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Structurally constrained hybrid derivatives containing octahydrobenzo[*g* or *f*]quinoline moieties for dopamine D2 and D3 receptors: Binding characterization at D2/D3 receptors and elucidation of a pharmacophore model

Dennis A. Brown[a], **Prashant S. Kharkar**[a], **Ingrid Parrington**[b], **Maarten E.A. Reith**[b], and **Aloke K. Dutta**[a,*]

a *Department of Pharmaceutical Sciences, Wayne State University, Detroit, Michigan 48202*

b *New York University School of Medicine, Millhauser Laboratories, Department of Psychiatry, New York, NY 10016*

Abstract

A series of structurally constrained analogues based on hybrid compounds containing octahydrobenzo[*g* or *f*]quinoline moieties were designed, synthesized and characterized for their binding to dopamine D2 and D3 receptors expressed in HEK-293 cells. Among the newly developed constrained molecules, *trans*-octahydrobenzo[*f*]-quinolin-7-ol (**8**) exhibited the highest affinity for D2 and D3 receptors; the (−)-isomer being the eutomer. Interestingly, this hybrid constrained version **8** showed significant affinity over the corresponding non-hybrid version **1** (representing a constrained version of the aminotetralin structure only) when assayed under same conditions (K_i 49.1 and 14.9 nM for **8** vs. 380 and 96.0 nM for **1** at D2 and D3, respectively). Similar results were found with other lead hybrid compounds, indicating a contribution of the piperazine moiety in the observed enhanced affinity. Based on the data of new lead constrained derivatives and other lead hybrid derivatives developed by us, a unique pharmacophore model was proposed consisting of three pharmacophoric centers, two with aromatic/hydrophobic and one with cationic features.

Introduction

The dopamine (DA) receptor system has been aggressively targeted for drug development for the treatment of psychiatric illnesses, neurodegeneration, drug abuse, and other therapeutic areas.[1,2] The DA receptors, belonging to a class of G-protein coupled receptors (GPCRs), are found in the central nervous system (CNS) and in the periphery.[3] In the CNS, DA receptors can be classified as being either D_1-like or D_2-like. The D_1-like receptors include the D1 and D5 subtypes, and the D_2-like receptors include the D2, D3, and D4 subtypes. These classifications are made on the basis of receptor pharmacology and function. Both D_1-like and D_2-like DA receptors share the same effector molecule, adenylate cyclase. Upon receptor activation, D_1-like receptors activate adenylate cyclase, whereas D_2-like receptors inhibit it.[4]

An enormous amount of work has been done towards the development of DA agonists.[5] The initial research was focused on elucidating the bioactive conformation of the natural ligand, DA.[6–10] These efforts yielded the constrained class of compounds known as 2-aminotetralins,

Corresponding author: Aloke K. Dutta, Ph.D., Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy & Health Sciences, Rm# 3128, Detroit, MI 48202, Tel: 1-313-577-1064, Fax: 1-313-577-2033, e-mail: adutta@wayne.edu.

including (S)-(−)-5-hydroxy-2-(N,N-di-n-propylamino)tetralin [(S)-(−)-5-OH-DPAT], Figure 1[6] and (R)-(+)-7-hydroxy-2-(N,N-di-n-propylamino)tetralin [(R)-(+)-7-OH-DPAT], Figure 1[11], corresponding to the α-and β-rotamers of DA, respectively. These studies revealed not only the bioactive conformation of the phenethyl side chain of DA but also that among the two hydroxyl groups in DA, the *m*-hydroxyl group is the most important in terms of receptor activation.[6] In regards to agonist interaction with the D2 and D3 subtype receptors at molecular level, a number of excellent studies with mutant D2 and D3 receptors have been published which delineated key binding residues in trans-membrane domains 3, 5, and 7 for receptor activation.[12–14] Briefly, these studies indicated that two serine residues in TM-5, and one aspartate residue in TM-3 are critical for activation by agonists of both D2 and D3 receptors. The Asp110 residue in TM-3 has been shown to interact with the basic N-atom in DA and aminotetralin molecules. In these studies, Ser192 has been especially shown to be crucial for D3 interaction and activation. All these results suggest the existence of multiple bioactive conformations available for different agonists, resulting from different degrees of interactions with these key residues producing one signaling pathway.

The influence of the freely rotating amino group in 2-aminotetralins has been explored by introducing further conformational constraint into derived structures by the addition of another annulated ring, giving rise to monophenolic cis- and trans-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolines[15] and monophenolic cis- and trans-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines.[16] Extensive SAR studies based on *in vitro* functional data have been conducted to determine the influence of hydroxyl group position, alkyl group chain length, and the geometry of ring fusion.[15–19] These studies showed that for phenolic 1,2,3,4,4a,5,10,10a-octahydrobenz[*g*]- and 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines, only compounds having *trans* ring fusion were active (**1**, **2**, **3**, Figure 1)[15,16]; the corresponding *cis* analogs were almost completely inactive. This is largely attributed to the protonated amino group being unfavorably positioned to interact with the key aspartate residue in the cis conformation.[15] Compounds that showed activity in the functional assays had hydroxyl group substitution at either the 6 position [for benzo[*g*]quinolines (**2**, Figure 1)] or the 7/9 position for benzo[*f*]quinolines (**1** and **3**, Figure 1), corresponding to the α-and β-rotameric forms, respectively.[15,17a] In this regard, it is important to mention that to the best of our knowledge no systematic receptor binding studies for DA receptor subtypes (D2 and D3) have been reported with these constrained derivatives and hence, there is a lack of information on precise binding affinity of these derivatives with the respective receptor.

The effect of N-alkyl chain length on functional activity has also been investigated.[15,16] Linearly fused *trans* compounds with hydroxyl group in the 6-position with alkyl groups *n*-propyl or smaller showed good functional activity. However, any compound containing an alkyl group larger than *n*-propyl was completely inactive, indicating the presence of a small alkyl-binding site in the receptor.[15] Also, all 8-hydroxy compounds (e.g., compound **4** in Figure 1) were inactive, regardless of alkyl substitution. Angularly fused compounds, e.g. **1** and **3**, like their linear counterparts with 6-OH substitution, also showed functional activity. Interestingly, 7-OH angular compounds tolerated alkyl group size larger than *n*-propyl in functional assays. In fact, *n*-butyl or larger substitution showed enhanced affinity, showing that there is an additional "large" alkyl-binding site in D_2-like DA receptors.[10,15] The relatively lower activity in octahydrobenzo[*g*]quinolinol series, compared to the octahydrobenzo[*f*]quinolinol series of compounds, was attributed to the unfavorable orientation of the nitrogen lone pair or protonated nitrogen atom and a sterically unfavorable orientation of the piperidine ring. Again, in all these studies, the precise nature of interaction was not available due to the lack of quantitative binding data for DA D2 and D3 receptor subtypes.

In an effort to develop novel, potent, and selective ligands for the DA D3 receptor subtype, our lab employed a hybrid structure approach, combining known DA agonist moieties with the

N-arylpiperazine moiety derived from known D3 antagonists (Figure 2).[20,21] This approach was based on the assumption that the aminotetralin moiety would interact with the agonist binding site in the DA receptor and the arylpiperazine fragment would interact with the accessory binding site residues in the D3 receptor to impart selectivity. Based on this approach, our group has been able to create highly potent DA D2/D3 agonists, with some compounds being very selective for the D3 receptor.[21–23] Compounds (−)-**7** and **11** (Figure 3), two of our promising lead structures, exhibited high D3 selectivity in the functional assays and high *in vivo* potency in Parkinson's disease animal models.[22,23] In our effort to develop a pharmacophore model for our hybrid structures, we designed and synthesized a series of compounds that contain varying degrees of conformational constraint in the agonist moiety of the hybrid template. These compounds were then evaluated for their binding affinities at human D2L and D3 receptors in human embryonic kidney (HEK)-293 cell lines. Using molecular modeling approaches we report in this paper the development of a 3-point pharmacophore model for the binding of hybrid compounds to D2/D3 receptors.

Chemistry

Scheme 1 outlines the synthesis of (±)-*cis*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-8-ol derivatives. Amides **13a–c** were prepared via condensation with appropriately substituted phenylpiperazines and chloroacyl chlorides in the presence of triethylamine. Originally, our aim was to synthesize only *trans* ring fused 1,2,3,4,4a,5,10,10a-octahydrobenzo[*f* and *g*] quinoline-8-ol molecules. When following the reported preparation procedure for *trans*-1,2,3,4,4a,5,10,10a-octahydrobenz[*g*]quinoline[24], we were unable to obtain the intermediate 8-methoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[*g*]quinoline in satisfactory yield, so we set out on devising an alternative synthesis. In the first step, 3-methoxybenzyl bromide **14** was treated with activated zinc dust in THF to give zinc bromide **15**, which underwent a trans-metallation reaction with methyl 2- chloronicotinate in the presence of $(PPh_3)_2NiCl_2$ to give intermediate **16**[25], which was then reduced catalytically with PtO_2 to yield substituted *cis*- and *trans*-piperidines **17**. The mixture of *cis*- and *trans*-isomers was not separated in the subsequent transformations. The amine **17** was then protected by conversion to its methyl carbamate. the ester was hydrolyzed by treatment with LiOH in $MeOH/H_2O$, and the resulting acid converted to its acid chloride by reaction with $SOCl_2$. A Friedel-Crafts acylation reaction with $TiCl_4$ was performed to yield benzylic ketone (±)-**19**. The ketone was reduced catalytically with Pd/C in the presence of perchloric acid, and then the carbamate was cleaved by treatment with hydrazine and KOH in ethylene glycol to give secondary amine (±)-**21**.

The relative stereochemical assignments of octahydrobenzoquinoline intermediates in this paper were made by converting the corresponding secondary amine intermediates e.g. compound **21** in Scheme 1, to their N-benzyl analogs and observing the ^1H NMR splitting pattern of the N-benzyl protons. It has been reported that the N-benzyl protons in N-benzyl substituted *cis*- and *trans*-fused octahydrobenzo[*f* and *g*]quinolines appear as an AB quartet, and that the chemical shift difference between the A and B portions differ between *cis*- and *trans*-fused compounds.[26] The observed chemical shift difference for *cis*- fused compounds is around 0.6 δ ppm, whereas the difference for the *trans*-fused counterparts is much larger, around 0.9 to 1.0 δ ppm. The chemical shift differences of our synthesized compounds are in accordance with these reported values. Please see the supporting information section for the syntheses and NMR data for N-benzyl compounds.

Amine (±)-**21** was condensed with chlorides **13a** and **13b**, to give amides (±)-**22a–b**, respectively. The amide carbonyls were then reduced with $LiAlH_4$ to provide **23a–b**. Demethylation of methyl ethers by BBr_3 in CH_2Cl_2, gave the final compounds (±)-**24a–b**.

The second attempt to synthesize (±)-*trans*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline derivatives is described in Scheme 2. The first aim of this synthesis was to selectively alkylate position 1 of 7-methoxy-2-tetralone **25.** This was accomplished by converting **25** to its enolate with NaH followed by trapping with dimethyl carbonate to give compound **26**.[27] This was then converted to its dianion with LDA and treated with chloroproionitrile to give **27**. This ester was decarboxylated in the presence of LiCl and H_2O in DMSO to yield ketone **28,** which was then protected by conversion to acetal. The cyano group was reduced in the presence of Raney Ni to give amine **30**, which was then treated with HCl/MeOH to give iminium **31**. The second aim of this synthesis was accomplished by controlling the stereoselectivity of iminium reduction of **31** by using $NaCNBH_3$. *Trans*-fused secondary amine (±)-**32** was the major product detected (stereochemistry assigned based on N-benzyl method).[26] Amine (±)-**32** was alkylated with **13a–c** to yield amides (±)-**33a–c**. These amides were reduced and demethylated in the same manner as described above to produce targets (±)-**35a–c**.

Scheme 3 outlines the synthesis of (±)-*trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo [*f*]quinolin-7-ol derivatives. Amine (±)-**36** was synthesized as previously described.[28] Racemic **37** was prepared by N-alkylating (±)-**36** with chloride **13a** to give amide (±)-**37**, which was then reduced and demethylated to give (±)-**8**. Compound (±)-**36** was next resolved into its enantiomers by following the procedure described by Wikström *et al*[16] as shown in Scheme 4. Experimental details for separation of enantiomers are provided in the supporting information section. Compounds (+)-**8** and (−)-**8** were obtained by following the same procedure as for the racemic version. Compound (±)-*trans*-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinolin-7-ol (**1**) was also synthesized from amine (±)-**36** as a reference compound.

Scheme 5 outlines the synthesis of (±)-*trans*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*] quinolin-6-ol derivatives. Secondary amine **40** was prepared as previously described.[29] Completion of the syntheses of (±)-**43a–b** was carried out in a similar manner as described for the previous compounds. The reference compound **2** was also synthesized from amine intermediate **40**.

In addition, the synthesis of (−)-5-OH-DPAT, (−)-**6** and racemic **9** were also carried out to use them as reference compound and in our SAR studies. The detailed synthesis of **9** is given in the supporting information section.

Results and Discussion

Our previous articles on hybrid drug development approach for D2/D3 receptors outlined the development of aminotetralin-arylpiperazine-based compounds exhibiting D3 preferential activity both in binding and in functional assays.[22,23] One of the very first compounds based on this hybrid template was compound **6** and its corresponding enantiomers (−)-**6** and (+)-**6**. The initial D2/D3 binding data of demonstrated very little difference in affinity between these two enantiomers. However, we recently realized that during the process of separation of these two enantiomers, we inadvertently converted most of the compounds back to its racemic version and thus, the binding data was erroneous. A newer approach to separate these enantiomers has been adopted by us recently which gave us the two enantiomers with high enantiomeric purity.[22,30] The new data show appreciable differences between the two enantiomers with the (+)-(R)-**6** isomer expectedly showing the highest affinity for the both D2 and D3 receptors. This is in line with the binding data of the corresponding enantiomers of the parent structure 7-OH-DPAT. Thus, the enantiomers (−)-**6** and (+)-**6** (Figure 3) possessed higher binding affinity for D3 receptors and lower binding affinity for D2 receptors (K_i 38.6 and 1.77 nM for D3 and, 809 and 40.6 nM for D2). A similar trend was observed for the hybrid structures derived from 5-OH-DPAT, compounds (−)-**7** and (+)-**7** (Figure 3). The observed

differences in the inhibition constants for (−)-**7** and its enantiomer (+)-**7** were ~ 20-fold for the D3 receptor (18.4 nM versus 0.82 nM) and ~ 9-fold for the D2L receptor (238 nM versus 26 nM).[22] This data is also in line with the data found from 5-OH-DPAT affinity. However, compound (−)-**7** exhibited more than four-fold higher affinity compared to (−)-5-OH-DPAT under our binding assay conditions for the both D2 and D3 receptors (K_i 26 vs. 220 nM for D2 and 0.82 vs. 4.73 nM for D3, respectively). This is an interesting finding since it indicates that the presence of piperazine moiety further enhanced the affinity of this hybrid compound while maintaining its strong agonist activity.[22] Thus, contribution of piperazine fragment increased the interaction with the D2/D3 receptors.

