Bioorganic & Medicinal Chemistry 22 (2014) 311–324

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Flexible and biomimetic analogs of triple uptake inhibitor 4-((((3*S*,6*S*)-6-benzhydryltetrahydro-2*H*-pyran-3-yl)amino)methyl) phenol: Synthesis, biological characterization, and development of a pharmacophore model

Horrick Sharma [a], Soumava Santra [a], Joy Debnath [a], Tamara Antonio [b], Maarten Reith [b,c], Aloke Dutta [a,*]

[a] Wayne State University, Department of Pharmaceutical Sciences, Applebaum College of Pharmacy & Health Sciences, Rm# 3128, Detroit, MI 48202, United States
[b] New York University, Department of Psychiatry, New York, NY 10016, United States
[c] New York University, Department of Pharmacology, New York, NY 10016, United States

ARTICLE INFO

Article history:
Received 28 September 2013
Revised 2 November 2013
Accepted 11 November 2013
Available online 19 November 2013

Keywords:
Depression
Antidepressants
Triple uptake inhibitors
Asymmetric synthesis
Pharmacophore model
Computational analysis

ABSTRACT

In this study we have generated a pharmacophore model of triple uptake inhibitor compounds based on novel asymmetric pyran derivatives and the newly developed asymmetric furan derivatives. The model revealed features important for inhibitors to exhibit a balanced activity against dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET). In particular, a 'folded' conformation was found common to the active pyran compounds in the training set and was crucial to triple uptake inhibitory activity. Furthermore, the distances between the benzhydryl moiety and the *N*-benzyl group as well as the orientation of the secondary nitrogen were also important for TUI activity. We have validated our findings by synthesizing and testing novel asymmetric pyran analogs. The present work has also resulted in the discovery of a new series of asymmetric tetrahydrofuran derivatives as novel TUIs. Lead compounds **41** and **42** exhibited moderate TUI activity. Interestingly, the highest TUI activity by lead tetrahydrofuran compounds for example, **41** and **42**, was exhibited in a stereochemical preference similar to pyran TUI for example, **D-161**.

1. Introduction

Major depressive disorder is a debilitating illness affecting 15–20% of the population in the United States.[1] According to the World Health Organization by 2020 it would be the second-most leading cause of disability worldwide making it a global health problem. It is believed that 20% of all individuals suffer from a major mood disorder at least once in their lifetime.

The 'monoamine' hypothesis has been the gold standard in understanding the underlying cause of depression. It is built on the idea that depression results from a deficiency in monoamine neurotransmission, by a reduction of monoamine levels in the synaptic cleft[2,3] or, consonant with monoaminergic volume transmission, a reduction in extracellular monoamine levels.[4] Consequently, drug development efforts have centered on increasing serotonin (5-HT) and norepinephrine (NE) neurotransmission.[5,6] Monoamine oxidase inhibitors (MAOIs) were the first class of antidepressants used.[7] They increased monoamine levels by preventing their metabolism. MAOIs were replaced by tricyclic antidepressants (TCAs) that block the reuptake of 5-HT and NE into the nerve terminal by inhibiting both 5-HT and NE transporters. TCAs were plagued by their non-specific interactions in the CNS including antagonism of adrenergic, histamine, and cholinergic receptors.[8] TCAs were subsequently superseded by selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) which were developed as second-generation antidepressants.[9–13] It has been shown that venlafaxine, an SNRI, exhibits greater response and remission rates than SSRIs.[14] Although SSRIs and SNRIs by virtue of their selective interactions at the 5-HT and NE transporters exhibited an improved profile with less adverse effects, they were not without shortcomings.[15,16] Foremost, these agents have failed to improve the efficacy and exhibit delayed onset of antidepressant response.[17] Moreover, because of relapse and unwanted side effects associated with SSRIs there is an unmet need to discover newer agents for the treatment of depression.[18,19]

Current treatment aims at alleviating the extraneuronal concentration 5-HT and NE but does not include a dopaminergic

Abbreviations: SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin/norepinephrine reuptake inhibitors; MAO, monoamine oxidase inhibitors; TCA, tricyclic antidepressants; DAT, dopamine transporter; SERT, serotonin transporter; NET, norepinephrine transporters; TUI, triple uptake inhibitor; SAR, structure–activity relationship.

* Corresponding author. Tel.: +1 313 577 1064; fax: +1 313 577 2033.
E-mail address: adutta@wayne.edu (A. Dutta).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.11.017

element. Preclinical and clinical studies have demonstrated that antidepressants can sensitize mesolimbic postsynaptic dopamine receptors thereby implicating a dopaminergic component in depression.[20–23] Mesolimbic dopamine is associated with motivation and reward-related behavior and, therefore, including dopaminergic activity should improve anhedonia that is the central component in depression.[24] This is validated by the findings that adjunct administration of the dopamine transporter blocker bupropion and an SSRI enhanced efficacy in patients refractory to SSRIs.[25,26] Moreover, Pramipexole, a D3 preferring agonist, was found to be effective in both unipolar and bipolar depression.[27]

Thus, an attractive strategy entails inhibiting the reuptake of all three monoamines: 5-HT, NE, and dopamine, and developing triple uptake inhibitors (TUIs) for the treatment of depression.[28,29] Inhibiting all the three transporters simultaneously is challenging and the desired ratio of relative potencies is still debated. It has been hypothesized that the TUIs, with their broad spectrum activity, would be able to provide faster onset, enhanced efficacy, and address anhedonia with reduced side effects that are associated with currently available antidepressants.[30] Recent efforts in this direction have led to the discovery of few potent TUIs (Fig. 1) that have proved to be efficacious in animal models of depression. These include DOV 216,303, PRC200-SS, JNJ-7925476, and GSK-372,475.[31,32] DOV 216,303 is currently undergoing clinical development and has been shown to possess promising pharmacokinetic properties and found to be as efficacious as citalopram.[32]

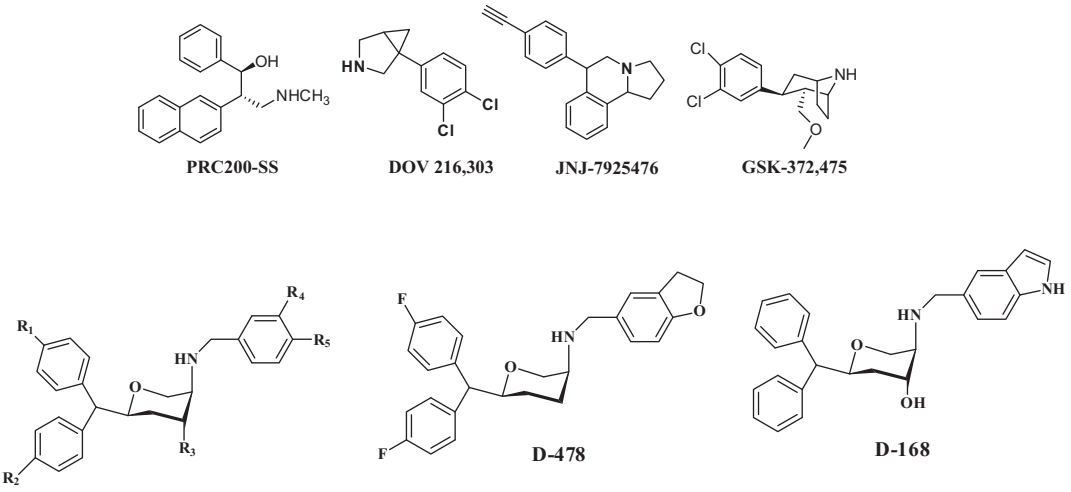
In our earlier studies we have synthesized piperidine derivatives against dopamine transporters (DAT). Further, optimization resulted in the discovery of a unique di- and tri-substituted pyran template, several derivatives of which (Fig. 1) inhibited the uptake of all three monoamine transporters.[33–36] Dual acting inhibitors as blockers of both 5-HT and NE transporters (SNRIs) or NE and dopamine transporters (DNRIs) have also been identified. Two of our lead TUIs **D-142** and **D-161** have shown to possess antidepressant activity and were found to be efficacious in animal models of depression.[37,38] In our continuous efforts to develop effective drugs to combat depression, in the present structure–activity relationship (SAR) study, we have carried out synthesis to further explore the structural requisites of asymmetric pyran derivatives, discovered new asymmetric tetrahydrofuran derivatives as TUIs, and developed a pharmacophore model.

2. Material and methods

2.1. Chemistry

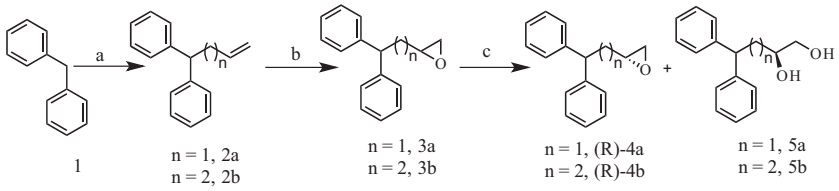
Scheme 1 shows the synthesis of (*R*)-epoxide starting materials **4a** and **4b** which were used to make target compounds **15** and **16**, respectively. Reaction of diphenylmethane with allyl bromide and 4-bromobut-1-ene in the presence of *n*-butyl lithium in anhydrous ether yielded alkene intermediates **2a** and **2b**, respectively, which upon epoxidation with *m*-CPBA gave the corresponding racemic epoxides **3a** and **3b**. The racemates **3a** and **3b** were resolved by hydrolytic kinetic resolution using Jacobsen catalyst, (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt, to yield (*R*)-**4a**,(*S*)-**5a** and (*R*)-**4b**, (*S*)-**5b**, respectively, in high enantioselectivity.

The synthesis of target compounds **15** and **16** is described in Scheme 2. The regioselective epoxide ring opening of **15** and **16** with allyl magnesium chloride and a catalytic amount of copper(I) iodide resulted in alcohol intermediates **6a** and **6b** in 93% yields. O-vinylation of **6a** and **6b** with ethyl vinyl ether and catalytic amount of mercury(II) trifluoroacetate at room temperature gave vinyl ethers **7a** (77%) and **7b** (74%), respectively. Intermediates **7a** and **7b** were immediately subjected to ring-closing metathesis (RCM) in the presence of Grubbs catalyst (1st generation) in refluxing anhydrous benzene to yield corresponding cyclic dihydropyran intermediates **8a** and **8b** in 95% and 96% yields, respectively. Intermediate **8a** was then subjected to hydroboration reaction with 9-BBN in anhydrous THF, followed by oxidation to give a

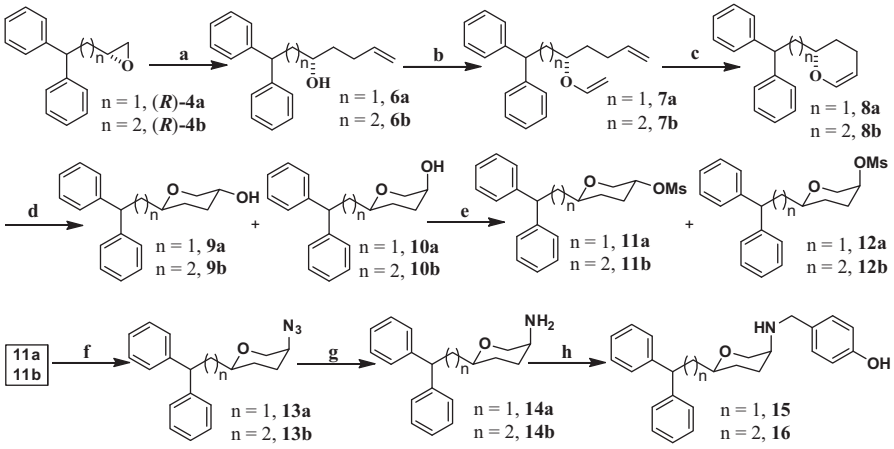


D-161: R^1 = H; R^2 = H; R^3 = H; R^4 = H; R^5 = OH
D-142: R^1 = H; R^2 = H; R^3 = OH; R^4 = H; R^5 = OCH_3
D-185: R^1 = H; R^2 = H; R^3 = H; R^4 = H; R^5 = NH_2
D-411: R^1 = H; R^2 = H; R^3 = H; R^4 = H; R^5 = OCH_3
D-391: R^1 = H; R^2 = H; R^3 = H; R^4 = OH; R^5 = H
D-199: R^1 = H; R^2 = H; R^3 = H; R^4 = H; R^5 = NO_2
D-471: R^1 = F; R^2 = F; R^3 = OH; R^4 = H; R^5 = OH
D-451: R^1 = F; R^2 = F; R^3 = H; R^4 = H; R^5 = NH_2

Figure 1. Structures of known and lead pyran-based TUIs.



Scheme 1. Reagents and conditions: (a) Anhyd THF, −78 °C, *n*-BuLi, allylbromide or 4-bromobut-1-ene, overnight, 83% for **2a**, 87% for **2b**; (b) Anhyd CH_2Cl_2, 0 °C, *m*-CPBA, overnight, 96% (c) (*R,R*)-(−)*N,N*/-bis(3,5-di-*tert*-butylsalicylidine)-1,2-cyclohexane diaminocobalt (Jacobsen's catalyst), H_2O, THF, over 99% ee and 46% yield for both **4a** and **4b**, 47% for both **5a** and **5b**.

