. At lease five triplicate concentrations of each test compound were studied, spaced evenly around the IC_{50} value. For DAT uptake assays, uptake of 50 nM [^{3}H]DA into rat striatal synaptosomes was measured exactly as described by us previously. Briefly, rat striatal P_2 membrane fractions were incubated with test compounds for 8 min followed by the additional presence of [^{3}H]DA for 4 min at 25 °C. Nonspecific uptake was defined with 100 μM cocaine. Construction of inhibition curves and dissolvement of test compounds were as described above.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2004.07.069.

Elemental analysis results of final compounds:

Compound	Found			Calculated		
	C	H	N	C	H	N
7a	69.57	6.07	3.01	69.66	6.06	3.01
7b	69.68	6.17	3.04	69.66	6.06	3.01
16a 0.65H_2O	67.93	6.02	3.02	67.96	6.19	2.94
16b	69.60	6.09	2.97	69.66	6.06	3.01
16c	70.92	6.00	5.88	71.17	5.97	5.93
16d	65.61	5.79	5.64	65.84	5.73	5.69
16e	70.45	6.57	2.97	70.42	6.54	2.93
16f 0.5H_2O	70.68	6.32	5.55	70.29	6.31	5.65
16g 0.5H_2O	70.68	6.32	5.55	70.29	6.31	5.65
16h	70.36	6.68	3.03	69.96	6.31	3.02
16i	62.52	5.23	2.66	62.80	5.27	2.71
16j	67.09	5.70	2.88	67.07	5.63	2.90
16k	71.86	6.65	3.11	71.88	6.57	3.10
16l	61.57	5.36	2.65	61.60	5.36	2.66
16m	56.43	4.94	2.45	56.55	4.92	2.45
16n	70.05	6.29	5.40	70.29	6.30	5.65
16o 0.3H_2O	62.11	5.73	4.92	62.42	5.89	5.02
16p	69.76	6.34	2.90	70.13	6.31	2.92
15 0.2H_2O	70.41	7.57	4.17	70.32	7.34	4.55

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