Monophenolic *cis*- and *trans*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolines had been evaluated for interactions with D_1-like and D_2-like dopamine receptors and compared with the effects of the corresponding unconstrained aminotetralins a couple of decades ago.[15] These molecules were mainly evaluated for functional activity in the membrane preparations. Similarly, *cis*- and *trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines were tested for central DA and serotonin receptor-stimulating activity using biochemical and behavioral tests in rats.[15,16] With the availability of cloned DA receptor subtypes, it is now possible to investigate the affinity and selectivity of these compounds for DA receptor subtypes which was not possible earlier. With this background, it was of interest to us to apply the hybrid structure approach to these octahydrobenzo[*f*]- and [*g*]quinolines to investigate the following goals: 1) evaluate binding affinity for the DA receptor subtypes, with the aim of delineating the factors responsible for the observed trend in binding affinity and D2/D3 selectivity, if any, in these derivatives and 2) to develop a pharmacophore model for our hybrid derivatives by using these conformationally constrained DA analogs including aminotetralins.

The binding data of the target compounds for DA D2 and D3 receptors are given in Table 1. In case of hybrid (±)-trans-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-6-ol derivatives, represented by compound (±)-**43a**, the binding affinities for the D3 and D2 receptors (K_i D3 = 736 and D2 = 1712 nM) were found to be low. The corresponding N-*n*-propyl analog **2** (Figure 1), of the parent structure of **43a**, were reported to be active for the DA receptors in functional assays.[15] However, the cis-analogs of **2** were reported to be inactive. Also, the transition from *n*-propyl to *n*-butyl led to complete loss of functional activity for the racemate of **2**.[15] Since no binding data was available for interaction of this compound **2** with DA receptors, this compound was re-synthesized by us to evaluate its binding interaction with the cloned DA receptor subtypes. As shown in Table 1, compound **2** exhibited very poor affinity for both D2 and D3 receptors. Thus the data from the hybrid structure (±)-**43a** correlated well with the binding affinity for the non-hybrid structure. No attempts were made to synthesize cis-analogs of **43a**. However, the dichloro derivative **43b** was significantly more potent and the effect was more significant for D2 receptor compared to D3 receptor. Thus, **43b** was twelve times more potent at D2 compared to **43a** and four fold more potent at D3 compared to **43a** (Ki; 136 nM vs. 1712 nM, respectively.

In the case of (±)-cis- and (±)-trans-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-8-ol hybrid derivatives, represented by compounds (±)-**24a–b** and (±)-**35a–c**, respectively, a similar trend was observed when compared to their corresponding 6-OH analogs (**43a–b**). Previously, all 8-OH N-*n*-propyl derivatives were reported to be inactive in DA receptor functional assays.[15] Compound (±)-**24a**, a cis derivative, exhibited very weak binding affinity at D3 receptor (K_i 419 nM) and even weaker affinity for the D2 receptor (K_i 3326 nM). As seen with **43b**, the corresponding dichloro analogue **24b** improved the affinity to a great extent, which can be attributed to the presence of 3,4-dichloro group possibly promoting hydrophobic interactions with the DA receptors. This phenomenon was observed with other known DA receptor ligands as well. A similar trend was observed for the *trans* compounds (±)-**35a** and (±)-**35b**. The *trans* compounds (±)-**35b** and (±)-**35c** were found to possess moderate affinity for the D3

receptor (Table 1). A change of spacer length between the octahydrobenzo[*g*]quinoline and the piperazine moieties from 2 to 4, as depicted in **35a** and **35c,** led to ~ 3-fold gain in affinity for the D3 and ~ 9-fold for the D2 receptors (K_i 473 vs. 102 nM for D3 and 2522 vs. 289 nM for D2, respectively) for **35c**. These benzo[*g*]quinoline derivatives exhibited moderate selectivity for the DA D3 receptor subtypes.

Having investigated the benzo[*g*]quinolines, we started analyzing the binding data for the hybrid 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolin-7-ol and 9-ol derivatives. The most active compound in the present study was (±)-**8** (K_i D3 = 14.9 nM, K_i D2 = 49.1 nM, respectively), which belongs to the 7-hydroxy series; the corresponding 9-OH compound **9** (Figure 3) which was synthesized by us, exhibited moderate affinity for the D3 receptor (K_i D3 = 72 nM, D2 = 219 nM, respectively). Even though the compound (±)-**8** possessed higher potency, it lacked high selectivity for the D3 receptor (Table 1). The *trans*-7-hydroxy-N-*n*-propyl derivatives were reported to be more active than their *cis* counterparts in this structural class.[17a] Also, the change from *n*-propyl to *n*-butyl substitution was reported to increase activity. We further resolved (±)-**8** and tested their binding affinities. Thus, in accordance with what has been previously reported[21], we observed higher binding affinity in the (−)-**8** isomer (corresponding to (4aS, 10bS) configuration) (Table 1). It is again important to point out here that complete binding characterization of the parent compound **1** and its analogues for D2/D3 receptors were never carried out. In agreement with the higher binding affinity of (−)-**7** (hybrid structure based on (S)-(−)-5-OH-DPAT) compared to its enantiomer, a good separation of affinity was found for the D3 and D2 receptors in (+)-**8** and (−)-**8** (K_i 89.3 and 4.95 nM for D3 and 835 and 23.6 nM for D2 receptor, Table 1). In order to judge correctly the impact of the hybrid version of 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolin-7-ol derivatives in binding, we synthesized and characterized the corresponding non-hybrid derivative **1** to evaluate its binding affinity for the D2/D3 receptors. Interestingly, as observed in the case of (−)-5-OH-DPAT and (−)-**7**, the hybrid racemic version (±)-**8** exhibited more than six-fold affinity compared to **1** (K_i 14.9 vs. 96 nM for D3 and 49 vs. 380 nM for D2, respectively, Table 1). This again demonstrated the unique contribution of the piperazine fragment in enhancing affinity of hybrid compounds compared to known ligands. Interestingly, hybrid constrained derivatives did not contain any free N-alkyl group, unlike non-hybrid constrained versions, which displayed an influence of nature of N-alkyl substitution on activity.[15,17a] The fact that an alkyl group could be replaced by a substituted piperazine fragment with enhancement of binding activity may indicate development of additional co-operative binding interactions of the hybrid derivatives with D2/D3 receptors.

The data taken together represent our SAR study with hybrid derivatives developed for D2/D3 receptors to understand the molecular mode of interactions and to derive a pharmacophore model. Thus, we designed and synthesized conformationally constrained versions in which the aminotetralin moiety was converted into *trans*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*] quinoline and *trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline structures. Hybrid compounds with a *trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline structure exhibited more affinity for D2/D3 receptors than those with a *trans*-1,2,3,4,4a,5,10,10a-octahydro-benzo [*g*]quinoline, indicating preference for one constrained conformation over the other. Overall, hybrid derivatives exhibited a significant increase of affinity compared the to corresponding non-hybrid counterparts, reflecting an important role of the piperazine moiety in affinity for dopamine receptors. Having acquired all the necessary data, our next task was to carry out a computational analysis to derive a reliable pharmacophore model of hybrid compounds for their binding to D2/D3 receptors.

Next, we extended our studies towards the generation of pharmacophore hypotheses based on these conformationally constrained bi- and tricyclic hybrid structures. There are few reports of DA receptor pharmacophoric requirements based on various ligands including

conformationally constrained tricyclic aminotetralins.[15–17a] The central theme of these receptor models was the importance of various positions taken by the N-substituents. One orientation disfavored any groups bigger than n-propyl (sterically defined) whereas other orientation tolerated bigger groups (e.g., McDermed's DA-receptor model[15], Wikström's extended model[16]) (sterically favorable). The hybrid compounds (linear and angular) described in the present investigation follow the general requirements depicted by abovementioned DA-receptor models. For additional description and illustration with the help of representative hybrid compounds of this DA-receptor model, readers are encouraged to see supporting information section.

In the initial trial runs of pharmacophore generation with the known D2/D3 ligands (S)-5-OH-DPAT, R-(+)-7-OH-DPAT and **5** (R-(+)-PD128907)[17b] (Figure 1), the best 3-point pharmacophore (based on overall alignment score), as depicted in Figure 4a, shows the presence of one aromatic/hydrophobic feature occupied by the aromatic ring (green), another hydrophobic feature present near the N-*n*-propyl groups (green) common to all three ligands and the quaternary N as the cationic feature (blue). Shown as purple are the two features depicting the directions of the phenolic hydroxyl H-bond donor and the H attached to cationic N (required for reinforced H-bonding). Figure 4a clearly shows the orientation of the H atom attached to cationic N in the direction of the purple sphere, representing a possible interaction with the Asp residue in TM-3. Similarly, another purple sphere located near phenolic hydroxyls represents the Ser residue(s) of the DA receptor subtypes. The distance between the aromatic/hydrophic feature near the aromatic ring and the cationic N was found in the narrow range of 5.06–5.16 Å. This distance falls within the range of 4.1–6.1 Å reported for the same interfeature distance in a pharmacophore derived from known D3 ligands.[31]

A pharmacophore model was generated based on the hybrid compounds (+)-**6** and (−)-**7,** representing bicyclic hybrid aminotetralins structures, along with (−)-**8**, a hybrid tricyclic aminotetralin, and (−)-**11** representing a 2-aminothiazole-based fused bicyclic system. Of the several pharmacophore hypotheses generated, two representative hypotheses were selected based on the overall alignment score, nature of features present and the molecules covered. Only the top ranked of the two hypotheses is shown in Figure 4b along with the hybrid analogs aligned onto these features. These two hypotheses differ in interfeature distances as shown in Figure 4c which depicts the features and the corresponding interfeature distance ranges. The range of distances results from changes in the conformation of the ethylene bridge connecting the cationic N with the arylpiperazine portion. In Figure 4b, this ethylene linker adopted the gauche conformation whereas in the second hypothesis (not shown), it adopted the anti conformation. These interfeature distances are shown in Table 2. These distances were measured from the gauche and anti conformations of the individual molecules whereas interfeature distance ranges shown in Figure 4c were measured from the individual pharmacophore hypotheses (representing gauche and anti conformations of the ethylene bridge). The distances between hydrophobic features one centered on the aminotetralin aryl portion (Ar^1) and the other on the phenyl ring of arylpiperazine portion (Ar^2), as well as the distances between cationic N and the arylpiperazine hydrophobic features, were greater in the case of the anti conformation (Table 2). The distances between the cationic N and Ar^1 were reduced in the case of the anti conformation compared to the gauche conformation (shown in Figure 4b). We strongly believe that these conformations and the associated interfeature distances coupled with other factors govern the selectivity for D2/D3, provided the abovementioned features (shown in Figure 4b) are present in the molecules. Figure 4b represents the DA receptor (D2 and D3) ligand pharmacophore depicting 3 features consisting of two aromatic/hydrophobic and one cationic feature. Along with these 3 features, it shows the Don2 feature, which represents the direction in which the H-bond donor attached to the aromatic portion should be oriented for optimal interaction with the receptor(s). The aromatic/hydrophobic features represent 1) Ar^1- the phenyl ring in hybrid aminotetralins (+)-**6**, (−)-**7**

and (−)-**8** and 2-aminothiazole ring in (−)-**11** and 2) Ar^2- the phenyl ring attached to N-4 of piperazine. One set of aromatic/hydrophobic and cationic features is common to Figures 4a and 4b. This set of two features is similar to that described for the D3 ligand pharmacophore by Varady, et al.[31] However, compared to the pharmacophore features shown in Figure 4a, the directional character of the H attached to a cationic N is absent in Figure 4b, even though in principle the H attached to a quaternary N is oriented in one direction only. The lack of directional feature in this case was probably due to the pharmacophore generation process itself (the methodological part). In addition, our current proposed model bears certain resemblance to earlier models.[15,17a]

The factors responsible for the D3 preference for most of these compounds ((+)-**6**, (−)-**7** and **1**) can not be addressed by the present pharmacophore completely. In our opinion, the highest selectivity for D3 exhibited by (−)-**11** may be due to the presence of an additional aryl ring extending beyond those present in rest of the molecules. Also, as seen from the representative top scoring hypotheses (gauche and anti conformation of the ethylene linker), we strongly believe that the conformation of this linker is critical for interaction with either or both D2/D3 receptors. In addition, at this point of time, no information is available regarding the role of either or both piperazine N-atom(s) on affinity and selectivity. Our future efforts will be focused on addressing these critical questions and further refining this pharmacophore model. The hybrid analog concept representing D2/D3 receptor interaction requirements could possibly address otherwise difficult to explore selectivity requirements. In addition to further enhancing our understanding of D2/D3 ligand structural requirements pertaining to selectivity, it may shed light on requirements for potency and aid in the design of potent and selective D2/D3 ligands/agonists. Certainly, the arylpiperazine portion of the hybrid structures has a vital, yet complex, role to play in imparting the higher potency compared to non-hybrid DA ligands and also potentially plays a role in endowing selectivity for one receptor over the other. Efforts are underway to identify molecular determinants for potency and selectivity of these hybrid structures and our forthcoming publications will attempt to address this with the help of carefully designed structures. This will further help us to refine the preliminary pharmacophore proposed in this article.

Conclusion

In this manuscript we have carried out further modification of our hybrid derivatives by converting them into structurally constrained versions to understand their mode of interaction in general with DA D2 and D3 receptors and also to obtain an insight into bioactive conformational structures of these molecules. For this purpose, several 1,2,3,4,4a,5,10,10a-octahydrobenz[*g*]quinoline-ol and 1,2,3,4,4a-5,6,10b-octahydrobenzo[*f*]quinolin-ol based hybrid derivatives were prepared and biologically characterized. In this regard, as pointed out earlier, octahydrobenzo[*f & g*]quinolinol related derivatives as constrained molecules of aminotetralin structures (7-OH-DPAT and 5-OH-DPAT) were synthesized before for interaction with DA receptors. However, none of those derivatives was evaluated in detailed binding interaction with D2 and D3 receptors as they were mainly characterized in functional assays and in some cases in binding assay for the D2 receptor. Therefore, precise information on binding interactions with D2/D3 receptors was not available. The present results from constrained hybrids indicate that a compound with structure 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolinol, e.g. (−)-**8**, exhibits high affinity for D2/D3 receptors and in this regard, is significantly more potent than the corresponding non-hybrid version. Similar results were found with other lead compounds when compared with the corresponding non-hybrid version. Our study with the hybrid version of these constrained derivatives as well as other lead hybrid compounds provide some unique information about the interaction of these compounds with DA receptors. These results clearly indicate a significant contribution of the piperazine moiety in enhancing interaction of hybrid derivatives with DA receptor subtypes.

Our results prompt the proposal of a unique pharmacophore structure for hybrid derivatives consisting of three pharmacophoric centers. This unique pharmacophore structure will be further refined by incorporating the results of future studies.

Experimental

Analytical silica gel-coated TLC plates (silica gel 60 F_{254}) were purchased from EMD Chemical, Inc. and were visualized with UV light, by treatment with phosphomolybdic acid (PMA), Dragendorff's reagent or ninhydrin. Flash column chromatography was carried out on Whatman Purasil® 60A silica gel 230–400 mesh. ^{1}H-NMR spectra were routinely obtained on Varian 400 MHz FT NMR equipment. The NMR solvent used was either $CDCl_3$, CD_3OD or d6-DMSO as indicated. TMS was used as an internal standard. Elemental analysis were performed by Atlantic Microlab, Inc., and were within ± 0.4 % of the theoretical value. Optical rotations were recorded on Perkin-Elmer 241 polarimeter.