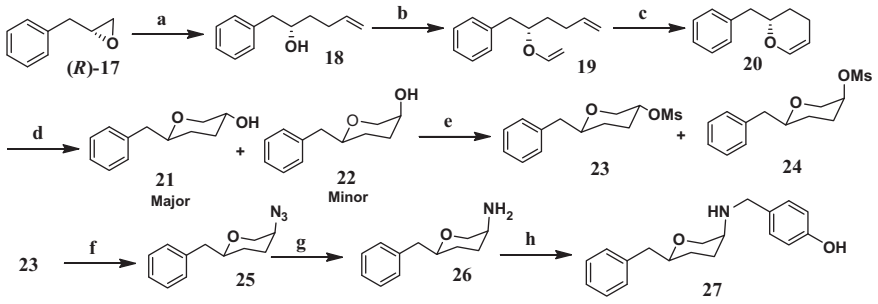


Scheme 2. Reagents and conditions: (a) allylmagnesium chloride, CuI, anhyd THF, −78 °C to rt, 24 h, 93% for **6a**, 84% for **6b**; (b) Ethylvinyl ether, $Hg(OCOCF_3)_2$,0 °C to rt, 4 h, 77% for **7a**, 74% for **7b**; (c) Grubb's catalyst (1st gen), anhyd benzene, reflux, 2 h, 95% for **8a**, 96% for **8b**; (d) (i) 9-BBN, anhyd THF, 0 °C to rt, overnight; (ii) 10% NaOH, 30% H_2O_2, 50 °C, 1 h, 95% for a mixture of **9a** and **10a**, 84% for a mixture of **9b** and **10b**; (e) CH_3SO_2Cl, Et_3N, anhyd DCM, rt, 0 °C 2 h, 69% for **11a**, 15% for **12a**, 67% for **11b**, 17% for **12b**; (f) NaN_3, DMF, 80 °C, 24 h, 86% for **13a**, 88% for **13b**; (g) H_2, Pd/C, MeOH, 1 atm, overnight, 98% for **14a**, 97% for **14b**; (h) RCHO, $Na(OAc)_3$ BH, AcOH, 1,2-dichloroethane/MeOH, 3:1, rt, overnight, 46% for **15**, 47% for **16**.

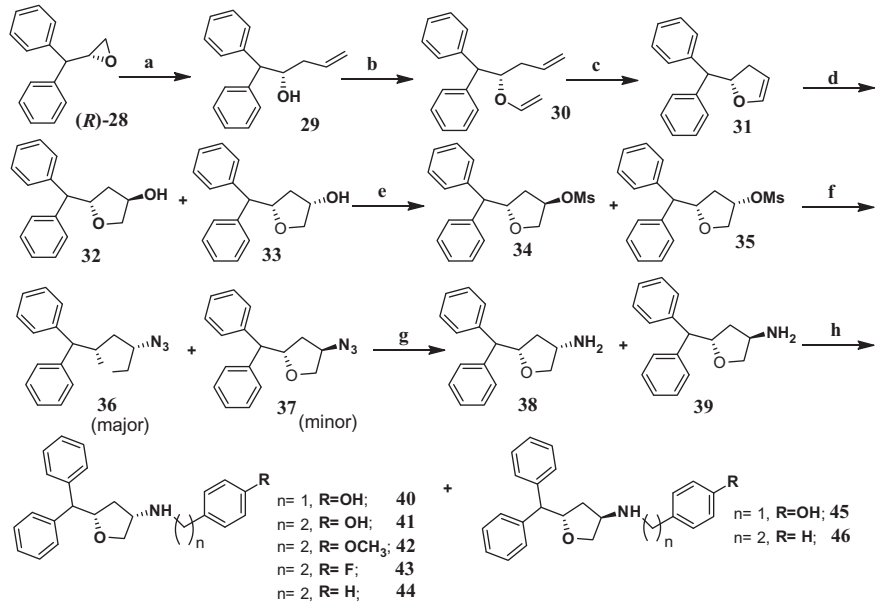
mixture of inseparable diastereomers (95%) exclusively in the favor of the *trans* isomer **9a**. Similarly, intermediate **8b**, upon hydroboration and oxidation reaction yielded inseparable diastereomers (84%) predominantly favoring the *trans* isomer **9b**. The diasteromeric mixture of **9a** and **10a** were then mesylated with methanesulfonyl chloride using triethylamine in anhydrous dichloromethane (DCM) and separated by column chromatography to afford compound **11a** as the major isomer in 69% and **12a** as the minor isomer in 15% yields. Similarly, diasteromeric mixture of **9b** and **10b**, upon mesylation gave separable isomers **11b** and **12b** in 67% and 17% yields, respectively. The stereochemistry of the *trans* isomer **9a** has been thoroughly established in our previous studies.[35] Major isomers **11a** and **11b** were then subjected to S_N2 nucleophilic substitution reaction using sodium azide in anhydrous DMF to give intermediates **13a** and **13b** in 86% and 88% yields, respectively. Hydrogenation of **13a** and **13b** with 10% Pd/C in methanol resulted in corresponding *cis*-amines **14a** and **14b** in quantitative yields. Finally, **14a** and **14b** were subjected to reductive amination reaction with benzaldehyde in the presence of sodium triacetoxyborohydride and acetic acid catalyst to yield corresponding final compounds **15** and **16** in 46% and 47% yields, respectively.

Scheme 3 shows the synthesis of compound **27**. The (*R*)-epoxide **17** was reacted with allyl magnesium chloride in the presence of copper(I) iodide catalyst to yield intermediate **18** which upon vinylation with ethylvinyl ether and mercury(II) trifluoroacetate, gave intermediate **19**. RCM reaction gave intermediate **20**, followed by regio- and stereo-specific hydroboration and oxidation that resulted in a mixture of inseparable diastereomers **21** and **22**. Mesylation reaction gave diastereomers **23** and **24** which were separated by column chromatography. The *trans* intermediate **23** was subjected to S_N2 nucleophilic substitution reaction using sodium azide to yield intermediate **25** which gave the *cis*-amine **26** upon hydrogenation with 10% Pd/C in methanol. Compound **27** was synthesized via reductive amination reaction by reacting **26** with benzaldehyde using sodium cyanoborohydride and catalytic amount of acetic acid.

The synthesis of tetrahydrofuran compounds **40–46** required some modifications in our reaction conditions and is depicted in scheme 4. Briefly, the epoxide ring in (*R*)-2-benzhydryloxirane (**28**)[36] was regioselectively opened with vinyl magnesium bromide and a catalytic amount of copper(I) iodide resulting in (*S*)-alcohol intermediate **29** in 75% yield. The alcohol intermediate was then subjected to *trans*-vinylation using ethyl vinyl ether and a catalytic amounts of mercury(II) trifluoroacetate. The reaction yielded the desired intermediate **30** in low yields (8–10%) along with the formation of an acetal side product that resulted from the reaction of in situ generated trifluoroacetic acid. Moreover, unreacted alcohol was also recovered in significant amounts. It was noted that addition of triethylamine neutralized free acid and significantly reduced the formation of the acetal side product.[39] The reaction was carried out in a sealed tube and heated to 50 °C to force the equilibrium in the forward direction. Thus, **30** was obtained in moderate yield (50%) along with the recovery of unreacted alcohol (38%) which was recycled in the synthesis. The unstable intermediate **30** was immediately subjected to RCM reaction in the presence of Grubbs catalyst (1st generation) at room temperature. The reaction was optimized by warming to 50 °C and carrying out for a longer time period (6 h) along with the portion-wise addition of the catalyst over 3 h. The resulting intermediate **31**, obtained in 53% yields, was then reacted with 9-BBN followed by oxidation to obtain an inseparable mixture of diastereomers **32** and **33**. The diasteromeric



Scheme 3. Reagents and conditions: (a) allylmagnesium chloride, anhyd Ditheyl ether, −78 °C to rt, overnight, 78%; (b) ethylvinyl ether, $Hg(OCOCF_3)_2$, rt, 4 h, 83%; (c) Grubb's catalyst (1st gen), anhyd benzene, reflux, 3 h, 84%; (d) (i) 9-BBN, anhyd THF, rt, overnight; (ii) 10% NaOH, 30% H_2O_2, 50 °C, 1 h, 86%; (e) CH_3SO_2Cl, Et_3N, DCM, rt, 2 h, 69% for **23**, 14% for **24**; (f) NaN_3, DMF, 80 °C, overnight, 83%; (g) H_2, Pd/C, MeOH, 50 psi, 2 h, quantitative yield; (h) 4-hydroxy benzaldehyde, $NaCNBH_3$, AcOH, 1,2-dichloroethane, rt, overnight, 70%.



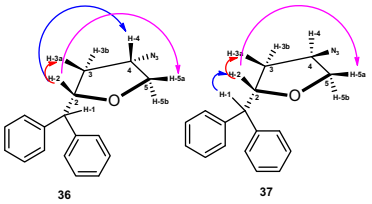
Scheme 4. Reagents and conditions: (a) vinylmagnesium bromide, CuI, anhyd THF, −78 °C to rt, overnight, 75%; (b) Ethylvinyl ether, $Hg(OCOCF_3)_2$, 50 °C, 12 h, 50%; (c) Grubb's catalyst (1st gen), anhyd benzene, 50 °C, 6 h, 53%; (d) (i) 9-BBN, anhyd THF, rt, overnight; (ii) 10% NaOH, 30% H_2O_2, 50 °C, 1 h, 53% for mixture of **32** and **33**; (e) CH_3SO_2Cl, Et_3N, DCM, rt, 2 h; (f) NaN_3, DMF, 80 °C, overnight, overall 36.0% for **36**, 12.6% for **37**; (g) H_2, 10% Pd/C, MeOH, 1 atm, overnight, quantitative yield for **38**, 80% for **39**; (h) aldehyde, $NaCNBH_3$/$Na(OAc)_3BH$,AcOH, 1,2-dichloroethane/MeOH, 3:1, rt, overnight, 35–45%.

mixture was mesylated with methanesulfonyl chloride using triethylamine in anhydrous dichloromethane. In contrast to the pyran derivatives, the resulting diastereomers **34** and **35** were inseparable at this stage, and were thus carried to the next step without further purification. The S_N2 nucleophilic substitution reaction with sodium azide gave separable diastereomers **36** (major) and **37** (minor) which were purified by column chromatography. The assignment of absolute stereochemistry and structural elucidation of major diasteromer **36** was performed using ^1H and 2D NMR experiments and details has been provided in the Supplementary data. Similar experiments were performed to characterize the minor azide diasteromer **37**. After determining their stereochemistry, the azide intermediates **36** and **37** were hydrogenated to obtain the corresponding amines **38** and **39** in quantitative yields. The amines were then subjected to reductive amination reaction with appropriate aldehydes according to the method described above to furnish the final compounds **40**–**46** in 35–45% yields.

2.2. Stereochemical assignment of the intermediate 36

Structural elucidation for compound **36** is summarized. By the knowledge of chemical shift, in the aliphatic region the most downfield proton at 4.66 ppm (^1H NMR ($CDCl_3$) spectrum) should be H-2 which is next to the H-1 (3.92 ppm) of the benzhydryl group. The splitting was doublet of triplet (dt) from couplings with H-1, H-3a (2.25 ppm), and H-3b (2.00 ppm) protons (Table 1). Furthermore, 2D gradient double quantum-filtered correlation spectroscopy (2D-gDQFCOSY) and ^1H–^1H homonuclear decoupling experiments also supported this observation. The decoupling experiment revealed that irradiation of protons at 1.75 and 2.25 ppm separately, has collapsed the doublet of triplet peak of H-2 into a triplet. This validated that the protons at 1.75 and 2.25 ppm, are the immediate neighbouring protons of H-2. Further experiments confirmed that the protons at 2.25 ppm is H-3a and 1.75 ppm is H-3b. The assignment of the remaining proton signals with their coupling constants are summarized in Table 1. The H-4 proton occurs as a multiplet at 4.04 ppm in the ^1H NMR (CD_3OD) spectrum resulting from the coupling interactions with H-3a, H-3b, H-5a, and H-5b protons. To determine through-space coupling and elucidate the absolute stereochemistry at the C-4 (Table 1) asymmetric center, nuclear Overhauser experiments (NOE) was performed. The NOE revealed that irradiation of the proton at 4.66 ppm (H-1) (in CD_3OD spectra) produced diagnostic NOEs between H-2 and H-4 with 1% enhancement of the H-4 multiplet signal at 4.05–4.10 ppm, suggesting that H-4 is *cis* to H-2. Since stereochemistry at the C-2 carbon has (*S*) configuration,

Table 1
^{1}H NMR ($CDCl_3$) signals of respective protons and NOE correlation observed in *major*- and *minors*-azides **36** and **37**



Proton	Compound **36** (ppm)	Compound **37** (ppm)
H-1	3.92[a] (d, J = 9.7 Hz)	3.94 (d, J = 8.4 Hz)
H-2	4.66 (dt, J_1 = 9.7 Hz, J_2 = 7.3 Hz)	4.86 (dt, J_1 = 9.4 Hz, J_2 = 7.3 Hz)
H-3a	2.25 (dt, J_1 = 13.7 Hz, J_2 = 7.3 Hz)	2.00 (dd, J_1 = 13.7 Hz, J_2 = 5.5 Hz)
H-3b	1.75 (ddd, J_1 = 11.3 Hz, J_2 = 7.0 Hz,J_3 = 4.0 Hz)	1.87 (ddd, J_1 = 13.7 Hz, J_2 = 9.4 Hz, J_3 = 6.4 Hz)
H-4	4.05–4.10[a] (m)	4.08–4.12 (m)
H-5a	3.84 (dd, J_1 = 10.0 Hz, J_2 = 5.5 Hz)	3.83 (dd, J_1 = 9.7 Hz, J_2 = 5.2 Hz)
H-5b	3.96 (dd, J_1 = 9.7 Hz, J_2 = 2.4 Hz)	4.02 (dd, J_1 = 9.7 Hz, J_2 = 2.2 Hz)

[a] CD_3OD solvent.

H-4 would be β with respect to the tetrahydrofuran ring; thus giving an (*S*) configuration at the C-4 chiral center and completing the assignment of absolute (+)(2*S*,4*S*) stereochemistry for the major isomer **36**. As expected, for the minor diasteromer **37**, irradiation of the H-2 proton did not produce any enhancement of the H-4 proton. It suggested that the H-4 proton is faced α-with respect to the plane of tetrahydrofuran ring installing an (*R*) configuration at the C-4 chiral center. The absolute configuration (−)(2*S*,4*R*) was thus assigned for the minor isomer.

3. Results and discussion

3.1. Structure–activity relationship (SAR)

Our SAR study is designed to investigate: (1) the role of distances between the phenyl rings of the benzhydryl moiety and the *N*-benzyl group for a balanced TUI activity; (2) the importance of the benzhydryl pharmacophoric feature and effects of introducing more flexibility in this part of the molecule for TUI activity, and (3) the effects of bioisosteric replacement of pyran ring with a five member tetrahydrofuran template on the activity for the monoamine transporters. In order to address these questions a series of novel pyran and tetrahydrofuran derivatives were synthesized, biologically screened, and conformationally analyzed. As described below orientation of the benzhydral moiety with respect to the pyran ring resulted in two distinct conformations. Our goal is to study the effect of introducing more flexibility in this part of the molecule.

When compared to **D-161**, which exhibited potent triple uptake activity (Table 2), compound **15** had an additional methylene group in between the benzhydral moiety and the pyran ring. It resulted in the loss of activity for all the three transporters, being only moderately active with K_i values of 245 nM, 346 nM, and 181 nM for the dopamine transporter (DAT), SERT, and NET respectively. The additional methylene perturbed the distances between the benzhydryl moiety and the *N*-benzyl group, the likely reason for its loss of activity. Introduction of a more flexible ethylene group in compound **16** gave an interesting biological profile. The compound was selectively potent against DAT and NET with K_i values of 45.7 nM and 37.7 nM, respectively and was weak against SERT (K_i of 473 nM). Thus, compound **16** exhibited a dopamine norepinephrine reuptake inhibitor (DNRI) profile.

Further, to validate the importance of the benzhydryl group for activity for the monoamine transporters, compound **27** bearing a single phenyl group on the methylene spacer, was synthesized. The compound was found to be inactive against DAT (K_i 0.92 μM) and SERT (K_i 2.49 μM) and weakly active (K_i 240 nM) against NET. This data underscores the importance of a benzhydryl group in potent inhibition of monoamine uptake. In the pursuit of expanding our SAR studies on pyran-based compounds further, we decided to substitute the pyran template with a novel disubstituted tetrahydrofuran moiety. Some modification of synthesis was adopted to synthesize the tetrahydrofuran derivatives. Our first attempt resulted in synthesis of *trans* compound **40** which, however, was inactive against all the three transporters with K_i uptake inhibition values of 0.94 μM, 1.15 μM, and 1.51 μM for DAT, SERT, and NET, respectively. The loss of activity might be due to less than optimal separation of pharmacophoric groups consisting of the benzhydryl and *N*-benzyl moieties compared to the pyran template. With an aim to bring the inter-pharmacophoric feature distances to an optimum range comparable to pyran derivatives, we designed tetrahydrofuran compounds with a phenyl ethyl moiety instead of our benzyl group. Such modification significantly enhanced activity at all the three transporters. Thus, when compared to **40**, compound **41** was about four times more active against DAT(K_i 260 nM), almost eight times more active against SERT (K_i 150 nM), and nine times more potent against NET (K_i 165 nM). It should be noted that similar to the pyran analogs, compounds **40** and **41** both have (*S*,*S*) stereochemistry at the C-2 and C-4 chiral centers, indicating similar stereospecificity for their interactions with the monoamine transporters. Further, structural modifications around *N*-phenylethyl moiety led to synthesis of compounds **42**–**44**. Substitution of a methoxy group at the *para* position in compound **42** also displayed moderate inhibition of uptake (K_i; 266 nM for DAT, 358 nM for SERT, and 198 nM for NET) at all the three transporters. Substitution of a *p*-fluoro group (compound **43**) was tolerated by NET (K_i; 196 nM) but resulted in a loss of activity for DAT and SERT (K_i; 586 nM and 1.35 μM, respectively). Our previous studies have shown that H-bonding and ionic interactions at this position brings selective activity against NET and gives support to our assumption that (2*S*,4*S*)-*N*-phenylethyl tetrahydrofuran derivatives may interact with monoamine transporters in a similar binding mode as their pyran counterparts.[40] Unsubstituted compound **44** was inactive against SERT and showed weak activity against DAT and NET which is similar to the corresponding pyran derivative (K_i; 303 nM for DAT, 1577 nM for SERT, and 274 nM for NET, see Ref. 40). In our further goal to investigate stereochemical preference in binding of tetrahydrofuran compounds, minor diasteromeric compounds, with (2*S*,4*R*) stereochemistry, **45** and **46** were also synthesized. When compared to

Table 2
Binding affinity at DAT, SERT, and NET in rat brain

Compound	DAT uptake, K_i, nM, [^{3}H]DA[a]	SERT uptake, K_i, nM, [^{3}H]5-HT[a]	NET uptake, K_i, nM [^{3}H]DA[a]
15 (**D-488**)	245 ± 80	346 ± 52	181 ± 41
16 (**D-487**)	45.7 ± 23.4	473 ± 126	37.7 ± 10.6
27 (**D-504**)	920 ± 89.0	2496 ± 519	240 ± 38
40 (**D-452**)	943 ± 238	1147 ± 158	1511 ± 686
41 (**D-470**)	260 ± 62	150 ± 37	165 ± 26
42 (**D-561**)	266 ± 70	358 ± 48	198 ± 16
43 (**D-562**)	586 ± 92	1353 ± 234	196 ± 52
44 (**D-560**)	642 ± 161	2046 ± 406	427 ± 80
45 (**D-469**)	3690 ± 513	408 ± 138	975 ± 250
46 (**D-564**)	454 ± 55	844 ± 187	739 ± 176
D-185[b]	62.4 ± 5.6	16.1 ± 1.6	12.6 ± 3.7
D-411[c]	15.9 ± 1.7	12.9 ± 1.3	29.3 ± 4.8
D-161[b]	42.0 ± 3.3	29.1 ± 3.5	30.5 ± 7.8
D-142[c]	37.4 ± 3.9	14.7 ± 2.1	29.3 ± 7.9
D-199[d]	34.6 ± 6.5	19.9 ± 1.5	54.3 ± 9.8
D-391[c]	31.3 ± 10.6	40.1 ± 4.9	38.5 ± 6.0
D-471[b]	38.4 ± 2.6	58.4 ± 4.0	4.20 ± 2.3
D-478[b]	11.2 ± 2.8	3.0 ± 0.3	6.1 ± 2.4
D-451[b]	32.5 ± 4.3	69.1 ± 19.8	8.4 ± 1.7
D-168[b]	85.2 ± 8.2	25.0 ± 8.4	25.5 ± 9.6
Fluoxetine	1092 ± 98	12.2 ± 2.4	158 ± 58
Reboxetine	>10,000	503 ± 61	0.69 ± 0.21

[a] Uptake by DAT, SERT and NET in rat brain tissue was monitored with [^{3}H]DA, [^{3}H]5-HT and [^{3}H]DA as described in Section 2. Results are average ± SEM of three to eight independent experiments assayed in triplicate.
[b] Previously reported compound.[42]
[c] Previously reported compound.[34]
[d] Previously reported compound.[33]

their (2*S*,4*S*) diasteromeric counterparts compounds **40** and **44**, biological results for **45** and **46** indicated no significant preference for the either isomer for activity.

3.2. Computational analysis

A pharmacophore model of monoamine triple uptake inhibitors was built using a training set of ten potent pyran compounds (Fig. 1) which we have reported in our previous studies.[34,37,38,42] The training set consisted of compounds with diverse structural features and included both 3,6-di- and tri-substituted classes of pyran derivatives. Furthermore, the training set compounds exhibited balanced potencies (Table 2) against all the three transporters and thus are representative of the TUIs developed in our laboratory. Analysis of conformations within dE of 3 kcal/mol revealed that pyran compounds in the training set (Fig. 1) existed in two distinct conformations. The lowest energy conformation of each molecule adopted a 'folded' orientation (Fig. 2a) in which ring A of the benzhydryl moiety was at 90° to the plane of the pyran ring and lied parallel to the *N*-benzyl group. It was observed that for all compounds, this conformation was favored and occurred predominantly. The next distinct conformations were within an energy difference of 2.3–2.8 kcal/mol from their respective lowest energy conformations. In this orientation, compounds assumed an extended conformation in which ring A of the benzhydryl group was tilted to lie in the plane of the pyran ring (see Supplementary data, Fig. S2). Thus, for this series of compounds, the orientation of the benzhydryl moiety with respect to the pyran ring resulted in two different conformations. Since a bioactive conformation does not always need to be of lowest energy, both conformations of the training set molecules were used for pharmacophore modeling. Pharmacophore elucidation with the lowest energy conformations gave 107 queries and top ten were considered for further analysis. Based on our structure–activity relationship (SAR) data, the number of coverage and degree of overlap, the second-ranked query (RRHH+) was selected as the representative pharmacophore. The query (model 1) consisted of two aromatic features (*R*), two hydrophobic features (H), and one cationic (+) feature (see Fig. 2a and c). The two aromatic features mapped over the benzyl group and ring A of the benzhydryl group, respectively. One hydrophobic feature resulted from ring B of the benzhydryl moiety while another hydrophobic region came from the pyran ring. Finally, the cationic feature superimposed well on the secondary nitrogen. The inter-pharmacophoric feature distances of the pharmacophore model 1 are listed in Table 3. Similarly, pharmacophore elucidation with the extended conformation was also performed (see Supplementary data, Fig. S2). However, we presumed that model 1 resulting from the lowest energy conformations was more plausible since the query included a pharmacophore for the pyran ring which is a characteristic molecular template of our TUIs; and a cationic feature which is a common element present in most monoamine transporter inhibitors. The computational study was further extended to include selected pyran and tetrahydrofuran derivatives synthesized in the present study. Conformational analysis of **16**, the most active compound of the series at DAT and NET, revealed that its lowest energy conformer assumed an extended orientation (Supplementary data, Fig. S3) with ring A of the benzhydryl moiety swung by 90° to lie in the plane of the pyran ring; thereby significantly altering the torsions and inter-pharmacophoric feature distances (refer Supplementary data, Table S1). Furthermore, because of conformational flexibility, no folded conformation, which was predominantly present in the pyran TUI compounds, was observed. It could imply that DAT and NET can accommodate inhibitors with multiple binding modes, including those with relatively extended conformations. On the other hand this may not be the case for SERT which appears to prefer inhibitors with 'folded' conformation. This could be one of the reasons why GBR 12909, a known selective DAT blocker, which is reported to adopt several flexible conformations, was most active for DAT (K_i 16.2 nM), followed by NET (K_i 48.5 nM), but only moderately active (K_i 198.0 nM), against SERT.[41] As expected, compound **16** which was identified as a DNRI could not be accommodated into TUI pharmacophore model 1, developed based on 'folded conformations'.