Procedure A

2-Chloro-1-(4-phenylpiperazin-1-yl)ethanone (13a)—1-Phenylpiperazine **12a** (3 g, 18.5 mmol) and triethylamine (3.34 ml, 22.2 mmol) were dissolved in 100 ml of CH_2Cl_2 and cooled to 0 °C. Chloroacetyl chloride (1.9 ml, 22.2 mmol) was added slowly over the course of five minutes. The mixture was allowed to stir at 0 °C for 30 min, at which time saturated $NaHCO_3$ (100 ml) was added. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The crude solid was then recrystallized from EtOAc to give 4.3 g (97%) of 2-chloro-1-(4-phenylpiperazin-1-yl)ethanone **13a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (bs, 4H), 3.59 (bs, 4H), 4.25 (s, 2H), 6.53–6.55 (d, 1H, *J* = 7.6 Hz), 6.64–6.66 (d, 1H, *J* = 7.6 Hz), 6.83–6.87 (t, 1H, *J* = 8 Hz).

2-Chloro-1-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethanone (13b)—This compound was prepared following Procedure A using 2 g (7.47 mmol) of 1-(2,3-dichlorophenyl)-piperazine, 0.92 ml (8.22 mmol) of chloroacetyl chloride, and 2 ml (15 mmol) of triethylamine to give 2.6 g (87%) of **13b** as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (bs, 4H), 4.27 (s, 2H), 3.61 (bs, 4H), 6.41–4.49 (m, 2H), 6.90–6.93 (t, 1H, *J* = 8 Hz).

4-chloro-1-(4-phenylpiperazin-1-yl)butan-1-one (13c)—This compound was prepared following Procedure A using 2 g (12.3 mmol) of 1-phenylpiperazine, 1.91 g (13.6 mmol) of 4-chlorobutanoyl chloride, and 2ml (15 mmol) of triethyl amine to give 3.19 g (97%) of solid **13c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94–1.98 (m, 2H), 2.32–2.34 (t, 2H, *J* = 8Hz), 3.33–3.35 (m, 4H), 3.48–3.50 (m, 4H), 3.67–3.67 (t, 2H, *J* = 8Hz), 6.53–6.55 (d, 1H, *J* = 7.6 Hz), 6.64–6.66 (d, 1H, *J* = 7.6 Hz), 6.83–6.87 (t, 1H, *J* = 8 Hz).

2-(3-Methoxybenzyl)nicotinic acid methyl ester (16)—Activated zinc dust (1.75 g, 27.3 mmol) was added to 20 ml of dry THF and the suspension cooled to 0 °C. 3-Methoxybenzyl bromide **14** (1.90 ml, 13.6 mmol) was added and this mixture was stirred at 0 °C under a N_2 atmosphere for 2 hr. Stirring was stopped and the excess zinc was allowed to settle. The benzyl zinc bromide was then added via cannulation to a suspension of bis (triphenylphoshine) nickel (II) chloride (1.78 g, 27.3 mmol) and methyl 2-chloronicotinate (1.17 g, 6.82 mmol) in 100 ml of dry THF. This mixture was stirred at ambient temperature for 48 hr. The reaction was quenched by the addition of 10 % NH_4Cl (100 ml) and the product was extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated. The crude mixture was dissolved in ether and ethereal HCl was added. The salt was recovered by filtration and used without further purification to yield 1.57 g of **16** (free base, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.87 (s, 3H), 4.56 (s, 2H), 6.70–6.73 (m, 1H), 6.81–6.85 (m, 1H), 7.15–

7.19 (t, 1H, J = 8 Hz), 7.22–7.26 (m, 2H), 8.16– 8.18 (dd, 1H, *J* = 1.6 Hz, *J* = 8 Hz), 8.68–8.7 (dd, 1H, *J* = 1.6 Hz, *J* = 8 Hz).

***cis*- and *trans*-2-(3-Methoxybenzyl)piperidine-3-carboxylic acid methyl ester (17)—**The hydrochloride salt of pyridine **16** (5.75 g, 19.2 mmol) was dissolved in 200 ml of MeOH and 200 mg of PtO_2 was added. The mixture was then hydrogenated at 45 psi for 24 hr. The mixture was filtered though a pad of celite and the solvent removed *in vacuo* to yield a mixure of cis- and trans-amine **17** as an oil (4.77 g, 95%), which were used without further purification and were not separated in the subsequent transformations. ^{1}H NMR ($CDCl_3$) δ 7.18–7.25 (t, 1H, J = 8 Hz), 6.72–6.79 (m, 3H), 3.80 (s, 3H) 3.72 (s, 3H), 3.0–3.12 (m, 2H), 2.84– 2.9 (m, 1H), 2.57–2.77 (m, 3H), 1.8–2.2 (m, 1H), 1.76–1.82 (m, 2H), 1.66–1.73 (m, 2H), 1.42–1.46 (m, 1H).

***cis*- and *trans-2*-(3-Methoxybenzyl)piperidine-1,3-dicarboxylic acid dimethyl ester (18)—**Amine **17** (1.58 g, 6.03 mmol) was added to a suspension of 1.9 g (13 mmol) of K_2CO_3 in 20 ml of dichloromethane. Methyl chloroformate (0.93 ml, 12 mmol) was added and the mixture was stirred for 3 hr at ambient temperature. Water (20 ml) was added and the product was extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated to yield the crude carbamate **18** as an oil (1.9 g, 100 %), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66–2.0 (m, 3H), 2.50–2.54 (m, 1H), 2.64–2.77 (m, 2H), 2.87–2.99 (m, 2H), 3.33 (m, 2H), 3.58–3.60 (m, 2H), 3.69 (s, 3H), 3.80 (s, 3H), 4.8– 4.98 (m, 1H), 4.1–4.16 (m, 1H), 6.62–6.80 (m, 3H), 7.15–1.18 (t, 1H, *J* = 8 Hz).

(±)-*cis*-8-Methoxy-5-oxo-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinoline-1-carboxylic acid methyl ester (19)—Methyl ester **18** (910 mg, 2.83 mmol) was dissolved in 30 ml of MeOH. LiOH (102 mg, 4.25 mmol) and water (7ml) were added and the mixture was allowed to stir at room temperature for 24 hr. Methanol was then evaporated and the mixture was partioned between water and ethyl acetate. The aqueous phase was then acidified and extracted with several portions of ethyl acetate. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated to yield the crude acid, which was used without further purification. 800 mg (2.6 mmol) of the acid was dissolved in 30 ml of dichloromethane and $SOCl_2$ (0.23 ml, 13.4 mmol) was added and the mixture was refluxed until no more HCl gas was produced. The mixture was cooled and concentrated to yield the crude acid chloride, which was dissolved in 40 ml of dry CH_2Cl_2 and cooled to 0 °C. $TiCl_4$ (1 M in CH_2Cl_2, 5.2 ml, 5.2 mmol) was added dropwise and this reaction was stirred in an ice bath for 2 hr. The reaction was quenched by the addition of sat. NaCl (20 ml) and the product was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The product was purified by column chromatography (94:5:1 EtOAc: MeOH: Et3N) to yield only the *cis*-isomer **19** as a yellow solid (480 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.62 (m, 1H), 1.78–1.82 (m, 1H), 1.91–1.97 (m, 1H), 2.69–2.72 (m, 1H), 2.72–2.82 (m, 1H), 2.92–3.1 (m, 1H), 3.3–3.4 (m, 1H), 3.72 (s, 3H), 3.89 (s, 3H), 4.1–4.18 (m, 1H), 4.79–4.81 (m, 1H), 6.65–6.67 (m, 1H), 6.83–6.87 (m, 1H), 8.01–8.04 (d, 1H, *J* = 8 Hz).

(±)-*cis*-8-Methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinoline-1-carboxylic acid methyl ester (20)—Ketone **(±)-19** (610 mg, 2.1 mmol) and 1.5 ml of 70% perchloric acid were dissolved in 25 ml of acetic acid. 60 mg of Pd/C was then added and the mixture was hydrogenated at 45 psi for 34 hr. The catalyst was filtered through a pad of celite and acetic acid was evaporated. The residue was washed with 20 % NaOH, dried (Na_2SO_4), filtered, and concentrated to yield 510 mg (88 %) of **20** as an oil, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.6 (m, 3H), 1.6–1.71 (m, 1H), 2.03–2.07 (m, 1H), 2.55–2.59 (d, 1H, *J* = 8 Hz), 2.85–3.1 (m, 3H), 2.71–2.82), 3.71 (m, 3H), 3.76

(m, 3H), 4.16–4.21 (m, 1H), 4.45–4.51 (m, 1H), 6.59–6.6 (m, 1H), 6.68–6.71 (m, 1H), 6.96–6.98 (d, 2H, *J* = 8 Hz).

(±)-*cis*-8-Methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (21)— Carbamate **20** (350 mg, 1.27 mmol) was added to a solution of KOH (240 mg, 7.64 mmol), water (0.13 ml, 7.64 mmol), and hydrazine hydrate (0.24 ml, 7.64 mmol) in ethylene glycol (20 ml). This mixture was refluxed for 3 hr, at which time the solution was cooled, poured into water, and the product was extracted with several portions of ethyl acetate. After drying, filtering, and concentration, 182 mg (90 %) of the titled product **21** was recovered as s sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.43 (m, 1H), 1.55 (s, 1H), 1.66–1.74 (m, 3H), 1.96–2.2 (m, 1H), 2.5–2.75 (m, 3H), 2.92–3.10 (m, 4H), 3.72 (s, 3H), 6.55–6.2 (m, 1H), 6.68– 6.67 (m, 1H), 6.96–7.00 (d, 2H, *J* = 8 Hz).

Procedure B

(±)-*cis*-2-(8-Methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinolin-1-yl)-1-(4-phenylpiperazin-1-yl)ethanone (22a)—A mixture of amine **(±)-21** (390 mg, 1.8 mmol), chloride **13a** (514 mg, 2.16 mmol), K_2CO_3 (745 mg, 5.4 mmol), in acetonitrile (40ml) was heated at reflux for 1 hr. The mixture was then cooled, filtered, and concentrated. The product was purified by column chromatography using ethyl acetate as an eluent to yield **22a** (460 mg, 61 %) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.5–1.6 (m, 4H), 1.72–1.8 (m, 1H), 2.9–3.1 (m, 4H), 2.7–2.82 (m, 7H), 3.2–3.29 (m, 1H), 3.38–3.5 (m, 2H), 3.54–3.58 (m, 1H), 3.78 (s, 3H), 7.25–7.30 (m, 2H), 6.62–6.64 (m, 1H), 6.68–6.7 (m, 1H), 6.84–6.9 (m, 3H), 6.96–7.0 (d, 1H, *J* = 8 Hz).

(±)-*cis*-1-[4-(2,3-Dichlorophenyl)piperazin-1-yl]-2-(8-methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinolin-1-yl)ethanone (22b)—Amine **(±)-21** (200 mg, 0.8 mmol), chloride **13b** (290 mg, 0.95 mmol), and K_2CO_3 (328 mg, 2.4 mmol) were reacted according to the Procedure B. The product was purified by column chromatography using ethyl acetate as an eluent to yield 354 mg (92 %) of **22b** as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.61 (m, 3H), 1.76–1.83 (m, 1H), 2.14 (bs, 1H), 2.3–2.4 (m, 1H), 2.52–2.8 (m, 10H), 3.01–3.07 (m, 2H), 3.32–3.40 (m, 2H), 3.51–3.56 (m, 2H), 3.75 (s, 3H), 6.61–6.62 (m, 1H), 6.65–6.68 (m, 1H), 6.82–6.86 (m, 1H), 6.94–6.96 (dd, 1H, J = 1.8 Hz, J = 8 Hz), 7.13–7.19 (m, 2H).

Procedure C

(±)-*cis*-1-[2-(4-Phenylpiperazin-1-yl)ethyl]-1,2,3,4,4a,5,10,10a-octahydro-benzo[*g*]-quinolin-8-ol (23a)—Lithium aluminum hydride (244 mg, 6.44 mmol) was added to dry THF (50 ml) and the suspension was cooled to 0°C. A solution of amide **22a** (450 mg, 1.0 mmol) in THF (15 ml) was added dropwise and the mixture was refluxed for 3 hr. The mixture was cooled in an ice bath and quenched with 10% NaOH and the resulting solids were filtered. The filtrate was dried (Na_2SO_4), filtered, and concentrated to yield amine **23a** (235 mg, 98%) as an oil, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.62 (m, 4H), 1.70–1.81 (m, 1H), 2.92–3.11 (m, 4H), 2.72–2.86 (m, 9H), 3.22–3.30 (m, 1H), 3.37–3.50 (m, 2H), 3.55–3.58 (m, 1H), 3.77 (s, 3H), 7.24– 7.29 (m, 2H), 6.63–6.65 (m, 1H), 6.67–6.7 (m, 1H), 6.85–6.9 (m, 3H), 6.97–7.01 (d, 1H, *J* = 8 Hz).

(±)-*cis*-1-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-2-(8-methoxy-3,4,4a,5,10,10a-hexahydro-2H-benzo[g]quinolin-1-yl)-ethanone (23b)—Compound **22b** (354 mg, 0.725 mmol) was reduced following Procedure C to yield 338 mg (98%) of **23b** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.60 (m, 3H), 1.75–1.82 (m, 1H), 2.15 (bs, 1H), 2.31–2.4 (m, 1H), 2.50–2.87 (m, 12H), 3.010–3.05 (m, 2H), 3.30–3.39 (m, 2H), 3.52–3.55 (m, 2H), 3.78 (s,

3H), 6.60–6.62 (m, 1H), 6.66–6.69 (m, 1H), 6.83–6.87 (m, 1H), 6.95–6.97 (dd, 1H, J = 1.8 Hz, J = 8 Hz), 7.14–7.20 (m, 2H).

Procedure D

***cis*-1-[2-(4-Phenylpiperazin-1-yl)ethyl]-1,2,3,4,4a,5,10,10a-octahydro-benzo[*g*] quinolin-8-ol (24a)—**Compound **(±)-23a (**310 mg, 0.76 mmol) was dissolved in 40 ml of dichloromethane and cooled to −78 °C. 1.5 ml of BBr_3 (1 M in CH_2Cl_2) was added dropwise and the mixture was allowed to warm to ambient temperature and stirred overnight. Saturated $NaHCO_3$ (50 ml) was added and the product was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered, and concentrated. The titled compound was then purified by column chromatography using 94:5:1 EtOAc: MeOH: Et3N to yield **(±)-24a** (233 mg, 78 %) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.43 (m, 2H), 1.6–1.77 (m, 2H), 2.1–2.19 (m, 1H), 2.55–2.84 (m, 14H), 2.92–3.0 (m, 1H), 3.09–3.2 (m, 1H), 3.18–3.22 (m, 4H), 6.36–6.38 (m, 1H), 6.52–6.55 (m, 1H), 6.82–6.91 (m, 4H), 7.22–7.28 (m, 2H). The free base was converted to its HCl salt. mp = 174–177 °C. Anal. ($C_{25}H_{33}N_3O$·2HCl). C, H, N.