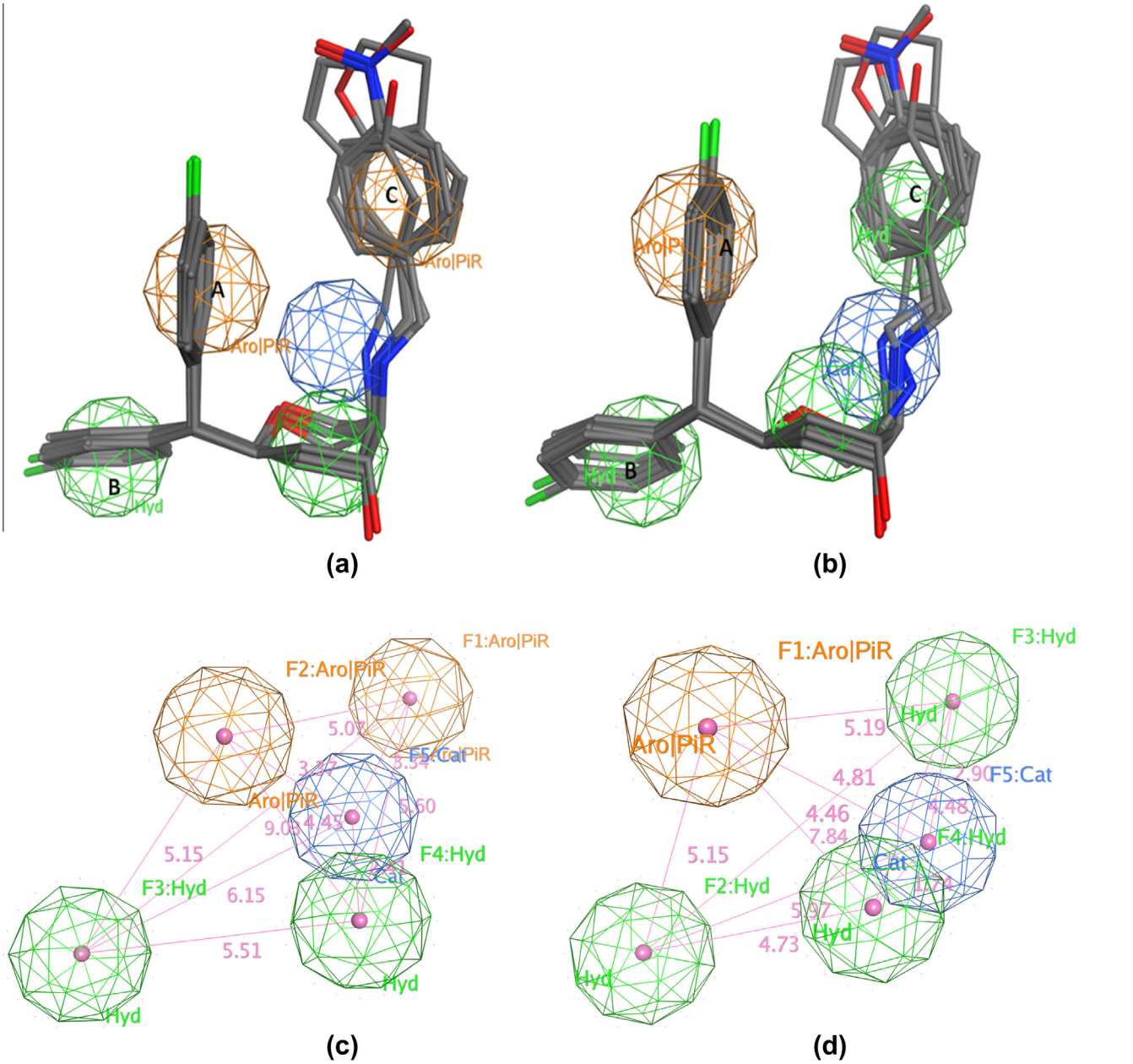


Figure 2. (a) Pharmacophore model 1 resulting from lowest energy folded conformations of pyran derivatives in the training set; (b) common pharmacophore model 2 resulting from lowest energy folded conformations of pyran and tetrahydrofuran derivatives. The pharmacophore color coding is represented as: green for hydrophobic; brown for aromatic; blue for cationic. Atoms in ligands are represented as: O, red; N, blue; C, gray; (c) pharmacophore features of model 1; (d) pharmacophore features of model 2.

Table 3
Inter-pharmacophore feature distances of pharmacophore model 1 and 2

Pharmacophore features	Model 1 distances (Å)	Model 2 distances (Å)
Distances (Å)		
PF1 aromatic/hydrophobic (ring C)–PF2 aromatic (ring A)	5.07	5.19
PF1 aromatic–PF3 hydrophobic (ring B)	9.03	7.84
PF1 aromatic–PF4 hydrophobic (pyran)	5.60	4.48
PF1 aromatic–PF5 cationic	3.34	2.90
PF2 aromatic–PF3 hydrophobic	5.15	5.15
PF2 aromatic–PF4 hydrophobic	4.45	4.46
PF2 aromatic–PF5 cationic	3.37	4.81
PF3 hydrophobic–PF4 hydrophobic	5.51	4.73
PF3 hydrophobic–PF5 cationic	6.15	5.97
PF4 hydrophobic–PF5 cationic	2.41	1.74

In the light of the development of novel tetrahydrofuran derivatives with moderate TUI profile, conformational analysis of compound **41** was also performed. We observed that similar to the pyran derivatives, **41** also predominantly, including the minimum energy, adopted a 'folded' conformation. Thus, a 'folded' orientation with an optimum distance between the benzhydryl moiety and the *N*-benzyl group is one of the critical requirements for this series of compounds to exhibit a balanced activity against all three transporters. In an attempt to find a possible reason for its diminished (while transporter-balanced) activity with respect to the pyran compounds in the training set, we decided to map compound **41** over the pyran pharmacophore. A revised common pharmacophore model was attempted with 12 compounds using ten potent pyran derivatives in the training set, a moderately active tetrahydrofuran derivative **41**, and an inactive compound **40**. Pharmacophore

elucidation resulted in 66 queries and the representative pharmacophore (model 2) is shown in Figure 2b and d. Model 2 consisted of five (RHHH+) features which were mostly similar to those observed in model 1, except that the aromatic feature of the benzyl group in model 1 was substituted with a hydrophobic feature in model 2. Comparison of the two models (Table 3) further revealed that the optimum separation between the key features was perturbed which might explain the diminished activity of compound **41** with respect to their pyran counterparts. However, tetrahydrofuran derivative **41**, included in model 2, retained the required conformation and the essential pharmacophoric features of our pyran-based compounds giving support to their further investigation as potential novel TUIs.

4. Conclusion

In conclusion, in this study we have generated a TUI pharmacophore model revealing features important for inhibitors to exhibit a balanced activity against DAT, SERT, and NET. In particular, a 'folded' conformation was found common to the active pyran compounds in the training set and was crucial to triple uptake inhibitory activity. Furthermore, the distances between the benzhydryl moiety and the *N*-benzyl group as well as the orientation of the secondary nitrogen were also important for TUI activity. We have validated these findings by synthesizing and testing novel pyran analogs. This study has revealed conformational preference of inhibitors for DAT/NET over SERT and suggests that DAT/NET could accommodate flexible ligands with multiple binding modes; thus providing insights to guide the design of novel TUI as well as selective transporter blockers. The present work has also resulted in the discovery of a new series of asymmetric tetrahydrofuran derivatives as novel TUIs. Interestingly, the highest TUI activity was exhibited in a stereochemical preference similar to pyran TUI for example, **D-161**.

5. Experimental

5.1. Chemistry

Reagents and solvents were obtained from commercial suppliers and used as received unless otherwise indicated. Anhydrous solvents were obtained according to the standard procedures. All reactions were performed under inert atmosphere (N_2) unless otherwise noted. Analytical silica gel-coated TLC plates (silica gel 60 F254) were purchased from EM Science and were visualized with UV light or by treatment with either phosphomolybdic acid (PMA) or ninhydrin. Flash chromatography was carried out on Baker Silica Gel 40 μM. ^{1}H NMR and ^{13}C spectra were routinely recorded with a Varian 400/500 spectrometer operating at 400/500 and 100/125 MHz, respectively. The NMR solvent used was either $CDCl_3$ or CD_3OD or as indicated. TMS was used as an internal standard. NMR and rotation of free bases were recorded. Salts of free bases were used for biological characterization. Elemental analyses were performed by Atlantic Microlab Inc. and were within ±0.4% of the theoretical value. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter.

5.1.1. Procedure A. But-3-ene-1,1-diyldibenzene (2a)

To an oven-dried round bottom flask containing magnetic stir bar, diphenylmethane (16.0 g, 117.67 mmol) was taken and dissolved in anhydrous THF (140 mL) under a continuous flow of nitrogen. After cooling the solution to 0 °C, *n*-BuLi (181.8 mL, 294.17 mmol) in anhydrous THF (1.6 M) was slowly added. The ice-bath was then removed, and the mixture was stirred at room temperature for 1 h. The mixture was cooled to 0 °C again and allyl bromide (12.2 mL, 141.2 mmol) was added slowly via a syringe. The ice-bath was removed and the resulting solution was stirred at room temperature for 24 h. Next, the reaction mixture was cooled to 0 °C and quenched by slow addition of methanol (5 mL), followed by water (150 mL). The organic layer was separated and the aqueous layer was extracted with ethyl ether (2 × 100 mL). The organic layers were combined and washed with brine (100 mL). The organic layer was separated again, dried over Na_2SO_4, and concentrated over rotary evaporator. The crude product was sufficiently pure (16.4 g, 83%) and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12–7.38 (m, 10H), 5.74 (ddd, J = 17.0, 9.8, 3.5 Hz, 1H), 4.80–5.17 (m, 2H), 4.03 (t, J = 7.9 Hz, 1H), 2.84 (t, J = 7.6 Hz, 2H).

5.1.2. Pent-4-ene-1,1-diyldibenzene (2b)

Diphenylmethane (15.0 g, 89.16 mmol) in anhydrous THF (174 mL) was reacted with *n*-BuLi (144.5 mL, 222.9 mmol) in anhydrous THF (1.6 M) and allyl bromide (9.98 mL, 98.45 mmol) following procedure A. The crude product was sufficiently pure (17.3 g, 87%) and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90–7.72 (m, 10H), 5.61–6.15 (m, 1H) 4.91–5.07 (m, 2H), 3.50–4.20 (m, 1H), 1.73–2.59 (m, 4H).

5.1.3. Procedure B. 2-(2,2-Diphenylethyl)oxirane (3a)

m-CPBA (29.0 g, 116.67 mmol, 70% wt/wt in water) was added to a solution of **2a** (16.2 g, 77.77 mmol) in DCM (173 mL) at 0 °C. The ice-bath was removed and the resulting solution was stirred at room temperature for 24 h. Next, the reaction mixture was cooled to 0 °C and quenched with saturated $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with additional DCM (2 × 50 mL). The organic layers were combined and washed with brine (100 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated over rotary evaporator. The crude product was purified via gradient silica gel column chromatography using 10–50% ethyl acetate in hexanes to obtain pure racemic epoxide **3a** (16.7 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.45 (m, 10H), 4.23 (t, J = 7.9 Hz, 1H), 2.78–2.96 (m, 1H), 2.70 (t, J = 4.7 Hz, 1H), 2.44 (dd, J = 4.7, 2.6 Hz, 1H), 2.21–2.36 (m, 2H)

5.1.4. 2-(3,3-Diphenylpropyl)oxirane (3b)

m-CPBA (28.52 g, 115.60 mmol, 70% wt/wt in water) was reacted with a solution of **2b** (17.0 g, 76.47 mmol) in DCM (170 mL) using procedure B. The crude product was purified via gradient silica gel column chromatography using 1–50% ethyl acetate in hexanes to obtain 17.5 g (96%) of pure racemic epoxide **3b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90–7.72 (m, 10H), 3.98 (t, J = 8.0 Hz, 1H), 2.84–3.05 (m, 1H), 2.74 (dd, J = 5.2, 3.6 Hz, 1H), 2.44 (dd, J = 4.8, 2.8 Hz, 1H), 1.98–2.42 (m, 2H), 1.34–1.79 (m, 2H).

5.1.5. Procedure C. (*R*)-2-(2,2-Diphenylethyl)oxirane (4a)

(*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diaminocobalt(II) (1.0 g, 1.52 mmol) was taken in a round bottom flask and dissolved in DCM (60 mL). After the addition of acetic acid (180 μL, 3.12 mmol), the mixture was stirred at room temperature for 1 h. Then, the solvent was removed on a rotary evaporator under reduced pressure and the residue was dried in air thoroughly for 2–3 days to obtain the activated catalyst. This solid residue (0.30 g, 0.46 mmol) was added to the racemic epoxide **3a** (20.4 g, 91.03 mmol) and the reaction mixture was cooled down in an ice bath. Next, THF (1.15 mL, 63.72 mmol) and H_2O (1.15 mL, 62.72 mmol) were added dropwise and the ice bath was removed. The reaction mixture was stirred at room temperature for 21 days following which the enantio-enriched epoxide was separated from the diol (**5a**) via gradient silica gel column

chromatography using 1–100% ethyl acetate in hexanes. To the enantio-enriched epoxide (13.76 g, 61.34 mmol), additional amount of the activated catalyst (0.095 g, 0.15 mmol), H_2O (0.38 mL, 20.72 mmol), and THF (0.38 mL, 20.72 mmol) were added and the mixture was stirred for additional 7 days at room temperature. The residue was purified by gradient silica gel column chromatography using 1–5% ethyl acetate in hexanes to give compound **4a** (9.96 g, 46%) and compound **5a** (9.98 g, 47%). $[\alpha]_D^{25}$ +26.6 (*c* 1, MeOH). ^{1}H NMR for (*R*)-**4a** (400 MHz, $CDCl_3$): δ 7.10–7.45 (m, 10H), 4.23 (t, *J* = 7.9 Hz, 1H), 2.78–2.96 (m, 1H), 2.70 (t, *J* = 4.7 Hz, 1H), 2.44 (dd, *J* = 4.7, 2.6 Hz, 1H), 2.21–2.36 (m, 2H).

5.1.6. *R*)-2-(3,3-Diphenylpropyl)oxirane (4b)

(*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diaminocobalt(II) (1.0 g, 1.52 mmol), acetic acid (180 μL, 3.12 mmol) in DCM (60 mL) was reacted following procedure C to obtain the activated catalyst. This solid residue (0.24 g, 0.37 mmol) was added to the racemic epoxide **3b** (17.4 g, 73.01 mmol) and reaction was continued using procedure C. The residue thus obtained was purified by gradient silica gel column chromatography using 1–5% ethyl acetate in hexanes to give compound **4b** (8.0 g, 46%) and compound **5b** (8.18 g, 47%). $[\alpha]_D^{25}$ +3.4 (*c* 1, MeOH). ^{1}H NMR for (*R*)-**4b** (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90–7.72 (m, 10H), 3.98 (t, *J* = 8.0 Hz, 1H), 2.84–3.05 (m, 1H), 2.74 (dd, *J* = 5.2, 3.6 Hz, 1H), 2.44 (dd, *J* = 4.8, 2.8 Hz, 1H), 1.98–2.42 (m, 2H), 1.34–1.79 (m, 2H).