(±)-*cis*-1-{2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl}-1,2,3,4,4a,5,10,10a-octahydro-benzo[*g*]quinolin-8-ol (24b)—Compound **22b (**338 mg, 0.714 mmol) was demethylated following Procedure D, giving **(±)-24b**, 267 mg (80 %) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.43 (m, 2H), 1.6–1.77 (m, 2H), 2.1–2.19 (m, 1H), 2.55–2.84 (m, 14H), 2.92–3.0 (m, 1H), 3.09–3.2 (m, 1H), 3.18–3.22 (m, 4H), 6.36–6.38 (m, 1H), 6.52–6.55 (m, 1H), 6.82–6.91 (m, 4H), 7.22–7.28 (m, 2H). The free base was then converted to its HCl salt. mp = 161–165 °C. Anal. ($C_{25}H_{31}Cl_2N_3O$·2HCl). C, H, N.

2-Hydroxy-7-methoxy-3,4-dihydronaphthalene-1-carboxylic acid methyl ester (26)—7-methoxy-2-tetralone **25** (12.5 g, 76 mmol), and NaH (5.6 g, 0.145 mol) were refluxed in benzene (200 ml) for 30 min, at which time dimethyl carbonate (12 ml, 0.145 mol) was added and refluxing was continued for 3 hr. The reaction was cooled and then carefully quenched by the addition of water (50 ml) and the product was extracted with ethyl acetate, dried (Na_2SO_4), filtered, and concentrated to yield the product, which was purified by column chromatography (1:1 Hexane: EtOAc) to give 16 g of **26** (96 %) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50–2.54 (t, 2H, *J* = 8 Hz), 2.73–2.77 (t, 2H, *J* = 8 Hz), 3.8 (s, 3H), 3.92 (s, 3H), 6.60–6.63 (dd, 1H, *J* = 2 Hz, 8 Hz), 7.02–7.05 (d, 1H, *J* = 8 Hz), 7.30–7.31 (d, 2H, *J* = 2 Hz), 13.38 (s, 1H).

3-(2-Cyanoethyl)-2-hydroxy-7-methoxy-3,4-dihydronaphthalene-1-carboxylic acid methyl ester (27)—n-Butyllithium (55.6 ml, 0.138mol) was added to a solution of diisopropylamine (19.3 ml, 0.138 mol) in dry THF (100 ml) at −78 °C and stirred for 15 minutes, then warmed to 0 °C and stirred for an additional 15 min. Next, a solution of **26** (12.9 g, 0.055 mol) dissolved in THF (20 ml) was added slowly and the mixture was stirred at 0 °C for 1 hr. Chloropropionitrile (5.6 ml, 0.071 mol) was then added and this solution was stirred at room temperature for 1 hr, and carefully quenched with 50 ml of 1 M HCl. The product was extracted with ethyl acetate (3×50 ml), dried (Na_2SO_4), filtered, and concentrated. The crude oil was then purified by column chromatography (1:1 Hexane: EtOAc) to yield **27**, 7.28 g (46 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70–1.76 (m, 1H), 1.88–1.94 (m, 1H), 2.41–2.50 (m, 2H), 2.57–2.67 (m, 1H), 2.82–2.86 (t, 1H, *J* = 6.8 Hz), 2.97–3.01 (m, 1H), 3.80 (s, 3H), 3.93 (s, 3H), 13.4 (s, 1H), 6.63–6.65 (dd, 1H, *J* = 2 Hz, *J* = 8 Hz), 7.03–7.05 (d, 1H, *J* = 8 Hz), 7.30–7.31 (d, 1H, *J* = 8 Hz).

3-(6-Methoxy-3-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propionitrile (28)—Methyl ester **27** (430 mg, 1.5 mmol), LiCl (63 mg, 1.5 mmol), water (2 ml), and DMSO (1 ml) were refluxed for 4 hr. The solution was then cooled and poured into water (15 ml) and the

product extracted with several portions of ethyl acetate (3 × 15ml). The organic extracts were pooled, dried (Na_2SO_4), filtered, and concentrated to yield 243 mg (81 %) of **28** as an oil, which was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63–1.79 (m, 1H), 2.16–2.21 (m, 1H), 2.54–2.56 (m, 2H), 2.62–2.67 (m, 1H), 2.76–2.88 (m, 1H), 3.05–3.10 (dd, 1H, *J* = 5.6 Hz, *J* = 8 Hz), 3.55–3.70 (q, 2H, *J* = 6 Hz), 6.65–6.66 (m, 1H), 3.80 (s, 3H), 6.76–6.79 (dd, 1H, *J* = 2.4 Hz, *J* = 8 Hz), 7.11–7.13 (d, 1H, *J* = 8 Hz).

3-(7′-Methoxy-3′,4′-dihydro-1′*H*-spiro[[1,3]dioxolane-2,2′-naphthalen]-3′-yl)-propionitrile (29)—A solution of ketone **28** (280 mg, 1.22 mmol), triethyl orthoformate (0.71 ml, 4.3 mmol), ethylene glycol (1.2 ml), and TsOH (5 mg, 0.012 mmol) in dichloromethane (20 ml) was stirred overnight at room temperature. The reaction mixture was then poured into water (30 ml) and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated to yield an oil which was purified by column chromatography (EtOAc) to yield **29** 332 mg (98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.62 (m, 1H), 2.01–2.19 (m, 2H), 2.40–2.59 (m, 2H), 2.65–2.71 (m, 1H), 2.82–3.32 (m, 2H), 3.76 (m, 3H), 3.80–4.09 (m, 4H), 6.56–6.57 (m, 1H), 6.70–6.72 (dd, 1H, *J* = 2.8 Hz, *J* = 8 Hz), 7.00–7.03 (d, 1H, *J* = 8 Hz).

3-(7′-Methoxy-3′,4′-dihydro-1′*H*-spiro[[1,3]dioxolane-2,2′-naphthalen]-3′-yl)-propylamine (30)—Nitrile **29 (**350 mg, 1.28 mmol) was dissolved in 30 ml of MeOH. Raney nickel (200 mg) was added and the mixture was hydrogenated overnight, reaction solution was filtered through a pad of celite and concentrated to give 300 mg of **30** (62 %) as a solid which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.79 (m, 6H), 1.92–2.0 (m, 1H), 2.60–3.16 (m, 6H), 3.67–3.79 (m, 3H), 3.82–4.10 (m, 4H), 6.56– 6.57 (m, 1H), 6.70–6.72 (dd, 1H, *J* = 2.8 Hz, *J* = 8 Hz),), 7.01–7.04 (d, 1H, *J* = 8 Hz).

(±)-*trans*-8-Methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline (32)—Amine **30** (300 mg, 1.1 mmol) was dissolved in 20 ml of MeOH and 5 ml of 6M HCl was added and the solution was refluxed for 2 hr, cooled, and concentrated to yield the iminium salt intermediate **31**. The crude solid was then dissolved in 40 ml of MeOH. $NaCNBH_3$ (65 mg, 1.02 mmol) was added and the solution stirred for 1 hr at ambient temperature. Methanol was then evaporated and the residue was partioned between sat. $NaHCO_3$ (50 ml) and ethyl acetate (50 ml). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The crude amine was then purified by column chromatography (95:4:1 EtOAc: MeOH: Et_3N) to give **32**, 187 mg (80 %) in solid form. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11–1.26 (m, 1H), 1.46–1.73 (m, 4H), 1.91–1.95 (m, 1H), 2.37–2.43 (m,1H), 2.57–2.76 (m, 4H), 2.83–2.88 (m, 1H), 3.10–3.14 (m, 1H), 3.77 (s, 3H), 6.61–6.62 (m, 1H), 6.67–6.97 (dd, 1H, *J* = 2.8 Hz, *J* = 8 Hz), 6.96–6.98 (d, 1H, *J* = 8 Hz).

(±)-*trans*-2-(8-Methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinolin-1-yl)-1-(4-phenylpiperazin-1-yl)ethanone (33a)—Amine **32** (110 mg, 0.5 mmol), chloride **13a** (202 mg, 0.66 mg), and K_2CO_3 (175 mg, 1.27 mmol) were refluxed following the Procedure B. The crude solid **33a** (190 mg) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.20 (m, 1H), 1.6–1.7 (m, 1H), 1.84–1.90 (m, 1H), 2.30–2.48 (m, 3H), 2.17 (s, H), 2.62–2.79 (m, 1H), 2.50–3.1 (m, 5H), 3.5–3.36 (m, 2H), 3.53–3.62 (m, 1H), 3.68–3.74 (m, 1H), 3.79 (s, 3H), 3.95–4.17 (m, 1H), 3.99–4.13 (m, 1H), 6.62–6.70 (m, 2H), 6.89–6.97 (m, 4H), 7.26–7.31 (m, 2H).

(±)-*trans*-1-[4-(2,3-Dichlorophenyl)piperazin-1-yl]-2-(8-methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinolin-1-yl)ethanone (33b)—Amine **32** (70 mg, 0.277 mmol) and chloride **13b** (93 mg, 0.30 mmol) were treated with K_2CO_3 (76 mg, 0.55 mmol) following the Procedure B, to yield 126 mg of crude solid **33b**, which was used without further purification. ^{1}H NMR δ (400 MHz, $CDCl_3$) 1.50–1.20 (m, 1H), 1.6–1.7 (m, 1H), 1.84–1.90

(m, 1H), 2.17 (s, H), 2.30–2.48 (m, 3H), 2.62–2.79 (m, 1H), 2.80–3.1 (m, 5H), 3.5–3.36 (m, 2H), 3.53–3.62 (m, 1H), 3.68–3.74 (m, 1H), 3.79 (s, 3H), 3.95–4.10 (m, 1H), 4.12–4.14 (m, 1H), 6.62–6.70 (m, 2H), 6.89–6.97 (m, 4H), 7.26–7.31 (m, 2H).

(±)-*trans*-(8-Methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinolin-1-yl)-1-(4-phenylpiperazin-1-yl)butan-1-one (33c)—This compound was prepared using 200 mg of amine **32** (0.79 mmol), 288 mg of chloride **13c** (0.945 mmol), and 327 mg of K_2CO_3 (2.37 mmol) according to Procedure B. Column chromatography using EtOAc as eluent afforded **33c** 330 mg (93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.34 (m, 1H), 1.79–1.81 (m, 1H), 1.91–2.23 (m, 5H), 2.41–2.50 (m, 5H), 2.79–2.82 (m, 1H), 3.0–3.41 (m, 9H), 3.62–3.80 (m, 7H), 6.60–6.63 (m, 1H), 6.68–6.72 (m, 1H), 6.89–6.95 (m, 4H), 7.26–7.31 (m, 2H).

(±)-*trans*-8-Methoxy-1-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (34a)—Amide **33a** (110 mg, 0.262 mg) was reduced with lithium aluminum hydride (70 mg, 1.31 mmol) following Procedure C to yield 105 mg of solid **34a** in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.23 (m, 1H), 1.61–1.76 (m, 2H), 1.82–1.90 (m, 1H), 2.22–2.41 (m, 3H), 2.52–2.81 (m, 10H), 3.0–3.20 (m, H), 3.21–3.30 (m, 5H), 3.78 (s, 3H), 6.62–672 (m, 2H), 6.82–7.10 (m, 4H), 7.22–7.30 (m, 2H).

(±)-*trans*-1-{2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl}-8-methoxy-1,2,3,4,4a,-5,10,10a-octahydrobenzo[*g*]quinoline (34b)—Amide **33b** (130 mg, 0.266 mmol) was reduced using 51 mg (1.33 mmol) of lithium aluminum hydride following Procedure C to give solid **34b,** 120 mg (97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.22 (m, 1H), 1.62–1.77 (m, 2H), 1.83–1.91 (m, 1H), 2.21–2.40 (m, 3H), 2.53–2.80 (m, 10H), 3.1–3.20 (m, H), 3.23–3.32 (m, 5H), 3.78 (s, 3H), 6.63–673 (m, 2H), 7.68–7.10 (m, 4H),7.22–7.30 (m, 2H).

(±)-*trans*-8-Methoxy-1-[4-(4-phenylpiperazin-1-yl)butyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (34c)—Amide **33c** (170 mg, 0.38 mmol) was reduced using 74 mg (1.9 mmol) of lithium aluminum hydride according to Procedure C. Column chromatography using EtOAc:MeOH (95:5) gave **34c,** 159 mg (96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.25 (m, 2H), 1.51–1.73 (m, 6H), 1.84–1.90 (m, 1H), 2.22–2.30 (m, 2H), 2.39–2.41 (m, 3H), 2.58–2.62 (m, 5H), 2.63–2.90 (m, 3H), 2.91–3.11 (m, 1H), 3.14–3.22 (m, 5H), 3.78 (s, 3H), 6.63–6.70 (m, 2H), 6.83–6.86 (t, 1H, J = 8 Hz), 6.92–6.97 (t, 3H, J = 8 Hz), 7.24–7.28 (t, 2H, J = 8 Hz).

(±)-*trans*-1-[2-(4-Phenylpiperazin-1-yl)ethyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo-[*g*]quinolin-8-ol (35a)—Ether **34a** (100mg, 0.47 mmol) was demethylated following Procedure D. The crude solid was purified by crystallization (EtOAc/MeOH) to give **35a**, 75 mg (78 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.24 (m, 1H), 1.62–1.75 (m, 2H), 1.83--1.92 (m, 1H), 2.24–2.42 (m, 3H), 2.50–2.82 (m, 10H), 3.13–3.20 (m, H), 3.20–3.31 (m, 5H), 6.63–6.74 (m, 2H), 6.83–7.11 (m, 4H), 7.21–7.30 (m, 2H). The free base was then converted to its HCl salt. mp = 167–170 °C. Anal. ($C_{25}H_{33}N_3O{\cdot}2HCl{\cdot}H_2O$) C, H, N.

(±)-*trans*-1-{2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl}-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-8-ol (35b)—Ether **34b** (140 mg, 0.30 mmol) was demethylated following the Procedure D. The crude solid was purified by crystallization (EtOAc/MeOH) to give **35b**, 100 mg (73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.24 (m, 1H), 1.63–1.79 (m, 2H), 1.84–1.92 (m, 1H), 2.20–2.41 (m, 3H), 2.55–2.83 (m, 10H), 3.2–3.23 (m, H), 3.22–3.34 (m, 5H), 6.60–6.72 (m, 2H), 6.92–7.14 (m, 3H), 7.33–7.40 (m, 1H). The free base was then converted to its HCl salt. mp = 182–185 °C. Anal. ($C_{25}H_{31}Cl_2N_3O{\cdot}2HCl$) C, H, N.