5.1.7. Procedure D. (*S*)-1,1-Diphenylhept-6-en-3-ol (6a)

In an oven-dried round bottom flask equipped with magnetic stir-bar, enantiomerically enriched (*R*)-epoxide **4a** (6.77 g, 30.18 mmol), and copper(I) iodide (0.58 g, 3.05 mmol) were taken and dissolved in anhydrous THF (64 mL) under a continuous flow of N_2. After cooling the solution to −78 °C, allylmagnesium chloride (18.75 mL, 2 M solution in THF, 37.12 mmol) was added dropwise. The reaction mixture was slowly allowed to reach room temperature and stirred overnight under a continuous flow of N_2. The reaction mixture was then cooled to 0 °C and quenched by the addition of saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure on a rotary evaporator. The crude residue was purified by gradient silica gel column chromatography using 2–50% ethyl acetate in hexanes to give compound **6a** (7.5 g, 93%) as a colorless syrup. $[\alpha]_D^{25}$ −17.6 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.40 (m, 10H), 5.78 (ddd, *J* = 17.0, 9.9, 3.2 Hz, 1H), 4.84–5.07 (m, 2H), 4.23 (dd, *J* = 10.0, 5.8 Hz, 1H), 3.36–5.57 (m, 1H), 2.04–2.32 (m, 4H), 1.52–1.65 (m, 1H), 1.42 (d, *J* = 4.1 Hz, 1H).

5.1.8. (*S*)-1,1-Diphenyloct-7-en-4-ol (6b)

Epoxide **4b** (8.0 g, 33.57 mmol) and CuI (0.64 g, 3.35 mmol) in anhydrous THF (85 mL) was reacted with reacted with allyl magnesium chloride (84.0 mL, 1 M solution in THF, 84.0 mmol) using procedure D. The syrupy residue obtained was purified by gradient silica gel column chromatography using a mixture of 10–25% ethyl acetate in hexanes to afford corresponding allylic alcohol **6b** as colorless syrup (7.99 g, 84%). $[\alpha]_D^{25}$ +5.8 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00–7.40 (m, 10H), 5.64–5.91 (m, 1H), 4.71–5.17 (m, 2H), 3.88 (t, *J* = 7.6 Hz, 1H), 3.46–3.72 (m, 1H), 1.80–2.39 (m, 4H), 1.19–1.71 (m, 4H).

5.1.9. Procedure E. (*S*)-(3-(Vinyloxy)hept-6-ene-1,1-diyl)dibenzene (7a)

The alcohol **6a** (0.833 g, 3.13 mmol) and mercury(II) trifluoroacetate (0.1 g, 0.313 mmol) were taken in an oven-dried round bottom flask equipped with magnetic stir bar under a continuous flow of N_2. After cooling the solution to 0 °C, excess of ethyl vinyl ether (29 mL) was added. The ice-bath was removed and stirring was continued for 4–5 h under a nitrogen atmosphere until TLC showed maximum conversion. The reaction mixture was concentrated under reduced pressure on a rotary evaporator at room temperature. The crude product was dissolved in 5% ethyl acetate in hexanes and filtered through a pad of basic alumina quickly. The filtrate was concentrated under reduced pressure at room temperature to give intermediate **7a** (0.7 g, 77%). The starting material was recovered from the alumina pad by eluting with ethyl acetate which was then concentrated and recycled again.

5.1.10. (*S*)-(4-(Vinyloxy)oct-7-ene-1,1-diyl)dibenzene (7b)

Alcohol **9b** (1.07 g, 3.83 mmol), mercury(II) trifluoroacetate (0.12 g, 0.382 mmol), and excess ethyl vinyl ether (36 mL) were reacted following procedure E to give intermediate **7b** (0.87 g, 74%) which was immediately taken to the next step.

5.1.11. Procedure F. (*S*)-2-(2,2-Diphenylethyl)-3,4-dihydro-2*H*-pyran (8a)

The vinyl ether **7a** (1.58 g, 5.4 mmol) was immediately dissolved in anhydrous benzene (59 mL) under a continuous flow of N_2 and Grubb's catalyst (1st generation, 0.223 g, 0.27 mmol) was added. The solution mixture was then refluxed at 90 °C for 2 h. The reaction mixture was then cooled and the solvent was removed under reduced pressure on a rotary evaporator. The black residue was purified by gradient column chromatography using 1–10% ethyl acetate in hexanes to obtain the cyclic olefin **8a** as a white solid (1.35 g, 95%). $[\alpha]_D^{25}$ +67.0 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96–7.44 (m, 10H), 6.29 (d, *J* = 5.9 Hz, 1H), 4.41–4.62 (m, 1H), 4.18 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.42–3.62 (m, 1H), 2.19–2.36 (m, 1H), 2.04–2.17 (m, 1H), 1.80–1.96 (m, 2H), 1.66–1.77 (m, 1H), 1.46–1.62 (m, 1H).

5.1.12. (*S*)-2-(3,3-Diphenylpropyl)-3,4-dihydro-2*H*-pyran (8b)

The vinyl ether **7b** (1.58 g, 5.2 mmol) was immediately reacted with Grubb's catalyst (1st generation, 0.212 g, 0.26 mmol) in anhydrous benzene (60 mL) following procedure F. The black residue was purified by gradient column chromatography using 1–10% ethyl acetate in hexanes to obtain the cyclic olefin **8b** as white solid (1.37 g, 96%). $[\alpha]_D^{25}$ +30.3 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69–7.38 (m, 10H), 6.34 (d, *J* = 5.9 Hz, 1H), 4.50–4.69 (m, 1H), 3.89 (t, *J* = 7.9 Hz, 1H), 3.69–3.83 (m, 1H), 1.29–2.39 (m, 8H).

5.1.13. Procedure G. 6-(2,2-Diphenylethyl)tetrahydro-2*H*-pyran-3-ol (mixture of 9a and 10a)

Compound **8a** (1.353 g, 5.12 mmol) was taken in an oven-dried round bottom flask equipped with magnetic stir-bar and dissolved in anhydrous THF (20 mL) under a continuous flow of N_2. After cooling the solution to 0 °C, 9-BBN (25.6 mL, 0.5 M solution in THF, 12.8 mmol) was added slowly. The ice-bath was removed and the reaction mixture was stirred overnight at room temperature. Then, the reaction mixture was cooled to 0 °C, quenched by the addition of ethanol (8 mL) and stirred for 10 min. Next, aqueous 10% NaOH solution (8 mL) and 30% H_2O_2 (7.3 mL) were added, and the resulting solution was heated to 50 °C for 1 h. After cooling to room temperature, the reaction mixture was treated with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (100 mL), the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure on a rotary evaporator. The crude residue was purified by column chromatography using 25% ethyl acetate in hexanes to give compounds **9a** (major) and **10a** (minor) (1.36 g, 95%) as a mixture. NMR data for major isomer **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.35 (m, 10H), 4.20 (dd, *J* = 10.0, 5.9 Hz, 1H), 3.92 (ddd, *J* = 8.8, 4.7, 1.8 Hz, 1H), 3.32–3.63

(m, 1H), 2.85–3.05 (m, 2H), 2.67 (br s, 1H), 2.05–2.25 (m, 2H), 1.90–2.01 (m, 1H), 1.11–1.40 (m, 2H).

5.1.14. 6-(3,3-Diphenylpropyl)tetrahydro-2*H*-pyran-3-ol (mixture of 9b and 10b)

Intermediate **8b** (0.746 g, 2.68 mmol) in anhydrous THF (11 mL) was reacted with 9-BBN (13.4 mL, 0.5 M solution in THF, 6.70 mmol) according to procedure G. The crude residue was purified by column chromatography using 25% ethyl acetate in hexanes to yield compounds **9b** (major) and **10b** (minor) (0.67 g, 84%) as a mixture. NMR data for major isomer **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.37 (m, 10H), 3.85–3.97 (m, 1H), 3.83 (t, J = 7.9 Hz, 1H), 3.49–3.63 (m, 1H), 3.10–3.21 (m, 1H), 3.01 (t, J = 10.6 Hz, 1H), 2.48 (s, 1H), 2.13–2.32 (m, 2H), 1.13–1.53 (m, 5H).

5.1.15. Procedure H. (3*R*,6*S*)-6-(2,2-Diphenylethyl)tetrahydro-2*H*-pyran-3-yl methanesulfonate (11a)

The mixture of compounds **9a** and **10a** (1.94 g, 5.30 mmol) was dissolved in anhydrous DCM (46 mL) following which triethylamine (1.48 mL, 10.6 mmol) was added at 0 °C under a continuous flow of nitrogen. Then, methanesulfonyl chloride (0.53 mL, 6.89 mmol) was added dropwise. Thereafter, the ice-bath was removed and the mixture was stirred for 2 h at room temperature. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ (30 mL) and extracted with DCM (3 × 40 mL). The organic layers were combined and washed with brine (100 mL). The organic layer was separated, dried over Na_2SO_4, and the solvent was removed under reduced pressure on a rotary evaporator. The isomers were separated from the crude product by gradient silica gel column chromatography using 2–50% of ethyl acetate in hexanes as eluent to first obtain the *trans* compound **11a** (1.71 g, 69%) followed by the *cis* compound **12a** (0.37 g, 15%). NMR data for the major isomer **11a**: $[\alpha]_D^{25}$ +40.6 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.45 (m, 10H), 4.53–4.71 (m, 1H), 4.20 (dd, J = 10.0, 5.9 Hz, 1H), 4.13 (ddd, J = 11.1, 5.0, 2.1 Hz, 1H), 3.19 (t, J = 10.6 Hz, 1H), 2.92–3.08 (m, 4H), 2.06–2.33 (m, 3H), 1.72–1.83 (m, 1H), 1.57–1.68 (m, 1H), 1.43–1.54 (m, 1H).

5.1.16. (3*R*,6*R*)-6-(3,3-Diphenylpropyl)tetrahydro-2*H*-pyran-3-yl methanesulfonate (11b)

The mixture of compounds **9b** and **10b** (1.25 g, 3.31 mmol), triethylamine (0.92 mL, 6.62 mmol), and methanesulfonyl chloride (0.33 mL, 4.30 mmol) in anhydrous DCM (28 mL) was reacted using procedure H to yield *trans* compound **11b** (1.06 g, 67%) which eluted first followed by the *cis* compound **12b** (0.26 g, 17%). NMR data for the major isomer **11b**: $[\alpha]_D^{25}$ +23.2 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.35 (m, 10H), 4.50–4.66 (m, 1H), 4.10 (ddd, J = 11.1, 4.91, 2.34 Hz, 1H), 3.85 (t, J = 7.6, 1H), 3.28 (t, J = 10.5 Hz, 1H), 3.17–3.27 (m, 1H), 2.97 (s, 3H), 2.14–2.34 (m, 2H), 1.96–2.12 (m, 1H), 1.59–1.81 (m, 2H), 1.26–1.55 (m, 3H). NMR data for the minor isomer **12b**: $[\alpha]_D^{25}$ −13.9 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06–7.42 (m, 10H), 4.70 (t, J = 19.9 Hz, 1H), 4.04–4.20 (m, 1H), 3.81–3.91 (m, 1H), 3.53 (d, J = 13.2 Hz, 1H), 3.20–3.33 (m, 1H), 2.98 (s, 3H3H), 1.96–2.38 (m, 2H), 1.20–1.88 (m, 6H).

5.1.17. Procedure I. (2*S*,5*S*)-5-Azido-2-(2,2-diphenylethyl)tetrahydro-2*H*-pyran (13a)

Compound **11a** (1.70 g, 4.72 mmol) was dissolved in anhydrous DMF (25 mL) and sodium azide (1.54 g, 23.62 mmol) was added at once. The mixture was then stirred overnight at 80 °C under a continuous flow of N_2, cooled to room temperature, and quenched with water (200 mL). The solution was extracted with diethyl ether (3 × 60 mL), the organic layers were combined and washed with brine (100 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure on a rotary evaporator. The crude product was purified by gradient silica gel column chromatography using 1–10% ethyl acetate in hexanes to afford compound **13a** (1.25 g, 86%). $[\alpha]_D^{25}$ −24.4 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.50 (m, 10H), 4.26 (dd, J = 10.6, 5.3 Hz, 1H), 3.89–4.07 (m, 1H), 3.32–3.62 (m, 2H), 2.90–3.20 (m, 1H), 2.06–2.32 (m, 2H), 1.86–2.04 (m, 1H), 1.58–1.80 (m, 2H), 1.38–1.54 (m, 1H).

5.1.18. (2*R*,5*S*)-5-Azido-2-(3,3-diphenylpropyl)tetrahydro-2*H*-pyran (13b)

Intermediate **11b** (1.06 g, 2.81 mmol), sodium azide (0.92 g, 14.17 mmol) in anhydrous DMF (20 mL) was reacted according to procedure I. The crude product was purified by gradient silica gel column chromatography using a mixture of 1–10% of ethyl acetate in hexanes to afford compound **13b** (0.81 g, 88%). $[\alpha]_D^{25}$ −8.0 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.48 (m, 10H), 3.91–4.01 (m, 1H), 3.86 (t, J = 7.8 Hz, 1H), 3.45–3.63 (m, 2H), 3.18–3.36 (m, 1H), 2.17–2.34 (m, 1H), 1.90–2.14 (m, 2H), 1.67–1.82 (m, 1H), 1.30–1.66 (m, 4H).

5.1.19. Procedure J. (3*S*,6*S*)-6-(2,2-Diphenylethyl)tetrahydro-2*H*-pyran-3-amine (14a)

The azide **13a** (0.887 g, 2.80 mmol) was dissolved in methanol (59 mL) and the mixture was hydrogenated (1 atm) in the presence of 10% Pd-C (88 mg, 10 wt %) for overnight. Then, the reaction mixture was filtered through a short bed of celite, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford the amine **14a** (0.79 g, 98%) as an off-white solid. The product was sufficiently pure and used in the next step without further purification. $[\alpha]_D^{25}$ +24.6 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 2H), 6.75–7.65 (m, 10H), 3.98–4.46 (m, 2H), 3.20–3.57 (m, 2H), 2.80–3.10 (m, 1H), 1.80–2.48 (m, 4H), 1.28–1.72 (m, 2H).