(±)-*trans*-1-[4-(4-Phenylpiperazin-1-yl)butyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo-[*g*]quinolin-8-ol (35c)—Methyl ether **34c** (90 mg, 0.207 mmol) was demethylated according to Procedure D to give **35c** 61 mg (70 %) after crystallization from EtOAc/MeOH. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.112–1.24 (m, 2H), 1.50–1.72 (m, 6H), 1.85–1.90 (m, 1H), 2.21–2.30 (m, 2H), 2.37–2.40 (m, 3H), 2.58–2.63 (m, 5H), 2.62–2.91 (m, 3H), 2.91–3.11 (m, 1H), 3.15–3.23 (m, 5H), 6.62–6.71 (m, 2H), 6.84–6.87 (t, 1H, *J* = 8 Hz), 6.93–6.98 (t, 3H, *J* = 8 Hz), 7.24–7.28 (t, 2H, *J* = 8 Hz), The free base was converted to its HCl salt. mp = 178–183 °C. Anal. ($C_{27}H_{37}N_3O$) C, H, N.

(±)-*trans-2*-(7-Methoxy-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]quinolin-4-yl)-1-(4-phenylpiperazin-1-yl)ethanone (37)—This compound was prepared using 200 mg of amine **36**[30] (0.79 mmol), 288 mg of chloride **13a** (0.945 mmol), and 327 mg of K_2CO_3 (2.37 mmol) according to Procedure B. Column chromatography using EtOAc as eluent afforded 330 mg of **(±)-37** (93%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.13–1.23 (m, 1H), 1.61–1.76 (m, 2H), 1.82–1.90 (m, 1H), 2.22–2.41 (m, 3H), 2.52–2.81 (m, 10H), 3.0–3.20 (m, H), 3.21–3.30 (m, 5H), 3.78 (s, 3H), 6.62–672 (m, 2H), 6.82–7.10 (m, 4H), 7.22–7.30 (m, 2H).

(+)-(4aR,10aR)-*trans*-2-(7-Methoxy-2,3,4a,5,6,10b-hexahydro-1H-benzo[f]quinolin-4-yl)-1-(4-phenylpiperazin-1-yl)-ethanone ((+)-37)—This compound was prepared following Procedure B, using 160 mg (0.632 mmol) of the **(+)-36**[16] isomer (HCl salt) and 166 mg (0.70 mmol) of chloride **13a** to give 260 mg (98 %) of **(+)-37** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14–1.24 (m, 1H), 1.63–1.75 (m, 2H), 1.80–1.91 (m, 1H), 2.23–2.41 (m, 3H), 2.51–2.81 (m, 10H), 2.1–3.22 (m, H), 3.20–3.31 (m, 5H), 3.75 (s, 3H), 6.64–6.73 (m, 2H), 6.83–7.12 (m, 4H), 7.21–7.31 (m, 2H).

(−)-(4aS,10bS)-*trans*-2-(7-Methoxy-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]quinolin-4-yl)-1-(4-phenylpiperazin-1-yl)ethanone ((−)-37)—This compound was prepared following Procedure B, using 150 mg (0.632 mmol) of the (−)-**36**16 isomer (HCl salt) and 183 mg (0.70 mmol) of chloride **13a** to give 293 mg (96 %) of (−)-**37** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.24 (m, 1H), 1.63–1.74 (m, 2H), 1.81–1.92 (m, 1H), 2.23–2.43 (m, 3H), 2.53–2.85 (m, 10H), 3.2–3.26 (m, H), 3.23–3.33 (m, 5H), 3.80 (s, 3H), 6.63–6.70 (m, 2H), 6.81–7.11 (m, 4H), 7.23–7.31 (m, 2H).

(±)-*trans*-7-Methoxy-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (38)—Compound **37** (361 mg, 0.833 mmol) was reduced with lithium aluminum hydride (250 mg, 6.66 mmol) according to Procedure C to give **(±)-38**, 335 mg (98 %) as an oil, which was sufficiently pure to use in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77–1.82 (m, 2H), 2.17–2.22 (m, 1H), 2.35–2.50 (m, 3H), 2.57–2.75 (m, 8H), 2.94–3.08 (m, 3H), 3.20–3.22 (t, 4H, *J* = 5.2 Hz), 3.81 (s, 3H), 6.69–6.71 (d, 1H, *J* = 8 Hz), 6.83–6.87 (t, 1H, *J* = 8 Hz), 6.92–6.94 (m, 3H), 7.13–7.17 (t, 1H, *J* = 8Hz), 7.24–7.28 (t, 2H, *J* = 8 Hz).

(+)-(4aR,10aR)-*trans*-7-Methoxy-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4,4a,5,6,-10b-octahydrobenzo[*f*]quinoline ((+)-38)—Compound **(+)-37** (260mg, 0.620 mmol) was reduced with lithium aluminum hydride (188 mg, 5.0 mmol) according to Procedure C to give **(+)-38**, 251 mg (99 %) as an oil, which was sufficiently pure to use in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75–1.80 (m, 2H), 2.16–2.23 (m, 1H), 2.34–2.51 (m, 3H), 2.58–2.76 (m, 8H), 2.94–3.10 (m, 3H), 3.20–3.22 (t, 4H, *J* = 5.2 Hz), 3.81 (s, 3H), 6.68–6.74 (d, 1H, *J* = 8 Hz), 6.84–6.85 (t, 1H, *J* = 8 Hz), 6.90–6.94 (m, 3H), 7.12–7.18 (t, 1H, *J* = 8Hz), 7.22–7.29 (t, 2H, *J* = 8 Hz).

(−)-(4aS,10bS)-*trans*-7-Methoxy-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4,4a, 5,6,-10b-octahydrobenzo[*f*]quinoline ((−)-38)—Compound (−)-**37** (293 mg, 0.70 mmol) was reduced with lithium aluminum hydride (212 mg, 5.59 mmol) according to Procedure C to give (−)-**38**, 265 mg (93 %) as an oil, which was sufficiently pure to use in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75–1.86 (m, 2H), 2.18–2.26 (m, 1H), 2.34–2.51 (m, 3H), 2.54–2.72 (m, 8H), 2.92–3.06 (m, 3H), 3.22–3.24 (t, 4H, *J* = 5.2 Hz), 3.81 (s, 3H), 6.69–6.70 (d, 1H, *J* = 8 Hz), 6.85–6.89 (t, 1H, *J* = 8 Hz), 6.91–6.95 (m, 3H), 7.12–7.18 (t, 1H, *J* = 8 Hz), 7.23–7.28 (t, 2H, *J* = 8 Hz).

(±)-*trans*-4-(2-(4-Phenylpiperazin-1-yl)ethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo [*f*]-quinolin-7-ol (8)—Compound **38** (335 mg, 8.27 mmol), was demethylated following Procedure D. The crude solid was purified by recrystallization (EtOAc/MeOH) to give **(±)-8**, 264 mg (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72–1.70 (m, 2H), 2.11–2.20 (m, 1H), 2.34–2.51 (m, 3H), 2.62–2.79 (m, 8H), 2.96–3.10 (m, 3H), 3.22–3.24 (t, 4H, *J* = 5.2 Hz), 6.70–6.72 (d, 1H, *J* = 8 Hz), 6.81–6.85 (t, 1H, *J* = 8 Hz), 6.94–6.96 (m, 3H), 7.15–7.19 (t, 1H, *J* = 8 Hz), 7.26–7.30 (t, 2H, *J* = 8 Hz). The free base was converted to its HCl salt. mp = 165–169 °C. Anal. ($C_{25}H_{33}N_3O{\cdot}2HCl{\cdot}0.5H_2O$) C, H, N.

(+)-(4aR,10aR)-*trans*-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-7-ol ((+)-8)—Compound **(+)-38** (250 mg, 0.616 mmol), was demethylated following Procedure D. The crude solid was purified by recrystallization (EtOAc/MeOH) to give **(+)-8**, 200 mg (82 %). $[\alpha]_D$ = +43.6° (c = 0.86 in MeOH) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71–1.70 (m, 2H), 2.13–2.21 (m, 1H), 2.35–2.53 (m, 3H), 2.60–2.77 (m, 8H), 2.97–3.11 (m, 3H), 3.20–3.22 (t, 4H, *J* = 5.2 Hz), 6.71–6.73 (d, 1H, *J* = 8 Hz), 6.84–6.88 (t, 1H, *J* = 8 Hz), 6.92–6.94 (m, 3H), 7.12–7.20 (t, 1H, *J* = 8 Hz), 7.25–7.31 (t, 2H, *J* = 8 Hz). The free base was converted to its HCl salt. mp = 163–167 °C. Anal. ($C_{25}H_{33}N_3O{\cdot}2HCl$) C, H, N.

(−)-(4aS,10bS)-*trans*-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolin-7-ol ((−)-8)—Compound (−)-**38** (265 mg, 0.653 mmol), was demethylated following Procedure D. The crude solid was purified by recrystallization (EtOAc/MeOH) to give (−)-**8**, 215 mg (84 %). $[\alpha]_D$ = −45.6° (c = 0.55 in MeOH) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71–1.68 (m, 2H), 2.12–2.21 (m, 1H), 2.32–2.49 (m, 3H), 2.61–2.77 (m, 8H), 2.95–3.05 (m, 3H), 3.21–3.23 (t, 4H, *J* = 5.2 Hz), 6.71–6.73 (d, 1H, *J* = 8 Hz), 6.80–6.84 (t, 1H, *J* = 8 Hz), 6.95–6.97 (m, 3H), 7.16–7.20 (t, 1H, *J* = 8 Hz), 7.22–7.26 (t, 2H, *J* = 8 Hz). The free base was converted to its HCl salt. mp = 166–169 °C. Anal. ($C_{25}H_{33}N_3O{\cdot}2HCl$) C, H, N.

***trans*-4-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolin-7-ol (1)—**To a solution of compound **(±)-36** (0.217 g, 1 mmol) and TEA (0.5 ml) in dichloromethane (15 ml) at 0 °C was added propionyl chloride (0.111g, 1.2 mmol) dropwise. The reaction mixture was allowed to stir for additional 1 hr. The reaction mixture was washed with sat. $NaHCO_3$ solution, followed by water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to yield viscous liquid (0.2 g) which was subjected to reduction with excess $LiAlH_4$ following Procedure C. Demethylation of the tertiary amine thus obtained was carried out in refluxing aq. HBr (48%) for 3 hr. The acid was removed in vacuo. The residue obtained was converted to free base using aq. Na_2CO_3. The free base was purified using column chromatography (dichloromethane:MeOH 8:2) to yield 187 mg of **(±)-1** (92%). NMR (400 MHz, $CDCl_3$) δ 1.04–1.07 (t, 3H, *J* = 8 Hz), 1.46–1.49 (m, 1H), 1.79 (m, 3H), 1.98–2.14 (m, 3H), 2.59–2.77 (m, 3H), 3.03–3.16 (m, 5H), 3.6–3.63 (m, 1H), 6.63–6.65 (d, 1H, *J* = 7.2 Hz), 6.18–6.83 (d, 1H, *J* = 8Hz), 7.00–7.04 (t, 1H, *J* = 7.2 Hz). The free base was then converted to its oxalte salt. mp = 156–160 °C. Anal. ($C_{18}H_{25}NO_5$) C, H, N

(±)-*trans*-2-(6-Methoxy-3,4,4a,5,10,10a-hexahydro-2*H*-benzo[*g*]quinolin-1-yl)-1-(4-phenylpiperazin-1-yl)ethanone (41a)—The hydrochloride salt of amine **40**[29] (350 mg, 1.38 mmol), chloride **13a** (383 mg, 1.25 mmol), and K_2CO_3 (573 mg, 4.15 mmol) in CH_3CN were reacted following Procedure B to yield **41a**, 501 mg (95 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.69 (m, 3H), 1.90–1.93 (m, 1H), 2.14–2.36 (m, 4H), 2.65–2.72 (m, 1H), 2.90–2.96 (m, 2H), 3.00–3.12 (m, 3H), 3.17–3.22 (m, 1H), 3.29 (bs, 1H), 3.57–3.60 (m, 1H), 3.69–3.73 (m, 2H), 3.81 (s, 3H), 3.88–3.92 (d, 1H, *J* = 13 Hz), 3.99–4.01 (m, 1H), 6.65–6.67 (d, 1H, *J* = 8 Hz), 6.70–6.72 (d, 1H, *J* = 8 Hz), 6.88–6.95 (m, 3H), 7.07–7.11 (t, 1H, *J* = 8 Hz), 7.23–7.31 (m, 2H).

(±)-*trans*-1-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-2-(6-methoxy-3,4,4a,5,10,10a-hexahydro-2H-benzo[*g*]quinolin-1-yl)-ethanone (41b)—The hydrochloride salt of amine **40** (100 mg, 0.386 mmol), chloride **13b** (118 mg, 0.386 mmol), and K_2CO_3 (106 mg, 0.772 mmol) in CH_3CN were reacted following Procedure B to yield **41b**, 170 mg (90%) as an oil, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61–1.68 (m, 3H), 1.91–1.94 (m, 1H), 2.13–2.35 (m, 4H), 2.66–2.73 (m, 1H), 2.91–2.97 (m, 2H), 3.01–3.13 (m, 3H), 3.17–3.22 (m, 1H), 3.29 (bs, 1H), 3.57–3.60 (m, 1H), 3.69–3.73 (m, 2H), 3.81 (s, 3H), 3.88–3.92 (d, 1H, *J* = 13 Hz), 3.99–4.01 (m, 1H), 6.58–6.59 (d, 1H, *J* = 8 Hz), 6.63–6.65 (d, 1H, *J* = 8 Hz), 6.85–6.84 (d, 1H, *J* = 8 Hz), 7.00–7.04 (t, 1H, *J* = 8 Hz), 7.07–7.13 (m, 2H).

(±)-*trans*-6-Methoxy-1-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (42a)—Amide **41a** (500 mg, 1.38 mmol) was reduced with lithium aluminum hydride (280 mg, 7.0 mmol) following procedure C to give 52, 480 mg (99 %) of **42a**, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60–1.72 (m, 4H), 2.21–2.27 (m, 2H), 1.90–1.94 (m, 1H), 2.59–2.74 (m, 8H), 2.33–2.39 (m, 1H), 2.91–3.09 (m, 3H), 3.22–3.27 (m, 5H), 3.81 (s, 3H), 6.65–6.67 (d, 1H, *J* = 8 Hz), 6.70–6.72 (d, 1H, *J* = 8 Hz), 6.88–6.95 (m, 3H), 7.07–7.11 (t, 1H, *J* = 8 Hz), 7.23–7.31 (m, 2H).

(±)-*trans*-1-a{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-6-methoxy-1,2,3,4,4a-5,10,10a-octahydro-benzo[*g*]quinoline (42b)—Amide **41b** (170 mg, 0.349 mmol) was reduced with lithium aluminum hydride (55 mg, 1.43 mmol) following procedure C to give **42b**, 152 mg (92 %) of the titled product, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.66 (m, 3H), 1.90–1.93 (m, 1H), 2.11–2.33 (m, 4H), 2.64–2.71 (m, 1H), 2.90–2.96 (m, 2H), 3.00–3.12 (m, 3H), 3.12–3.29 (m, 8H), 3.81 (s, 3H), 6.58–6.59 (d, 1H, *J* = 8 Hz), 6.63–6.65 (d, 1H, *J* = 8 Hz), 6.85–6.84 (d, 1H, *J* = 8 Hz), 7.00–7.04 (t, 1H, *J* = 8 Hz), 7.07–7.13 (m, 2H).

(±)-*trans*-1-[2-(4-Phenylpiperazin-1-yl)ethyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo-[*g*]quinolin-6-ol (43a)—Compound **42a** (470 mg, 1.16 mmol) was demethylated following Procedure D. The crude solid was purified by column chromatography (1:10 MeOH:EtOAc) to give **43a**, 400 mg (88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.15 (m, 2H), 1.90–1.92 (m, 1H), 2.15–2.27 (m, 3H), 2.33–2.39 (m, 1H), 2.60–2.75 (m, 9H), 2.85–2.91 (m, 1H), 3.03–3.11 (m, 2H), 3.17–3.23 (m, 5H), 6.53–6.55 (d, 1H, *J* = 7.6 Hz), 6.64–6.66 (d, 1H, *J* = 8 Hz), 7.24–7.28 (t, 2H, *J* = 8 Hz), 6.83–6.87 (t, 1H, *J* = 8 Hz), 6.91–6.99 (m, 3H), The free base was then converted to its HCl salt. mp = 174–179 °C. Anal. ($C_{25}H_{33}N_3O$·3HCl) C, H, N.

(±)-*trans*-1-{2-[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-ethyl}-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-6-ol (43b)—Compound **42b** (152 mg, 0.321 mmol) was demethylated –following Procedure D. The crude solid was purified by column chromatography (1:10 MeOH:EtOAc) to give **43b**, 102 mg (69 %). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.12–1.25 (m, 2H), 1.82–1.91 (m, 1H), 2.21–2.42 (m, 3H), 2.51–2.63 (m, 9H), 2.78–2.81 (m, 1H), 2.98–3.12 (m, 8H), 6.53–6.54 (d, 1H, *J* = 8 Hz), 6.58–6.60 (d, 1H, *J* = 8 Hz), 6.80–6.79 (d, 1H, *J* = 8 Hz), 6.95–7.00 (t, 1H, *J* = 8 Hz), 7.02–7.09 (m, 2H). The free base was then converted to its HCl salt. mp = 161–165 °C. Anal. ($C_{25}H_{31}N_3OCl_2 \cdot 2HCl$) C, H, N.

(±)-*trans*-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-6-ol (2)—To a solution of compound (±)-**40** (0.217 g, 1 mmol) and TEA (0.5 ml) in dichloromethane (15 ml) at 0 °C was added propionyl chloride (0.111g, 1.2 mmol) dropwise. The reaction mixture was allowed to stir for additional 1 hr. The reaction mixture was washed with sat. $NaHCO_3$ solution, followed by water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to yield thick oil (0.2 g) which was subjected to reduction with excess $LiAlH_4$ following Procedure C. Demethylation of the tertiary amine thus obtained was carried out in refluxing aq. HBr (48%) for 3 hr. The acid was removed in vacuo. The residue obtained was converted to free base using aq. Na_2CO_3. The free base was purified using column chromatography (dichloromethane:MeOH 8:2) to give 0.1 g of **2**. The purified free base was converted to HCl salt. ^{1}H NMR (400 MHz, CD_3OD): δ 1.0–1.04 (t, 3H), 1.45–1.51 (m, 2H), 1.67–1.86 (m, 5H), 1.91–1.94 (m, 1H), 2.10–2.16 (m, 1H), 2.74–2.78 (m, 2H), 2.89–3.04 (m, 5H), 6.52–6.55 (m, 2H), 6.85–6.89 (m, 1H). The free base was converted to HCl salt. mp = 165–167 °C. Analysis. ($C_{16}H_{25}ClNO.HCl.0.3C_2H_5OC_2H_5$) C, H, N.

Molecular Modeling

All molecular modeling studies reported herein were performed on a Hewlett-Packard xw4300 computer workstation with main memory of 2 GB and Intel® Pentium® 4 CPU of 3.4 GHz running under the operating system Linux Red Hat 3. The molecular modeling software packages Sybyl 7.1[32] and Molecular Operating Environment (MOE) 2007.09[33] were employed for the present work.

The structures used in the present study were either constructed from X-ray crystal structure or using fragments in Sybyl's fragment library. All the structures were generated in their N-protonated form. Partial atomic charges were calculated using Gasteiger-Hückel method in Sybyl 7.1. Each structure was fully geometry-optimized using Tripos Force Field[34] with a distance-dependent dielectric function until a root-mean-square (rms) deviation of 0.001 kcal/mol Å was achieved. Ring conformations of bi- and tricyclic aminotetralin derivatives were generated using simulated annealing protocol with default settings (No. of cycles: 10, heating: 700 K for 1000 fs, annealing: 50 K for 1000 fs, annealing function: exponential) in Sybyl 7.1. The minimum energy conformations for each of the bi- and tricyclic ring systems were further minimized in Sybyl using the settings mentioned above. Further, rotatable bonds in all molecules were searched from 0–359 ° in 10° increments using systematic search protocol in Sybyl. The minimum energy conformations were minimized further as described above. The molecules were imported in TriposMol2 (.mol2) format in MOE 2007.09 and stored in a molecular database. This database was used as an input in Pharmacophore Elucidation functionality in MOE. The structures of molecules used for generating pharmacophore queries are shown Figures 1 and 3.

The objective of Pharmacophore Elucidation is to generate all popular pharmacophore queries (with coverage *n*, typically 90 % of all active molecules) considering all possible discrete geometries with all possible combinations of input query expressions. The Pharmacophore Elucidator operates on 3D conformations of the molecules present in the input database. In present study the Conformations option in Pharmacophore Elucidation panel was set to bond rotation wherein the rotatable bonds of each molecule were set systematically to specific torsion angles from a collection of rules. The ring conformations were not searched. The default annotation scheme CHD was used for determining the pharmacophore features of each

molecule. Pharmacophore Elucidator generates pharmacophores compatible with the specified scheme. Other parameter values in the Pharmacophore Elucidation panel were kept at their default values. The alignment options (emphasize aromatic atoms and emphasize donor and acceptor atoms) which influence the overlap scoring were enabled. The results of the pharmacophore generation were written to an output database, which was analyzed further to select appropriate pharmacophore hypothesis.

The set of compounds used for pharmacophore generation consisted of conformationally constrained (bi- and tricyclic aminotetralin derivatives) structures shown in Figure 3 with their dopamine D2 and D3 receptor binding affinities listed in Table 1. To determine the appropriate annotation scheme, several runs with other annotation schemes given in Pharmacophore Elucidation functionality such as PCH, CHD, PCHD, PPCH, PCHD, Unified, etc. were tried keeping all other parameters constant (data not shown). For these initial trial runs, compounds R-(+)-7-OH-DPAT, S-(−)-5-OH-DPAT and R-(+)-**5**, known D2/D3 agonists, were used. It is well-known from earlier dopamine pharmacophores that an aromatic H-bond donor and cationic nitrogen (reinforced H-bonding) are necessary to interact with dopamine receptor Serine and Aspartate residues, respectively.[15] To include these highly directional pharmacophore requirements such as reinforced H-bonding, the annotation scheme CHD was selected. This scheme avoids use of atomic H-bond/acceptor features but includes the directional character of the atomic H-bond donor/acceptor features. This is particularly useful for DA ligands since these possess varying nature of the H-bond donor, which interact with Serine. Also, enabling the alignment options emphasize aromatic atoms and emphasize donor and acceptor atoms led to meaningful pharmacophore hypotheses. The final pharmacophores were generated using the CHD annotation scheme with abovementioned alignment options. For the generation of pharmacophore hypotheses based on hybrid analogs, compounds **(+)-6**, **(−)-7**, **(−)-8 (4aS, 10bS)** and **(−)-11** (S-enantiomer) were used. Selection of the appropriate hypotheses was based on overall alignment score and the associated pharmacophore features.

Measurement of affinity in inhibiting [^{3}H]spiperone binding to dopamine D2 and D3 receptors

Binding affinities were assessed according to the general procedure described in our previous study.[22] Briefly, membranes from HEK 293 cells expressing rat D2L and D3 receptors were incubated with each test compound and [^{3}H]spiperone (0.4 nM, 15 Ci/mmole, Perkin Elmer) for 1 h at 30°C in 50 mM Tris-HCl (pH 7.4), with 0.9% NaCl, and 0.025% ascorbic acid in the absence of GTP. (+)-Butaclamol (2 μM) was used to define nonspecific binding. Assays were terminated by addition of ice-cold buffer and filtration in the MACH 3–96 Tomtec harvester (Wallac, Gaithersburg, MD). IC_{50} values were estimated by nonlinear regression analysis with the logistic model in the least squares fitting program ORIGIN, and converted to inhibition constants (K_i) by the Cheng-Prusoff equation.[35] In this conversion, the K_d values for [^{3}H] spiperone binding were 0.057 nM for D2 receptors and 0.125 nM for D3 receptors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

DA
Dopamine

GPCR
G-protein coupled receptor

CNS
central nervous system

MOE
Molecular Operating Environment

HEK
human embryonic kidney

5-OH-DPAT
5-hydroxy-2-(dipropylamino)tetralin

7-OH-DPAT
7-hydroxy-2-(dipropylamino)tetralin

PMA
Phosphomolybdic acid

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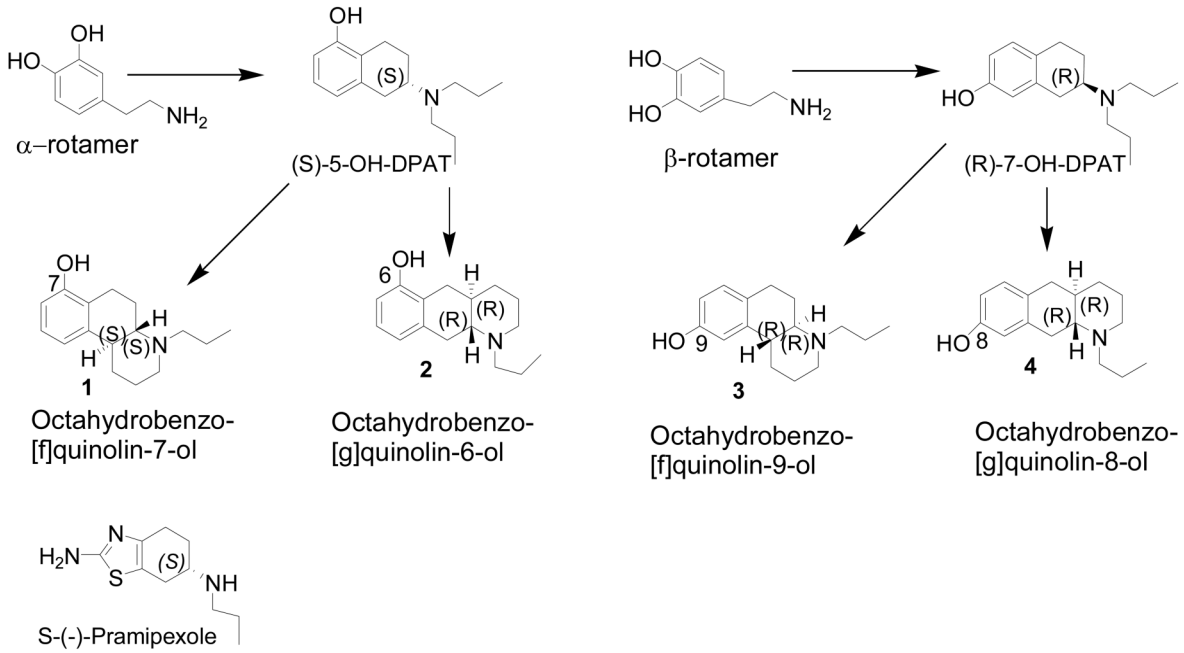