5.1.20. (3*S*,6*R*)-6-(3,3-Diphenylpropyl)tetrahydro-2*H*-pyran-3-amine (14b)

The azide **13b** (0.80 g, 2.70 mmol) was hydrogenated using procedure J to afford the amine **14b** (0.71 g, 97%) as an off-white solid. The product was sufficiently pure and used in the next step without further purification. $[\alpha]_D^{25}$ +3.6 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (br s, 2H), 6.95–7.45 (m, 10H), 4.13 (d, J = 12.6 Hz, 1H), 3.81 (t, J = 7.6 Hz, 1H), 3.31–3.60 (m, 2H), 3.05–3.30 (m, 1H), 1.88–2.38 (m, 3H), 1.24–1.86 (m, 5H).

5.1.21. Procedure K. 4-((((3*S*,6*S*)-6-(2,2-Diphenylethyl)tetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol (15)

4-Hydroxy-benzaldehyde (66 mg, 0.57 mmol) was dissolved in a mixture of 1,2-dichloroethane (3 mL)/methanol (1 mL) and glacial acetic acid (32 μL, 0.57 mmol) was added. Then, amine **14a** (0.107 g, 0.38 mmol) was added and the solution stirred at room temperature for 2 h following which $Na(OAc)_3BH$ (0.12 g, 0.57 mmol) was added. The resulting mixture was then stirred at room temperature for 24 h, cooled to 0 °C, diluted with DCM (20 mL) and quenched by the addition of water (30 mL). The organic layer was separated and the aqueous layer was extracted with additional DCM (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure on a rotary evaporator. The crude residue was purified by gradient silica gel column chromatography using 1–10% methanol in DCM as the eluent to afford compound **15** (68 mg, 46%). $[\alpha]_D^{25}$ +20.6 (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98–7.40 (m, 12H), 6.81 (d, J = 8.5 Hz, 2H), 4.20 (dd, J = 10.6, 5.3 Hz, 1H), 3.94 (dd, J = 41.6, 12.6 Hz, 2H), 3.58 (br s, 1H), 3.28–3.46 (m, 2H), 2.90–3.15 (m, 2H), 1.90–2.34 (m, 4H), 1.45–1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 144.6, 144.0, 131.2, 128.4, 128.3, 127.9, 127.5, 126.2, 126.1, 121.7, 116.0, 75.8, 66.7, 50.5, 48.6, 46.2, 41.3, 25.7,

24.7. The free base was converted into corresponding hydrochloride salt. Mp = 180–185 °C. Anal. ($C_{26}H_{29}NO_2$·HCl) C, H, N.

5.1.22. 4-((((3*S*,6*R*)-6-(3,3-Diphenylpropyl)tetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol (16)

Amine intermediate **14b** (0.112 g, 0.38 mmol) and 4-hydroxy benzaldehyde (66 mg, 0.57 mmol) were dissolved in DCM (3 mL). MeOH (1 mL) and AcOH (33 μL) were then added and reaction stirred for 2 h. $Na(OAc)_3BH$ (0.115 g, 0.545 mmol) was thereafter added and reaction continued following procedure K. The crude residue thus obtained was purified by gradient silica gel column chromatography using 1–10% methanol in DCM as the eluent to afford compound **16** (68 mg, 47%). $[\alpha]_D^{25}$ −4.5 (*c* 1, MeOH). MS (ESI): *m*/*z* 402.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91–7.40 (m, 12), 6.72 (d, *J* = 7.9 Hz, 2H), 5.03 (br s, 3H), 3.84–4.42 (m, 3H), 3.80 (t, *J* = 7.6 Hz, 1H), 3.32–3.50 (m, 1H), 2.94–3.30 (m, 2H), 1.82–2.26 (m, 3H), 1.18–1.80 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 144.8, 131.6, 128.4, 127.8, 126.1, 116.3, 78.4, 66.6, 51.8, 51.1, 49.0, 34.0, 31.3, 25.5, 24.3. The free base was converted into corresponding hydrochloride salt. Mp = 210–218 °C. Anal. ($C_{27}H_{31}NO_2$.1.4HCl, 0.7H_2O) C, H, N.

5.1.23. (*S*)-1-Phenylhex-5-en-2-ol (18)

A stirred solution of (*R*)-(2,3-epoxypropyl)benzene **18** (4.0 g, 29.81 mmol) in anhydrous diethyl ether (40 mL) was reacted with copper(I) iodide (0.57 g, 2.98 mmol) and allylmagnesium chloride (2 M solution in THF, 18.90 mL, 37.81 mmol) following procedure D. The crude residue obtained was purified by silica-gel column chromatography using 10% ethyl acetate in hexanes to give compound **18** (4.1 g, 78%) as a thick colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.66 (m, 3H3H), 2.11–2.32 (m, 2H), 2.67(dd, *J* = 13.2, 8.4 Hz, 1H), 2.84 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.78–3.90 (m, 1H), 4.94–5.00 (m, 1H), 5.04 (t, *J* = 1.6 Hz, 1H), 5.05–5.09 (m, 1H), 5.78–5.90 (m 1H), 7.20–7.34 (m, 5H).

5.1.24. (*S*)-(2-(Vinyloxy)hex-5-en-1-yl)benzene (19)

To a stirred solution of alcohol **16** (2.2 g, 12.48 mmol) in excess of ethylvinyl ether (80 mL) was added mercury(II) trifluoroacetate (1.06 g, 2.50 mmol) at room temperature, and stirring was continued for 4 h according to procedure E. The crude product was dissolved in 5% ethyl acetate in hexanes, filtered through a basic alumina pad quickly, and the filtrate was concentrated under reduced pressure at room temperature to give product **19** (2.1 g, 83%) as a thick light-yellow syrup. Compound **19** was carried out to next step without purification and characterization.

5.1.25. (*S*)-2-Benzyl-3,4-dihydro-2*H*-pyran (20)

To a stirred solution of compound **19** (2.1 g, 10.38 mmol) in anhydrous benzene (100 mL) was added Grubb's (1st generation) catalyst (0.43 g, 0.52 mmol). The reaction mixture was slowly heated to reflux following procedure F. The crude residue was purified by column chromatography using 5% ethyl acetate in hexanes and recrystallized in hexanes to give compound **20** (1.52 g, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.63 (m, 1H), 1.78–1.88 (m, 1H), 1.90–2.06 (m, 2H), 2.78 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.99 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.94–4.06 (m, 1H), 4.64–4.70 (m, 1H), 6.34 (d, *J* = 6.4 Hz, 1H), 7.18–7.34 (m, 5H).

5.1.26. 6-Benzyltetrahydro-2*H*-pyran-3-ol (mixture of 21 and 22)

A stirred solution of compound **20** (1.5 g, 8.62 mmol) in anhydrous THF (10 mL) was reacted with 9-BBN (0.5 M solution in THF, 43 mL, 21.54 mmol) following procedure G. The crude residue was purified by column chromatography using 30% ethyl acetate in hexanes to give mixture of inseparable compounds **21** and **22** (1.42 g, 86%) as a thick syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.41 (m, 1H), 1.45–1.51 (m, 1H), 1.67–1.74 (m, 1H), 2.06–2.12 (m, 1H), 2.66 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.88 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.10 (t, *J* = 10.4 Hz, 1H), 3.40–3.49 (m, 1H), 3.64–3.77 (m, 1H), 4.00 (ddd, *J* = 7.2, 4.8, 2.4 Hz, 1H), 7.18–7.32(m, 5H).

5.1.27. (3*R*,6*S*)-6-Benzyltetrahydro-2*H*-pyran-3-yl methanesulfonate (23)

To an ice cooled stirred mixture of compounds **21** and **22** (0.5 g, 2.60 mmol) and triethylamine (0.72 mL, 5.20 mmol) in anhydrous DCM (15 mL) was added methanesulfonyl chloride (0.3 mL, 3.90 mmol) and reaction continued following procedure H. The residue was purified by column chromatography using 25% ethyl acetate in hexanes to elute the *trans* compound **23** (0.48 g, 69%) first as a white solid followed by the *cis* compound **24** (95 mg, 14%) as a white solid. Spectral data for **23**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41–1.52 (m, 1H), 1.62–1.72 (m 1H), 1.76–1.82 (m, 1H), 2.22–2.31 (m, 1H), 2.67 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.88 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.01 (s, 3H), 3.32 (t, *J* = 10.4 Hz, 1H), 3.45–3.53 (m, 1H), 4.13 (ddd, *J* = 7.6, 4.8, 2.4 Hz, 1H), 4.63 (ddd, *J* = 15.2, 10.8, 4.8 Hz, 1H), 7.17–7.32 (m, 5H).

5.1.28. (2*S*,5*S*)-5-Azido-2-benzyltetrahydro-2*H*-pyran (25)

A stirred solution of compound **23** (0.45 g, 1.66 mmol) in DMF (10 mL) was reacted with sodium azide (0.54 g, 8.30 mmol) using procedure I. The crude residue thus obtained was purified by column chromatography using 5% ethyl acetate in hexanes to give compound **25** (0.3 g, 83%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46–1.54 (m, 1H), 1.60–1.79 (m, 2H), 2.00 (dt, *J* = 8.8, 3.2 Hz, 1H), 2.68 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.95 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.48–3.60 (m, 3H), 3.99 (dd, *J* = 10.8, 2.4 Hz, 1H), 7.18–7.32 (m, 5H).

5.1.29. (3*S*,6*S*)-6-Benzyltetrahydro-2*H*-pyran-3-amine (26)

Azide **25** (0.3 g, 1.38 mmol) in methanol (25 mL) was hydrogenated with 10% Pd-C (30 mg, 10 wt %) using procedure J to afford amine **26** (0.3 g) as a light yellow solid in quantitative yield. The product was pure enough for continuation to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40–1.48 (m, 1H), 1.50–1.62 (m, 3H), 1.65–1.74 (m, 2H), 2.69 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.88 (br s, 1H), 2.91 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.44–3.55 (m, 1H), 3.58 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.74 (d, *J* = 11.2 Hz, 1H), 7.18–7.30 (m, 5H).

5.1.30. 4-((((3*S*,6*S*)-6-Benzyltetrahydro-2*H*-pyran-3-yl)amino)methyl)phenol (27)

To a stirred solution of amine **26** (60 mg, 0.31 mmol) and 4-hydroxy benzaldehyde (38 mg, 0.31 mmol) in 1,2-dichloroethane (6 mL) glacial acetic acid (18 μL, 0.31 mmol) was added. After being stirred for 30 min, $NaCNBH_3$ (26 mg, 0.41 mmol) was added portion-wise followed by methanol (1 mL) and reaction stirred following procedure K. Crude product was purified by column chromatography using 1–5% methanol in ethyl acetate to give compound **27** (65 mg, 70%) as a thick syrup. $[\alpha]_D^{25}$ −11.8 (*c* 0.5, MeOH). MS (ESI): *m*/*z* 298.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$ and few drops of CD_3OD): δ 1.30–1.40 (m, 2H), 1.42–1.54 (m, 1H), 1.78–1.88 (m, 1H), 2.53 (dd, *J* = 6.4, 14.0 Hz, 1H), 2.58 (br s, 1H), 2.73 (dd, *J* = 6.4, 13.6 Hz, 1H), 3.35 (dd, *J* = 1.6, 12.0 Hz, 1H), 3.38–3.42 (m, 1H), 3.58–3.64 (m, 2H), 3.82 (d, *J* = 12.8 Hz, 1H), 4.40 (br s, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 6.98–7.23 (m, 7H). ^{13}C (100 MHz, $CDCl_3$ and few drops of CD_3OD): δ 25.64, 26.09, 42.26, 49.59, 50.17, 68.91, 78.93, 115.56, 126.31, 128.31, 129.36, 130.14, 138.16, 156.68. The product was converted into the corresponding hydrochloride salt; Mp 170–172 °C. Anal. ($C_{19}H_{23}NO_2$·HCl·0.7H_2O) C, H, N.

5.1.31. (*S*)-1,1-Diphenylpent-4-en-2-ol (29)

A stirring solution of (*R*)-2-benzhydryloxirane **28** (5.14 g, 24.47 mmol) and copper(I) iodide (0.49 g, 2.61 mmol) in THF

(50 mL) was reacted with vinyl magnesium bromide (1 M solution in THF, 32.73 mL, 32.73 mmol) at −78 °C following procedure D. The crude thus obtained was purified by column chromatography using 10% ethyl acetate in hexanes to afford compound **29** (4.37 g, 75%) as colorless liquid. $[\alpha]_D^{25}$ −30.6 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08–2.16 (m, 1H), 2.25–2.32 (m, 1H), 3.91 (d, *J* = 8.4 Hz, 1H), 4.38–4.43 (m, 1H), 5.03–5.12 (m, 2H), 5.89 (sextet, *J* = 6.4 Hz, 1H), 7.16–7.47 (m, 10H).

5.1.32. (*S*)-(2-(Vinyloxy)pent-4-ene-1,1-diyl)dibenzene (30)

In a sealed tube fitted with a screw-cap was taken excess ethyl vinyl ether (10.0 mL). Mercury(II) trifluoroacetate (0.14 g, 0.33 mmol) was then added followed by alcohol **29** (0.8 g, 3.35 mmol) and triethylamine (0.14 mL, 1.00 mmol). The reaction mixture was heated to 50 °C and stirred for 6 h. Thereafter, another portion of ethyl vinyl ether (10.0 mL), mercury(II) trifluoroacetate (0.14 g, 0.33 mmol) and triethylamine (0.14 mL, 1.00 mmol) was added and the reaction stirred at 50 °C for another 6 h. After the reaction, the reaction mixture was concentrated under reduced pressure. The crude obtained was purified by eluting a short bed of three-fourth silica and one-fourth charcoal with 3% ether in hexanes. Purified compound **30** (0.44 g, 50%), along with unreacted alcohol **29** (0.34 g, 38%), was obtained as colorless oil (unstable) and was immediately taken to the next step. The reaction was done in parallel batches to obtain a total of 2.4 g of compound **30**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15–2.28 (m,1H), 2.36–2.43 (m, 1H), 3.92 (d, *J* = 7.2 Hz, 1H), 4.14 (d, *J* = 8.4 Hz, 1H), 4.24 (dd, *J* = 14.4 Hz, 1.6 Hz, 1H), 4.51–4.55 (m,1H), 5.0 (dd, *J* = 17.2 Hz, 1.6 Hz, 1H), 5.05–5.13 (m, 1H), 5.78–5.91 (m, 1H), 6.19 (dd, *J* = 13.6 Hz, 6.4 Hz, 1H), 7.18–7.40 (m, 10H).

5.1.33. (*S*)-2-Benzhydryl-2,3-dihydrofuran (31)

Compound **27** (2.4 g, 9.07 mmol) was dissolved in benzene (40 mL) and Grubb's (1st gen) catalyst (2.24 g, 2.72 mmol) was added portion-wise over 3 h. The reaction mixture was heated at 50 °C for 6 h under N_2 atmosphere. The reaction mixture was then filtered over a short bed of Celite and the filtrate concentrated under reduced pressure. The crude obtained was purified by column chromatography using 5% ether in hexanes to afford compound **31** (1.14 g, 53%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33–2.41 (m, 1H), 2.56–2.65 (m, 1H), 4.12 (d, *J* = 9.2 Hz, 1H), 4.84 (q, *J* = 2.4 Hz, 1H), 5.31 (q, *J* = 9.2 Hz, 1H), 6.32 (q, *J* = 2.4 Hz, 1H), 7.16–7.36 (m, 10H).

5.1.34. 5-Benzhydryltetrahydrofuran-3-ol (mixture of 32 and 33)

A stirred solution of compound **31** (1.14 g, 4.82 mmol) in THF (15 mL) was reacted with 9-BBN (0.5 M solution in THF, 14.47 mL, 7.23 mmol) following procedure G. The crude was purified by column chromatography using 15% ether in hexanes to yield a mixture of two inseparable diastereomer **32** and **33** (0.65 g, 53%); which was taken to the next step without further purification.

5.1.35. 5-Benzhydryltetrahydrofuran-3-yl methanesulfonate (mixture of 34 and 35)

A stirred solution of a mixture of compounds **32** and **33** (0.65 g, 2.55 mmol), triethylamine (0.70 mL, 5.10 mmol) and methanesulfonyl chloride (0.236 mL, 3.06 mmol) was reacted using procedure H. The crude (0.91 g) containing a mixture of two diastereomers **34** and **35** was inseparable chromatographically and was taken to the next step without purification.

5.1.36. (2*S*,4*S*)-4-Azido-2-benzhydryltetrahydrofuran (36) and (2*S*,4*R*)-4-azido-2-benzhydryltetrahydrofuran (37)

A stirred solution of a mixture of compounds **34** and **35** (0.90 g, crude) in DMF (20 mL) was reacted with sodium azide (0.668 g, 10.27 mmol) using procedure I. The crude residue thus obtained was purified by column chromatography using 1–5% ethyl acetate in hexanes to give two separable diastereomers in an isomeric ratio of about 3:1. Compound **36** (0.26 g, overall 36%) was obtained as a major component and compound **37** as a minor diastereomer (0.090 g, overall 12%). For compound **36** $[\alpha]_D^{25}$ +9.8 (*c* 1, MeOH); for compound **37** $[\alpha]_D^{25}$ −13.8 (*c* 0.5, MeOH).

5.1.37. (2*S*,4*S*)-4-Azido-2-benzhydryltetrahydrofuran (36)

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75 (ddd, *J* = 13.4 Hz, 7.0 Hz, 3.6 Hz, 1H), 2.25 (dt, *J* = 13.7 Hz, 7.3 Hz, 1H), 3.84 (dd, *J* = 10.0 Hz, 5.5 Hz, 1H), 3.96 (dd, *J* = 9.7 Hz, 2.4 Hz, 1H), 4.05–4.10 (m, 2H), 4.66 (dt, *J* = 9.4 Hz, 7.3 Hz, 1H), 7.16–7.36 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 37.3, 57.0, 61.2, 73.0, 81.3, 126.8, 127.0, 128.5, 128.6, 128.7, 128.9, 142.2, 142.4.

5.1.38. (2*S*,4*R*)-4-Azido-2-benzhydryltetrahydrofuran (37)

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.81–1.86 (m, 1H1H), 1.99 (dd, *J* = 13.2 Hz, 5.2 Hz, 1H), 3.83 (dd, *J* = 10.0 Hz, 2.4 Hz, 1H), 3.92 (d, *J* = 8.4 Hz, 1H), 3.98 (dd, *J* = 9.7 Hz, 5.2 Hz, 1H1H), 4.08–4.12 (m, 1H), 4.84 (dt, *J* = 9.4 Hz, 7.3 Hz, 1H), 7.12–7.36 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 34.0, 56.9, 61.6, 72.8, 80.5, 126.8, 127.0, 128.5, 128.7, 128.7, 128.9, 142.0, 142.4.

5.1.39. (3*S*,5*S*)-5-Benzhydryltetrahydrofuran-3-amine (38)

Compound **36** (0.26 g, 0.73 mmol) was hydrogenated with 10% Pd/C (26 mg, 10 wt %) using procedure J to afford compound **38** (0.23 g) as colorless oil in quantitative yield which was pure enough for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36–1.41 (m, 1H), 2.11–2.19 (m, 1H1H), 3.29–3.34 (m, 1H), 3.44–3.51 (m, 1H), 3.78–3.81 (m, 1H), 4.01–4.07 (m, 1H1H), 4.63–4.69 (m, 1H), 7.12–7.35 (m, 10H).

5.1.40. (3*R*,5*S*)-5-Benzhydryltetrahydrofuran-3-amine (39)

Compound **37** (0.09 g, 0.32 mmol) was stirred with 10% Pd/C (9 mg, 10 wt %) under hydrogen atmosphere following procedure J to yield compound **39** (0.065 g, 80.2%) which was taken to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39–1.46 (m, 1H), 2.17–2.24 (m, 1H), 3.54–3.59 (m, 2H), 3.81–3.87 (m, 1H), 4.08 (d, *J* = 8.3 Hz, 1H1H), 4.60–4.66 (m, 1H), 7.12–7.35 (m, 10H).

5.1.41. 3-((((3*S*,5*S*)-5-Benzhydryltetrahydrofuran-3-yl)amino)methyl)phenol (40)

Amine intermediate **38** (20 mg, 0.06 mmol) and 4-hydroxybenzaldehyde (10 mg, 0.06 mmol) were dissolved in DCM (1.3 mL). MeOH (0.3 mL) and AcOH (3.2 μL) were then added and reaction stirred for 30 min. $NaCNBH_3$ (10 mg, 0.09 mmol) was added and reaction continued following procedure K to obtain crude which was purified by column chromatography using 1–5% MeOH in DCM to afford target compound **40** (10 mg, 36%). $[\alpha]_D^{25}$ −2.62 (*c* 0.5, MeOH). MS (ESI): *m*/*z* 360.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49–1.56 (m, 1H), 2.17–2.24 (m, 1H), 3.41 (quintet, *J* = 6.4 Hz, 1H), 3.53–3.61 (m, 2H), 3.76 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.81 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.06 (d, *J* = 8.4 Hz, 1H), 4.62 (q, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 2H), 7.02–7.34 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 38.4, 51.9, 57.2, 58.2, 73.1, 81.2, 115.8, 126.7, 126.8, 128.6, 128.7, 128.8, 129.9, 142.3, 142.7. The free base was converted into its corresponding hydrochloride salt. Mp 142–148 °C. Anal. ($C_{24}H_{25}NO_3 \cdot HCl \cdot 1.8H_2O$) C, H, N.

5.1.42. 4-(2-(((3*S*,5*S*)-5-Benzhydryltetrahydrofuran-3-yl)amino)ethyl)phenol (41)

Compound **38** (30 mg, 0.12 mmol) and 4-hydroxyphenyl acetaldehyde (20 mg, 0.12 mmol) were dissolved in DCM (2.4 mL). MeOH (0.6 mL) and AcOH (15 μL) were then added and reaction

stirred for 30 min. $NaCNBH_3$ (10.0 mg, 0.18 mmol) was added and reaction continued according to procedure K. The crude obtained was purified by column chromatography using 1–5% MeOH in DCM to afford target compound **41** (20 mg, 46%) as colorless oil. $[\alpha]_D^{25}$ −0.6 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43–1.50 (m, 1H), 2.12–2.17 (m, 1H), 2.59–2.74 (m, 4H), 3.35–3.40 (m, 1H), 3.72 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.81 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.98 (d, *J* = 8.8 Hz, 1H), 4.59 (q, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H) 7.15–7.31 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 35.2, 38.1, 49.7, 57.2, 58.8, 73.0, 81.2, 115.8, 126.7, 126.8, 128.6, 128.7, 128.7, 129.9, 131.0, 142.4, 142.7, 154.9. The free base was converted into its corresponding hydrochloride salt. Mp = 152–158 °C. Anal. ($C_{25}H_{27}NO_3{\cdot}HCl{\cdot}0.8H_2O$) C, H, N.

5.1.43. (3*S*,5*S*)-5-Benzhydryl-*N*-(4-methoxyphenethyl)tetrahydrofuran-3-amine (42)

Amine intermediate **38** (70 mg, 0.27 mmol) and 4-methoxyphenyl acetaldehyde (50 mg, 0.33 mmol) were dissolved in 1,2-DCE (7 mL). MeOH (0.5 mL) and AcOH (16 μL) were then added and reaction stirred for 30 min. $Na(OAc)_3BH$ (0.117 g, 0.54 mmol) was thereafter added and reaction continued using procedure K. The crude obtained was purified by column chromatography using 1–5% MeOH in DCM to afford target compound **42** (43 mg, 41%). $[\alpha]_D^{25}$ −10.3 (*c* 0.82, DCM). MS (ESI): *m*/*z* 388.5 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.35–1.50 (m, 1H), 2.09–2.16 (m, 1H), 2.65–2.75 (m, 4H), 3.35–3.41 (m, 1H), 3.64 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.78 (s, 3H), 3.76–3.80 (m, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 4.59 (q, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H) 7.17–7.21 (m, 2H), 7.27–7.34 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 35.3, 38.2, 49.7, 55.1, 57.2, 58.6, 73.1, 80.8, 113.7, 126.2, 126.4, 128.2, 128.2, 128.3, 128.4, 129.5, 131.9, 142.7, 142.9, 158.0. The free base was converted into its corresponding hydrochloride salt. Mp = 172–174 °C. Anal. ($C_{26}H_{29}NO_2{\cdot}HCl{\cdot}0.1H_2O$) C, H, N.

5.1.44. (3*S*,5*S*)-5-Benzhydryl-*N*-(4-fluorophenethyl)tetrahydrofuran-3-amine (43)

Amine intermediate **38** (70 mg, 0.27 mmol) and 4-fluoro phenyl acetaldehyde (46 mg, 0.33 mmol) were dissolved in 1,2-DCE (6 mL). MeOH (0.5 mL) and AcOH (16 μL) were then added and reaction stirred for 30 min. $Na(OAc)_3BH$ (70 mg, 0.33 mmol) was thereafter added and reaction continued following procedure K. The crude obtained was purified by column chromatography using 1–5% MeOH in DCM to yield compound **43** (40 mg, 39%). $[\alpha]_D^{25}$ −2.7 (*c* 0.78, DCM). MS (ESI): *m*/*z* 376.5 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.33–1.41 (m, 1H), 2.09–2.16 (m, 1H), 2.66–2.77 (m, 4H), 3.39 (quintet, *J* = 6.12 Hz, 1H), 3.64 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.79 (dd, *J* = 8.8, 6.11 Hz, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 4.61 (q, *J* = 8.56 Hz, 1H), 7.00 (t, *J* = 8.8 Hz, 2H), 7.19 (m, 4H), 7.26–7.36 (m, 8H). ^{13}C NMR (CD_2Cl_2) δ 36.0, 38.7, 49.9, 57.6, 59.0, 73.5, 81.2, 115.2, 115.4, 126.6, 126.8, 128.5, 128.6, 128.7, 128.8, 130.4, 130.5, 136.3, 143.1, 143.2. The free base was converted into its corresponding hydrochloride salt. Mp = 168–170 °C. Anal. ($C_{25}H_{26}FNO_1{\cdot}HCl{\cdot}0.1H_2O$)C, H, N.