Figure 1.
Molecular structures of Dopamine D2/D3 receptor Ligands

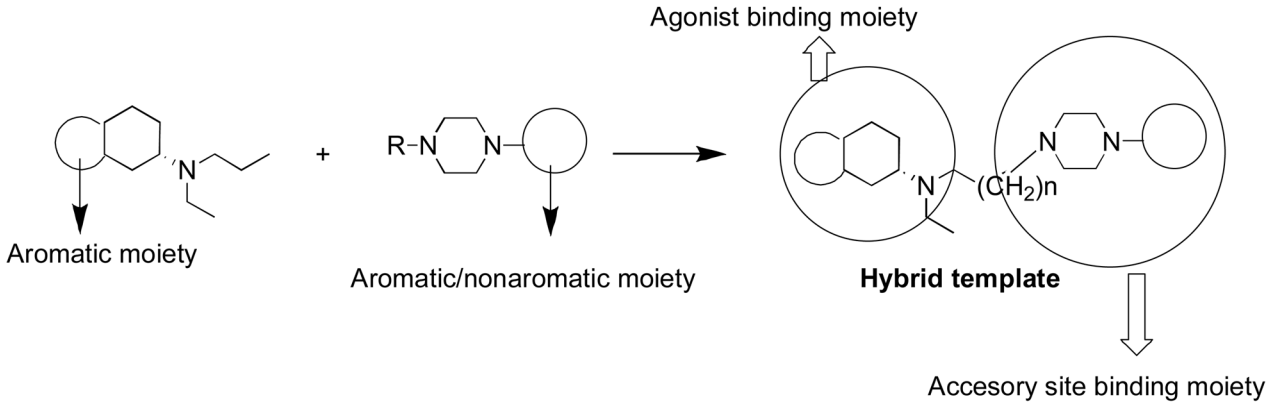


Figure 2.
Hybrid template design

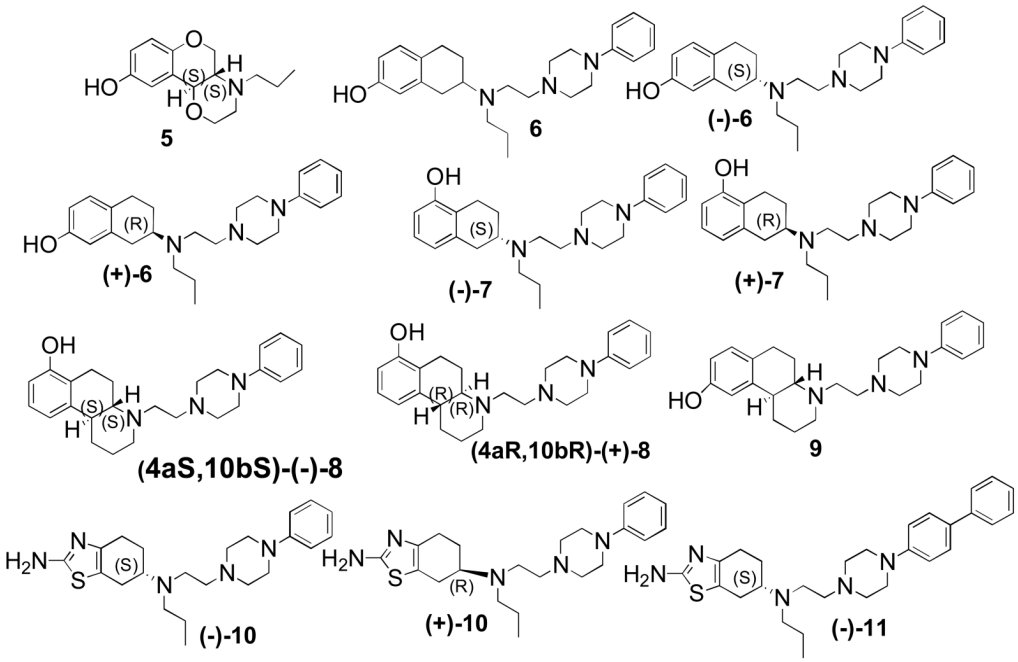
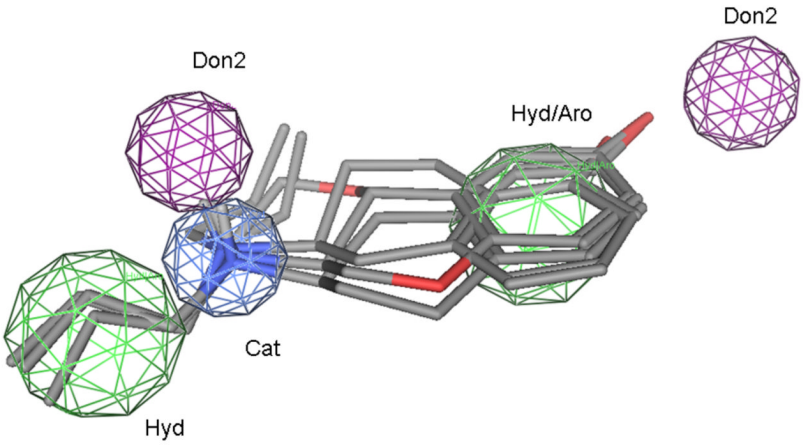
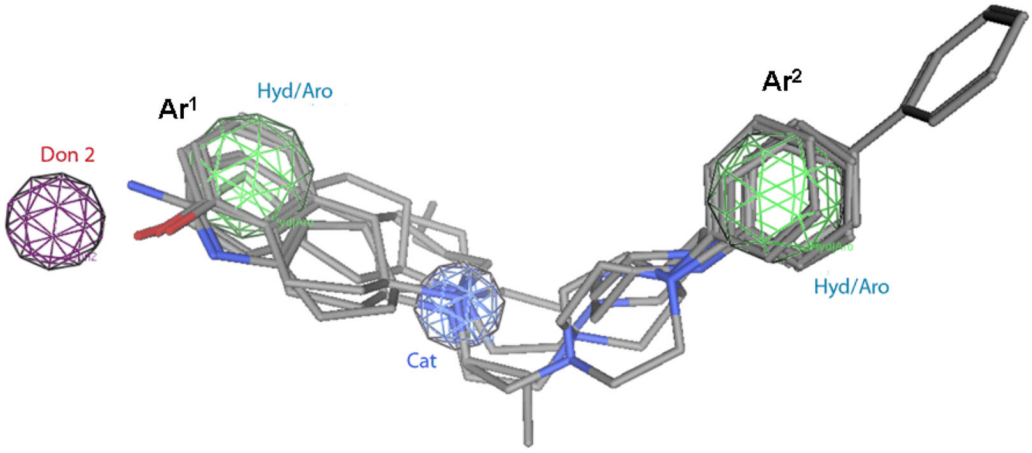


Figure 3.
Molecular structures of compounds used for development of pharmacophore hypothesis

a)



b)



c)

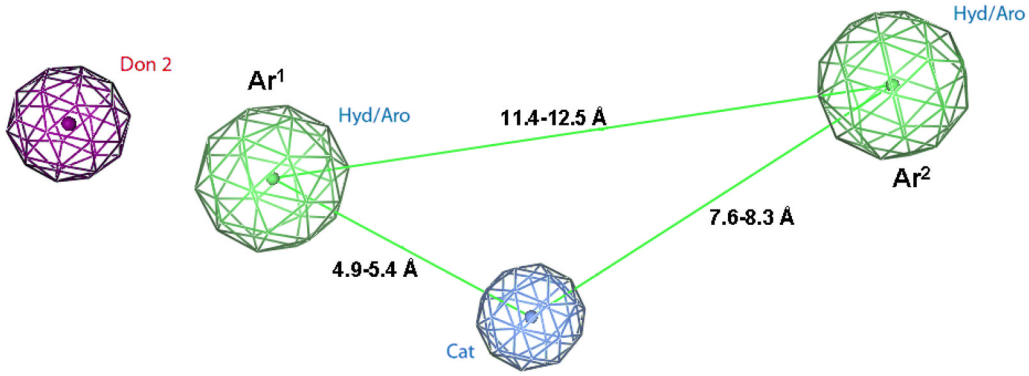
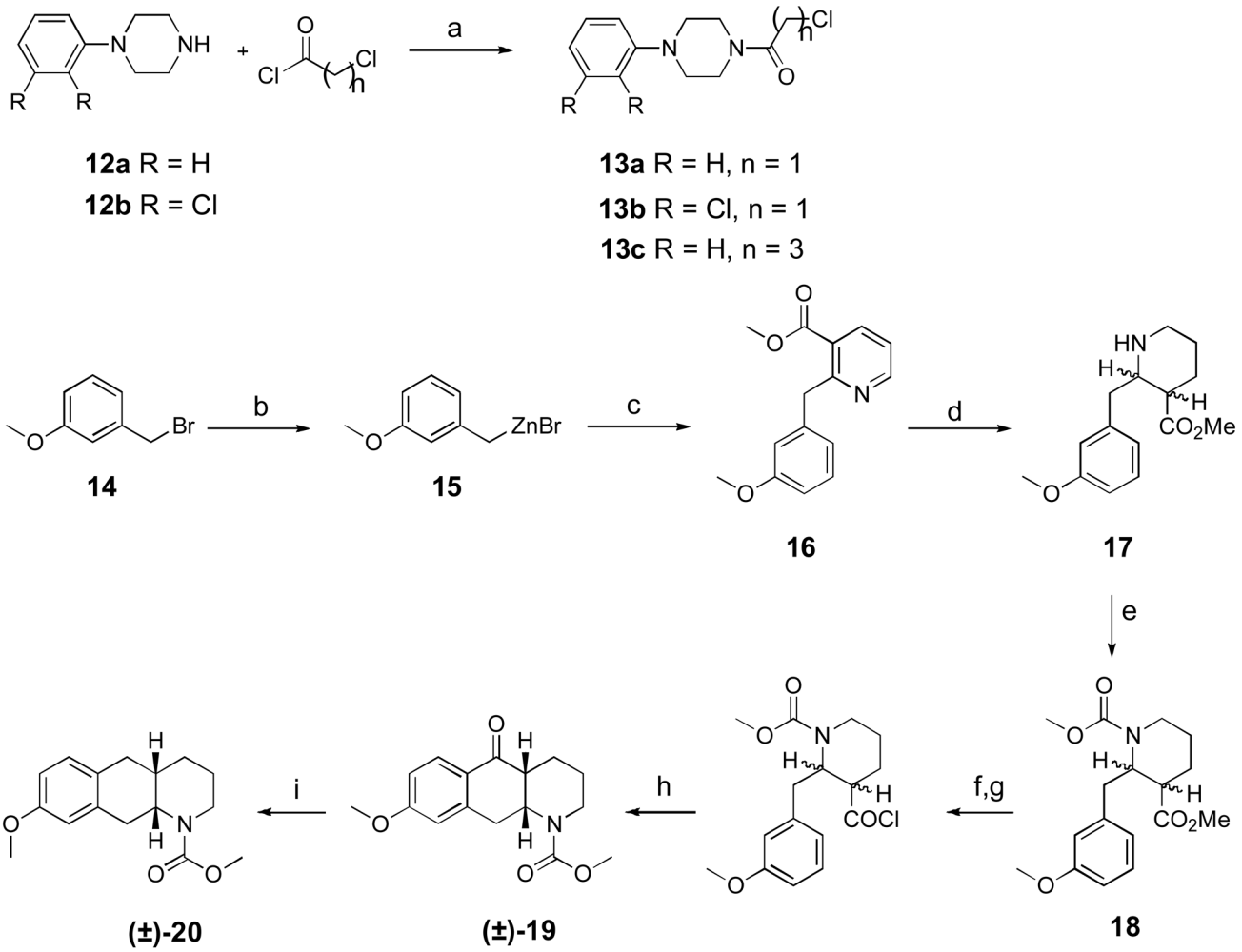
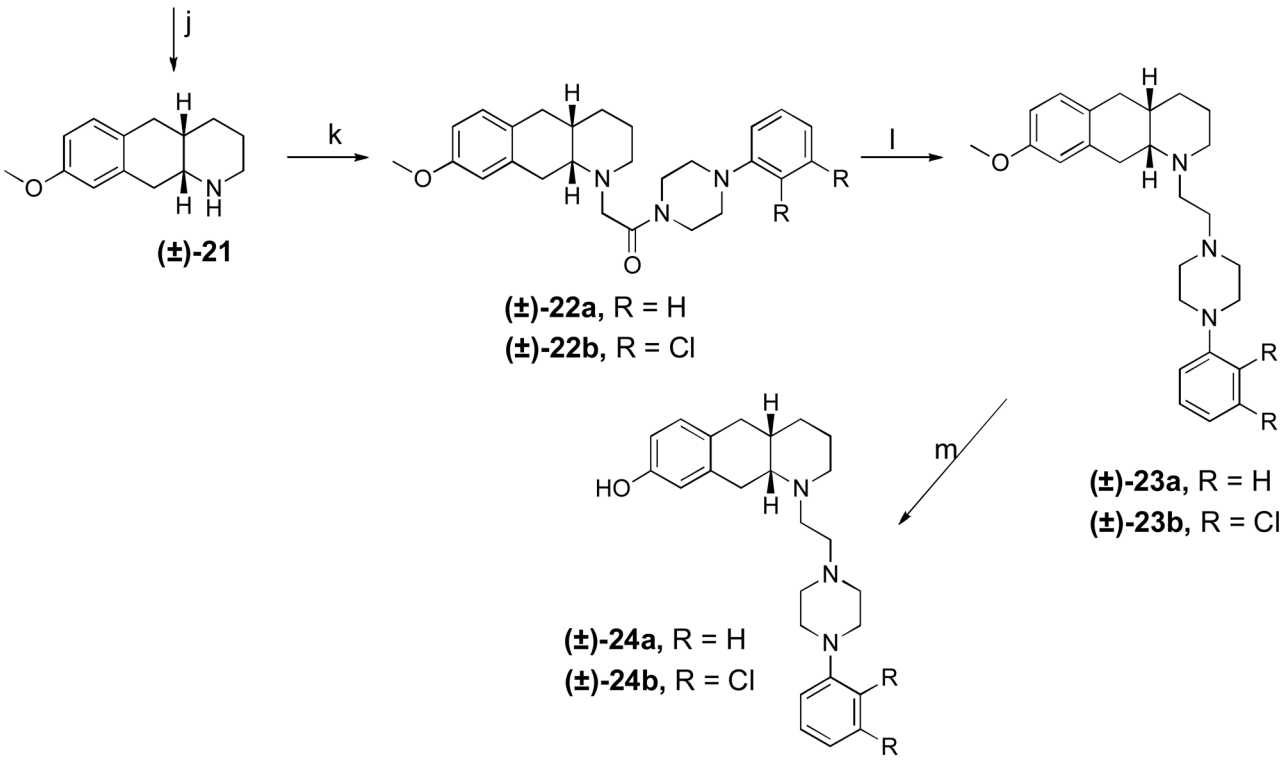


Figure 4.

a) 3-Point pharmacophore generated using known D2/D3 ligands[a] b) 3-point pharmacophore derived from D2/D3 ligand hybrid analogues[a] c) 3-Point pharmacophore derived from hybrid analogs with corresponding interfeature distances[a]

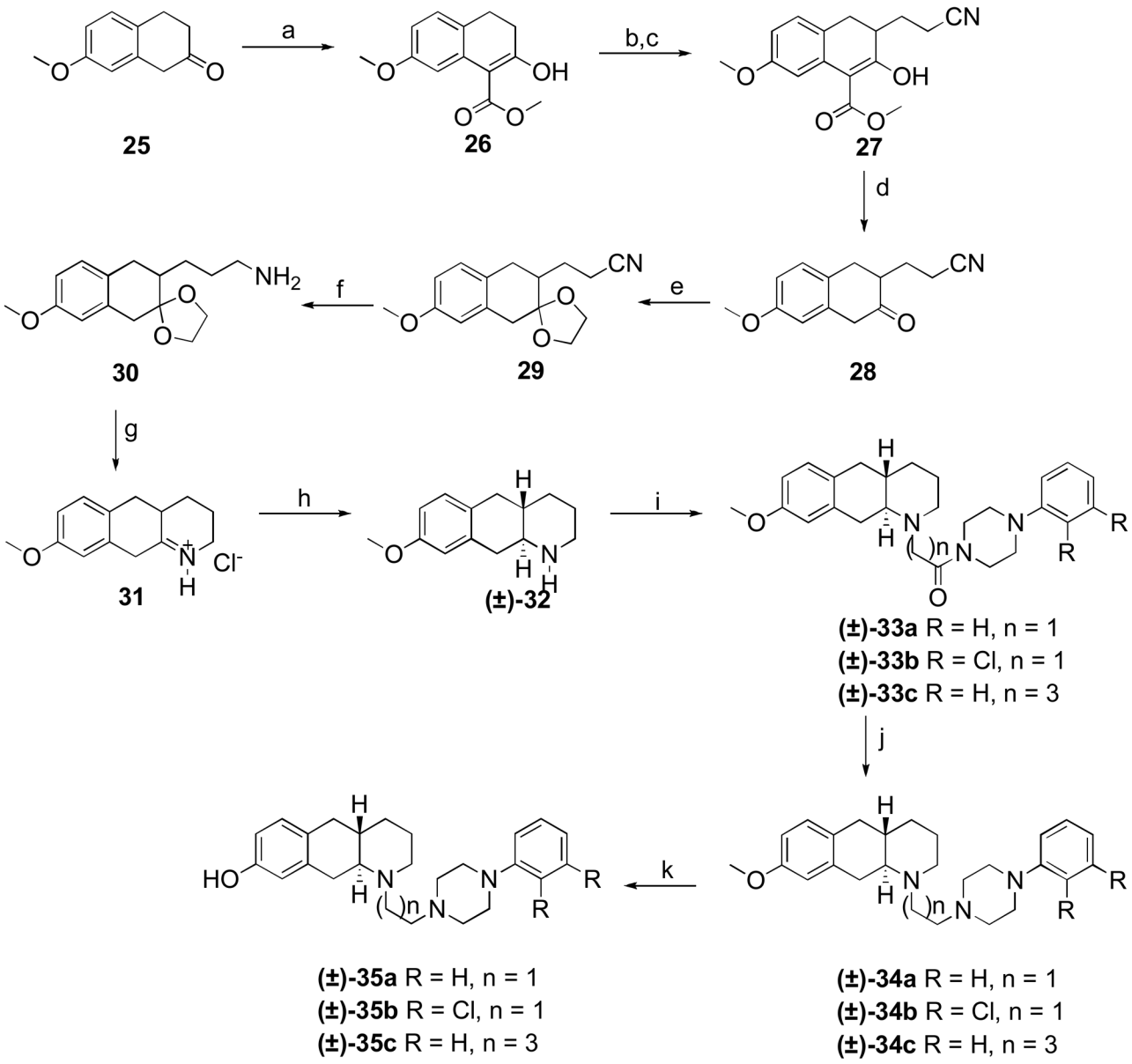
[a] Aro/Hyd: Aromatic/Hydrophobic; cat: cationic; Don2: The directional feature towards which the H-bond donor should be oriented. Ar^1 denotes the aromatic ring of either aminotetralin or 2-aminothiazole moieties and Ar^2 is the phenyl ring attached to one of the piperazine Ns.