5.1.45. (3*S*,5*S*)-5-Benzhydryl-*N*-phenethyltetrahydrofuran-3-amine (44)

Amine intermediate **38** (30 mg, 0.118 mmol) and phenyl acetaldehyde (17 mg, 0.142 mmol) were dissolved in 1,2-DCE (3 mL). MeOH (0.3 mL) and AcOH (8 μL) were then added and reaction stirred for 30 min. $Na(OAc)_3BH$ (10 mg, 0.142 mmol) was thereafter added and reaction continued following procedure K. The crude obtained was purified by column chromatography using 1–5% MeOH in DCM to yield compound **44** (15 mg, 36%). $[\alpha]_D^{25}$ −12.7 (*c* 0.66, DCM). MS (ESI): *m*/*z* 358.5 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.33–1.40 (m, 1H), 2.09–2.16 (m, 1H), 2.69–2.78 (m, 4H), 3.39 (quintet, *J* = 6.40 Hz, 1H), 3.64 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.79 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 4.61 (q, *J* = 9.2 Hz, 1H), 7.19–7.34 (m, 15H). ^{13}C NMR (CD_2Cl_2) δ 33.3, 35.1, 47.7, 55.9, 58.0, 70.3, 81.0, 126.6, 126.7, 126.9, 128.2, 128.3, 128.3, 128.4, 128.6, 128.6, 128.7, 141.6, 141.7. The free base was converted into its corresponding hydrochloride salt. Mp = 132–134 °C. Anal. $C_{25}H_{27}NO{\cdot}HCl{\cdot}0.1H_2O$. C, H, N.

5.1.46. 3-((((3*R*,5*S*)-5-Benzhydryltetrahydrofuran-3-yl)amino)methyl)phenol (45)

Compound **39** (20 mg, 0.14 mmol) and 4-hydroxyphenyl acetaldehyde (20 mg, 0.14 mmol) were dissolved in DCM (1.3 mL). MeOH (0.6 Ml) and AcOH (20 μL) were then added and reaction stirred for 30 min. $NaCNBH_3$ (10.0 mg, 0.21 mmol) was added and reaction continued according to procedure K. The crude obtained was purified by column chromatography using 1–5% MeOH in DCM to afford target compound **45** (10 mg, 19%) as colorless liquid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.26–1.38 (m, 1H), 1.97 (m, 1H), 3.44–3.51 (m, 1H), 3.74–3.77 (m, 1H), 3.93–4.03 (m, 2H), 4.21–4.27 (m, 1H), 4.31–4.48 (m, 2H), 6.87–6.95 (m, 4H), 7.10–7.37 (m, 10H). ^{13}C NMR (CD_3OD) δ 38.4, 51.9, 57.2, 58.2, 73.1, 81.2, 115.8, 126.7, 126.8, 128.6, 128.7, 128.8, 129.9, 142.3, 142.7. The free base was converted into its corresponding hydrochloride salt. Mp = 132–138 °C. HRMS calcd for $C_{24}H_{25}NO_3$ (M^+): 359.19. Found: 359.18.

5.1.47. (3*R*,5*S*)-5-Benzhydryl-*N*-benzyltetrahydrofuran-3-amine (46)

Compound **39** (36 mg, 0.14 mmol) and phenylacetaldehyde (20 mg, 0.17 mmol) were dissolved in DCM (3.5 mL). MeOH (0.6 mL) and AcOH (10 μL) were then added and reaction stirred for 30 min. $Na(OAc)_3BH$ (36 mg, 0.17 mmol) was thereafter added and reaction continued following procedure K. The crude obtained was purified by column chromatography using 1–5% MeOH in DCM to afford target compound **46** (15 mg, 31%) as colorless liquid. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.68–1.78 (m, 2H), 2.70–2.84 (m, 4H), 3.94 (m, 1H), 3.52 (m, 1H), 3.79 (m, 1H), 3.97 (m, 1H), 4.61 (m, 1H), 7.15–7.35 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 36.7, 38.5, 49.8, 57.5, 58.8, 73.9, 80.5, 126.4, 126.5, 126.7, 128.5, 128.6, 128.7, 128.7, 128.8, 128.9, 140.5, 143.1, 143.3. The free base was converted into its corresponding hydrochloride salt. Mp = 112–114 °C. HRMS calcd for $C_{25}H_{28}NO$ (M^+): 358.2162. Found: 358.2171.

5.2. Transporter assays

The ability of test compounds to inhibit substrate uptake by rat monoamine transporters was monitored exactly as described by us previously.[42] Briefly, accumulation was measured of [^{3}H]DA ([Ring 2,5,6-^{3}H]dopamine (45.0 Ci/mmol, Perkin–Elmer, Boston, MA, U.S.A.) for 5 min for monitoring DAT (rat striatum), and 7 min for NET (rat cerebral cortex) (please note that DA is an excellent substrate for NET, for our previous discussion see Ref. 43). Uptake of [^{3}H]5-HT ([1,2-3*H*]serotonin (27.9 Ci/mmol, Perkin–Elmer) was measured for 10 min for monitoring SERT (rat cerebral cortex). Drug stocks contained an additional 0.01% (w/v) bovine serum albumin in order to reduce absorption of drug to the walls of the assay plates. At least five triplicate concentrations of each test compound were studied, spaced evenly around the IC_{50} value which was converted to K_i with the Cheng–Prusoff equation.[43] With observed K_m values and [^{3}H]ligand concentrations used, the conversion factors (multipliers applied to IC_{50} for calculating K_i) were $\geqslant$0.84.

5.3. Pharmacophore model

Computational studies were conducted on Hewlett–Packard xw4300 computer workstation under the Red Hat Enterprise Linux

5 operating system using Molecular Operating Environment (MOE, 2012.10 from chemical computing group, Montreal, Canada) software package. Structures, drawn using the Builder module, were assigned partial atomic charges and then energy minimized using the MMFF94x force field available in MOE. The secondary amines were converted into their respective protonated states. Conformational search was performed using systemic and stochastic method both of which generated similar output of conformers. Stochastic method was preferred over systemic for further analysis as it is computationally less expensive and is a method of choice to locate the global energy minima for small molecules. Moreover, literature studies have suggested that systemic search algorithm may present difficulties in compounds containing tetrahydropyran or other aliphatic rings.[43] Stochastic search generates conformations by a random (usually 30 degrees) increment of rotatable bonds (including rings). RMS gradient of 0.005 and an iteration limit of 10,000 were kept for energy minimization. The conformational limit was set to 500. Rejection limit cut off prior to termination was kept at 100. Energy window cut off of E = 10 kcal/mol of the lowest energy was kept to access all reasonable conformations and rmsd of $\leqslant$0.1 Å was used to remove all duplicate conformations. The selected conformations were subjected to flexible alignment and aligned molecules were subsequently used to build pharmacophore model using pharmacophore elucidator module in MOE. The elucidator identifies common functional groups and aligns the pharmacophoric features present in the molecules. Unified scheme with default parameters were used for the pharmacophore development.

Acknowledgment

This work is supported by National Institute of Mental Health/ National Institute of Health MH084888 (A.K.D.).

Supplementary data

Supplementary data (2D stereochemical characterization of the major azide intermediate **36**, molecular modeling, and elemental analysis data for final targets) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.11.017.

References and notes

1. Millan, M. J. *Neurotherapeutics* **2009**, *6*, 53.
2. Coppen, A. *Br. J. Psychiatry* **1967**, *113*, 1237.
3. Hensler, J. G. *Life Sci.* **2003**, *72*, 1665.
4. Bel, N.; Artigas, F. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 1064.
5. Richelson, E. *J. Clin. Psychiatry* **2003**, *64*, 5.
6. Svensson, T. H. *Acta Psychiatr. Scand. Suppl.* **2000**, *402*, 18.
7. Shulman, K. I.; Herrmann, N.; Walker, S. E. *CNS Drugs* **2013**.
8. Rose, J. B. *Clin. Toxicol.* **1977**, *11*, 391.
9. Spinks, D.; Spinks, G. *Curr. Med. Chem.* **2002**, *9*, 799.
10. Wong, D. T.; Bymaster, F. P. *Adv. Exp. Med. Biol.* **1995**, *363*, 77.
11. Hiemke, C.; Hartter, S. *Pharmacol. Ther.* **2000**, *85*, 11.
12. Owens, M. J.; Nemeroff, C. B. *Depress Anxiety* **1998**, *8*, 5.
13. Di Giovanni, G.; Esposito, E.; Di Matteo, V. *CNS Neurosci. Ther.* **2010**, *16*, 179.
14. Thase, M. E.; Entsuah, A. R.; Rudolph, R. L. *Br. J. Psychiatry* **2001**, *178*, 234.
15. Barbey, J. T.; Roose, S. P. *J. Clin. Psychiatry* **1998**, *59*, 42.
16. Goldstein, B. J.; Goodnick, P. J. *J. Psychopharmacol.* **1998**, *12*, S55.
17. Gumnick, J. F.; Nemeroff, C. B. *J. Clin. Psychiatry* **2000**, *61*, 5.
18. Steffens, D. C.; Krishnan, K. R.; Helms, M. J. *Depress Anxiety* **1997**, *6*, 10.
19. Rush, A. J.; Trivedi, M. H.; Wisniewski, S. R.; Nierenberg, A. A.; Stewart, J. W.; Warden, D.; Niederehe, G.; Thase, M. E.; Lavori, P. W.; Lebowitz, B. D.; McGrath, P. J.; Rosenbaum, J. F.; Sackeim, H. A.; Kupfer, D. J.; Luther, J.; Fava, M. *Am. J. Psychiatry* **1905**, *2006*, 163.
20. D'Aquila, P. S.; Collu, M.; Gessa, G. L.; Serra, G. *Eur. J. Pharmacol.* **2000**, *405*, 365.
21. Papakostas, G. I. *Eur. Neuropsychopharmacol.* **2006**, *16*, 391.
22. Dunlop, B. W.; Nemeroff, C. B. *Arch. Gen. Psychiatry* **2007**, *64*, 327.
23. Nutt, D.; Demyttenaere, K.; Janka, Z.; Aarre, T.; Bourin, M.; Canonico, P. L.; Carrasco, J. L.; Stahl, S. *J. Psychopharmacol.* **2007**, *21*, 461.
24. Nestler, E. J.; Carlezon, W. A., Jr. *Biol. Psychiatry* **2006**, *59*, 1151.
25. Mischoulon, D.; Nierenberg, A. A.; Kizilbash, L.; Rosenbaum, J. F.; Fava, M. *Can. J. Psychiatry* **2000**, *45*, 476.
26. Ascher, J. A.; Cole, J. O.; Colin, J. N.; Feighner, J. P.; Ferris, R. M.; Fibiger, H. C.; Golden, R. N.; Martin, P.; Potter, W. Z.; Richelson, E., et al *J. Clin. Psychiatry* **1995**, *56*, 395.
27. Sporn, J.; Ghaemi, S. N.; Sambur, M. R.; Rankin, M. A.; Recht, J.; Sachs, G. S.; Rosenbaum, J. F.; Fava, M. *Ann. Clin. Psychiatry* **2000**, *12*, 137.
28. Marks, D. M.; Pae, C. U.; Patkar, A. A. *Curr. Neuropharmacol.* **2008**, *6*, 338.
29. Guiard, B. P.; El Mansari, M.; Blier, P. *Curr. Drug Targets* **2009**, *10*, 1069.
30. Prins, J.; Olivier, B.; Korte, S. M. *Exp. Opin. Investig. Drugs* **2011**, *20*, 1107.
31. Liang, Y.; Shaw, A. M.; Boules, M.; Briody, S.; Robinson, J.; Oliveros, A.; Blazar, E.; Williams, K.; Zhang, Y.; Carlier, P. R.; Richelson, E. *J. Pharmacol. Exp. Ther.* **2008**, *327*, 573.
32. Skolnick, P.; Krieter, P.; Tizzano, J.; Basile, A.; Popik, P.; Czobor, P.; Lippa, A. *CNS Drug Rev.* **2006**, *12*, 123.
33. Zhang, S.; Fernandez, F.; Hazeldine, S.; Deschamps, J.; Zhen, J.; Reith, M. E.; Dutta, A. K. *J. Med. Chem.* **2006**, *49*, 4239.
34. Gopishetty, B.; Hazeldine, S.; Santra, S.; Johnson, M.; Modi, G.; Ali, S.; Zhen, J.; Reith, M.; Dutta, A. *J. Med. Chem.* **2011**, *54*, 2924.
35. Zhang, S.; Zhen, J.; Reith, M. E.; Dutta, A. K. *J. Med. Chem.* **2005**, *48*, 4962.
36. Gopishetty, B.; Gogoi, S.; Dutta, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1081.
37. Dutta, A. K.; Ghosh, B.; Biswas, S.; Reith, M. E. *Eur. J. Pharmacol.* **2008**, *589*, 73.
38. Dutta, A. K.; Gopishetty, B.; Gogoi, S.; Ali, S.; Zhen, J.; Reith, M. *Eur. J. Pharmacol.* **2011**, *671*, 39.
39. Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225.
40. Zhang, S.; Zhen, J.; Reith, M. E.; Dutta, A. K. *Bioorg. Med. Chem.* **2004**, *12*, 6301.
41. Pandit, D.; Roosma, W.; Misra, M.; Gilbert, K. M.; Skawinski, W. J.; Venanzi, C. A. *J. Mol. Model.* **2011**, *17*, 181.
42. Santra, S.; Gogoi, S.; Gopishetty, B.; Antonio, T.; Zhen, J.; Reith, M. E.; Dutta, A. K. *ChemMedChem* **2012**, *7*, 2093.
43. Chen, I. J.; Foloppe, N. *J. Chem. Inf. Model.* **2008**, *48*, 1773.