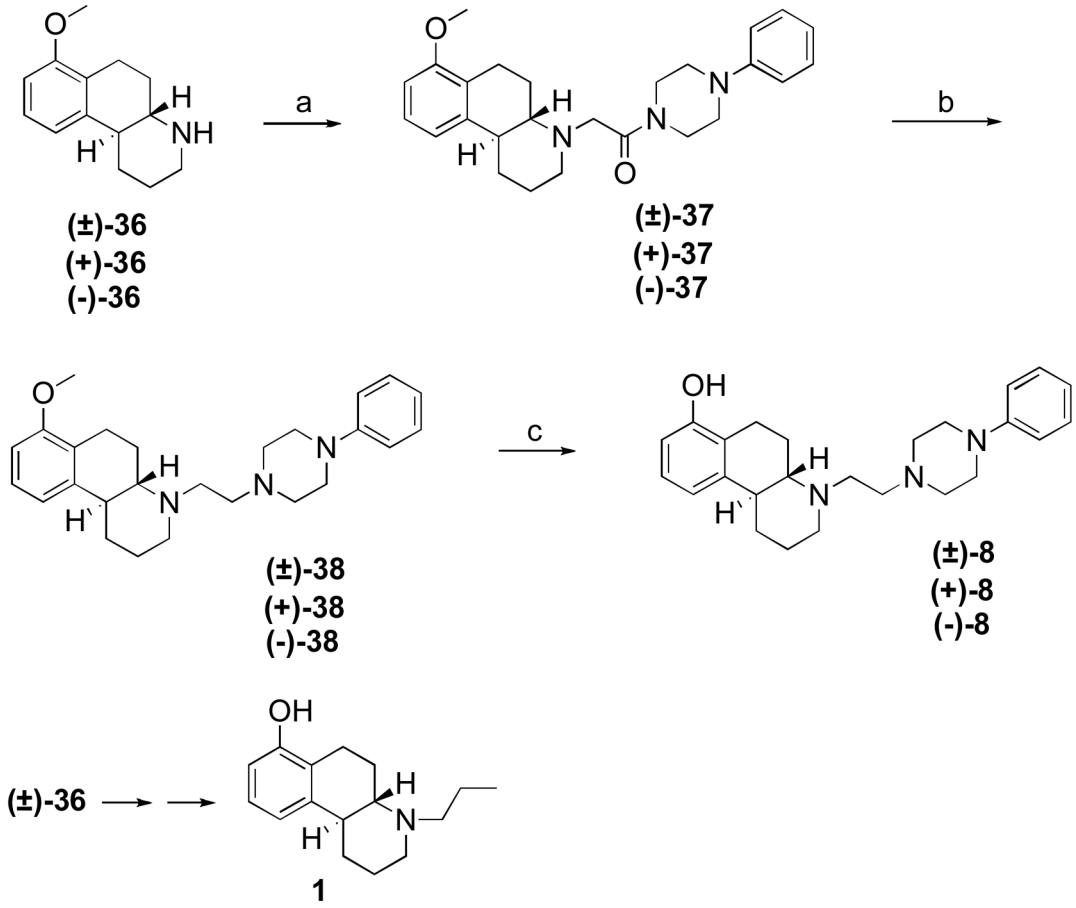
Scheme 1a.

[a]Reagents and conditions: (a) Et_3N, CH_2Cl_2, 0 °C (b) Zn dust, THF, 0 °C; (c) methyl 2-chloronicotinate, $(PPh_3)_2NiCl_2$, THF; (d) (i) HCl, Et_2O (ii) PtO_2, MeOH; (e) methyl chloroformate, K_2CO_3, CH_2Cl_2; (f) LiOH, MeOH, H_2O; (g) $SOCl_2$, CH_2Cl_2, cat. DMF; (h) $TiCl_4$, CH_2Cl_2, 0 °C; (i) Pd/C, AcOH, $HClO_4$; (j) NH_2NH_2, KOH, H_2O, $(CH_2OH)_2$, reflux; (k) **13a/b**, K_2CO_3, CH_3CN; (l) $LiAlH_4$, THF, reflux; (m) BBr_3, CH_2Cl_2, −78 °C



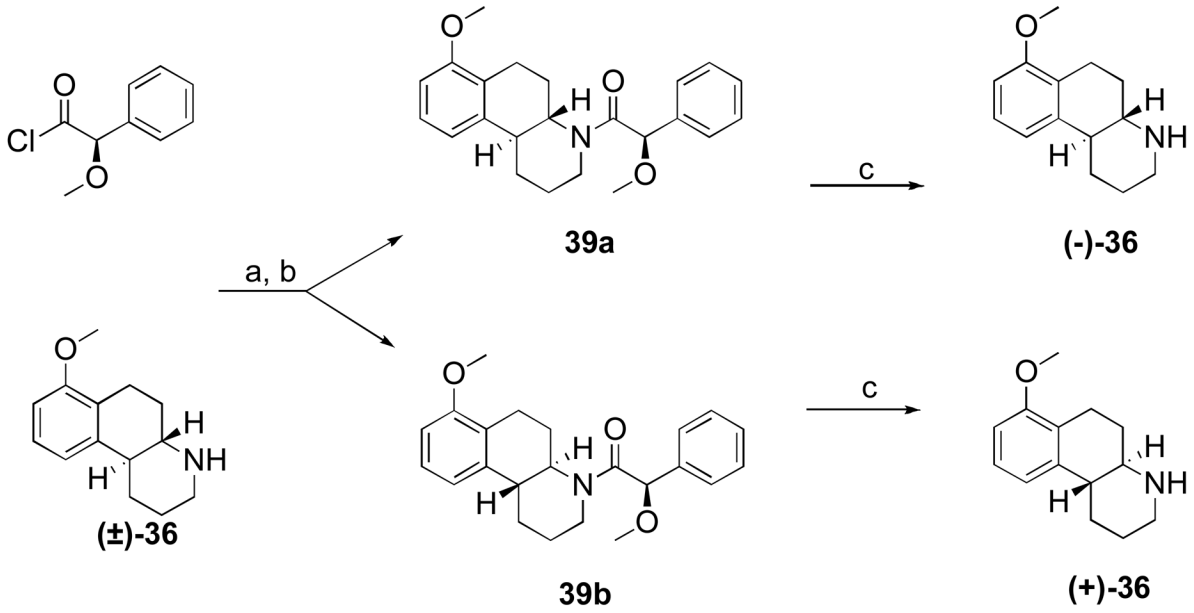
Scheme 2a.

[a] Reagents and conditions: (a) NaH, $PhCH_3$, dimethyl carbonate, reflux; (b) 2 eq. LDA, THF, −78 °C; (c) bromopropionitrile; (d) LiCl, H_2O, DMSO, reflux; (e) $(CH_2OH)_2$, TsOH, triethyl orthoformate, CH_2Cl_2; (f) Raney Ni, MeOH; (g) 6 M HCl, MeOH, reflux; (h) $NaCNBH_3$, MeOH; (i) **13a**/**13b**/**13c,** K_2CO_3, CH_3CN, cat. KI, reflux; (j) $LiAlH_4$, THF, reflux; (k) BBr_3, CH_2Cl_2, −78 °C



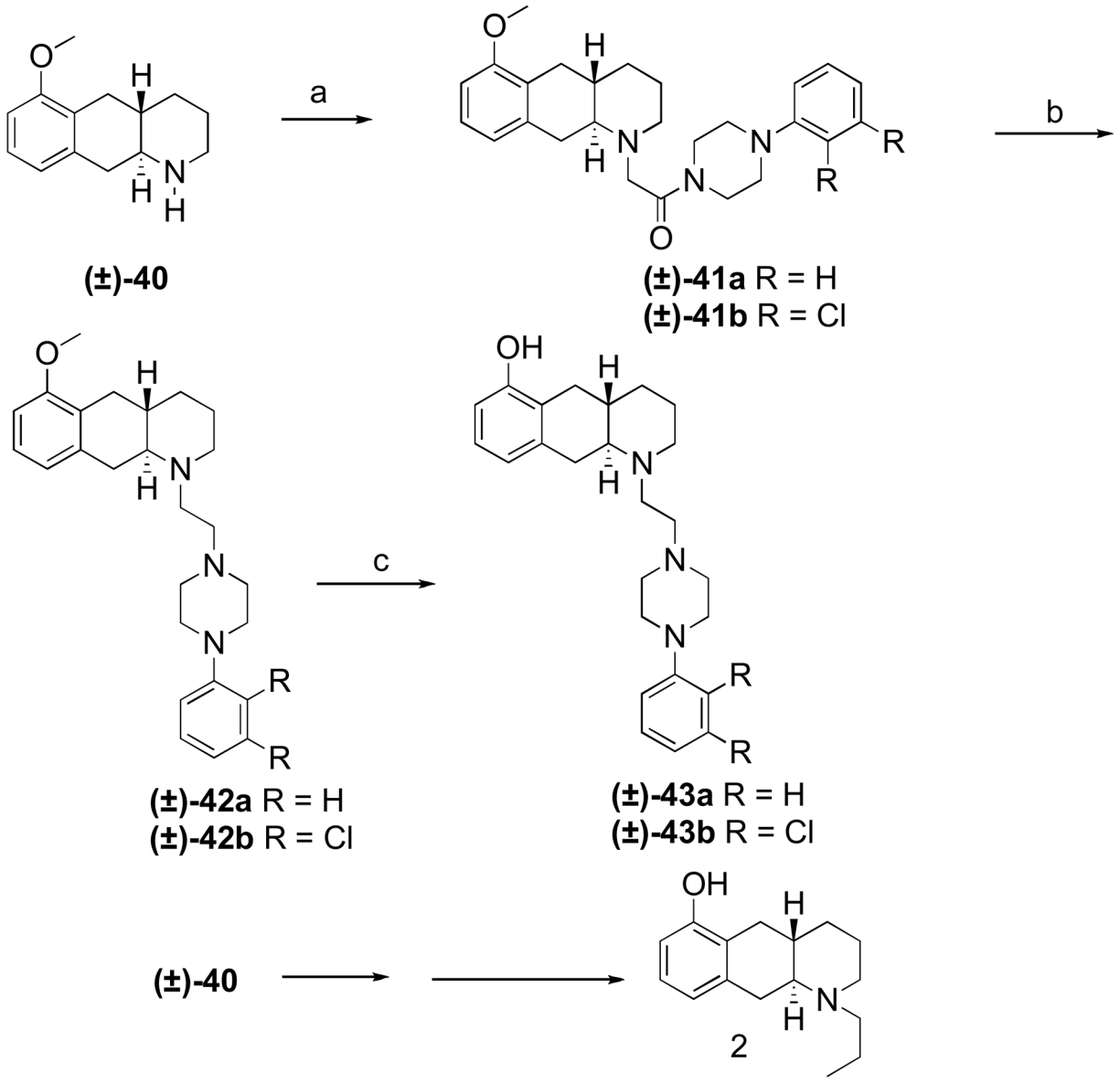
Scheme 3a.

[a] Reagents and conditions: (a) **13a**, K_2CO_3, CH_3CN, reflux; (b) $LiAlH_4$ (c) BBr_3, CH_2Cl_2, −78 °C



Scheme 4a.

[a] Reagents and conditions: (a) NaOH, H_2O/CH_2Cl_2; (b) crystallization followed by HPLC (c) (i) Na*t*-butoxide, H_2O, THF (ii) HCl, MeOH



Scheme 5a.

[a] Reagents and conditions: (a) **13a/b**, K_2CO_3, CH_3CN, reflux; (b) $LiAlH_4$, THF, reflux; (c) BBr_3, CH_2Cl_2, −78 °C

Table 1

Affinity for cloned D_{2L} and D_3 receptors expressed in HEK cells measured by inhibition of [^{3}H]spiperone binding. Results are means ± SEM for 3–8 experiments each performed in triplicate.

Compound	K_i, (nM), D_{2L} [^{3}H]Spiperone	K_i, (nM), D_3 [^{3}H]Spiperone	D_{2L}/D_3
(±)-7-OH-DPAT	311 ± 47	6.19 ± 1.4	50.2
(−)-5-OH-DPAT	220 ± 37.7	4.73 ± 0.64	46.5
2	2,780 ± 457	395 ± 75	7.03
1	347 ± 51	96.0 ± 4.7	3.61
(−)-**6**	809 ± 65	38.6 ± 0.7	21
(+)-**6**	40.6 ± 3.6	1.77 ± 0.42	22.9
(−)-**7**	26.0 ± 7.5	0.825 ± 0.136	31.5
(+)-**7**	238 ± 14	18.4 ± 1.0	12.9
9	219 ± 30	72.2 ± 17.2	3
(−)-**10**	243 ± 65	4.15 ± 0.76	58.6
(+)-**10**	1,979 ± 567	44.0 ± 10.6	45.0
11	234 ± 40	0.925 ± 0.234	253
(±)-**24a**	3,326 ± 788	419 ± 119	7.94
(±)-**24b**	148 ± 30	187 ± 24	0.79
(±)-**35a**	2,522 ± 554	473 ± 167	5.33
(±)-**35b**	338 ± 35	256 ± 69	1.3
(±)-**35c**	289 ± 56	102 ± 20	2.83
(±)-**8**	49.1 ± 10.3	14.9 ± 4.3	3.30
(+)-**8**	835 ± 182	89.3 ± 19.4	9.35
(−)-**8**	23.6 ± 1.1	4.95 ± 1.08	4.77
(±)-**43a**	1,712 ± 355	736 ± 206	2.33
(±)-**43b**	136 ± 23	168 ± 24	0.80

Table 2

Pharmacophoric distances for the gauche and anti-conformations of the hybrid analogs

Compound	Interfeature distances (Å)[a]					
	Gauche[b]			Anti[b]		
	$N^+ – Ar^1$	$N^+ – Ar^2$	$Ar^1 – Ar^1$	$N^+ – Ar^1$	$N^+ – Ar^2$	$Ar^1 – Ar^2$
(+)-**6**	5.06	8.50	12.26	5.00	8.73	12.95
(−)-**6**	5.14	8.57	12.62	5.13	9.26	13.66
11	4.92	8.51	12.00	4.89	8.59	12.24
(−)-**8**	5.13	8.52	12.66	5.15	9.26	13.72

[a] N^+ represents the cationic feature, Ar^1 denotes the aromatic ring of either aminotetralin or 2-aminothiazole moieties and Ar^2 is the phenyl ring attached to one of the piperazine Ns. The distance N^+ - Ar^1 is the distance between the cationic N and the ring centroid of Ar^1

[b] The terms gauche and anti represent the conformation of the ethylene bridge connecting cationic N with the arylpiperazine moiety