# Synthesis and Structure – Activity Relationship of the Isoindolinyl Benzisoxazolpiperidines as Potent, Selective, and Orally Active Human Dopamine $D_4$ Receptor Antagonists

*In memory of Thomas J. (Roy) Corbett.*

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*A new class of potent dopamine $D_4$ antagonists was discovered with selectivity over dopamine $D_2$ and the $\alpha$-1 adrenoceptor. The lead compound was discovered by screening our compound collection. The structure – activity relationships of substituted isoindoline rings and the chirality about the hydroxymethyl side chain were explored. The isoindoline analogues showed modest differences in potency and selectivity. The S enantiomer proved to be the more potent enantiomer at the $D_4$ receptor. Several analogues with greater than 100-fold selectivity for $D_4$ over $D_2$ and the $\alpha$-1 adrenoreceptor were discovered. Several selective analogues were active in vivo upon oral or intraperitoneal administration. A chiral synthesis starting from either D- or L-O-benzylserine is also described.*

**KEYWORDS:**

alcohols · chirality · dopamines · G-protein-coupled receptors · isoindolines · schizophrenia

## Introduction

Schizophrenia is a debilitating and potentially deadly disease that strikes approximately 1% of the world's population. The symptoms of schizophrenia are categorized into positive symptoms (for example, hallucinations and delusions), negative symptoms (for example, social withdrawal and inability to experience pleasure), and cognitive symptoms (for example, impaired attention and lack of recall memory).[1] It has long been held that hyperactivity of dopamine neurotransmission is a major cause of schizophrenic symptoms. Five distinct subtypes within two broad types, the $D_1$ type ($D_1$ and $D_5$ subtypes) and the $D_2$ type ($D_2$, $D_3$, and $D_4$), have been used to categorize dopamine receptors.[2] Traditional $D_2$ antagonists are effective in the treatment of positive symptoms but give no relief from negative or cognitive symptoms. In addition, many of these classical neuroleptic treatments are associated with side effects such as extrapyramidal syndrome (EPS) and tardive dyskinesia.[3]

The development of atypical antipsycotics such as clozapine (**1**) has resulted in therapies that can treat negative symptoms as well as positive symptoms without significant EPS. The use of clozapine is, however, limited by its potential to cause agranulocytosis, a potentially fatal blood disorder that affects about

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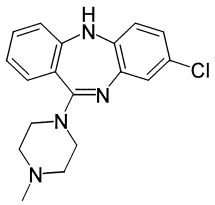
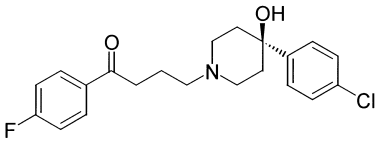


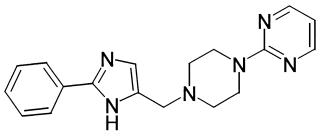
Clozapine (**1**)



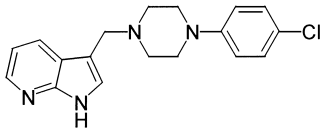
Haloperidol (**2**)

1% of clozapine-treated patients.[4] The dopamine $D_4$ receptor was first cloned in 1991[5] and has been shown to be localized in the limbic regions of the brain, areas associated with cognitive and emotional behaviors.[6] Clozapine has good affinity for the $D_4$ receptor and has ten to fifteenfold greater affinity for $D_4$ than for the $D_2$ receptor.[7] In contrast, typical antipsychotics such as haloperidol (**2**) also have high affinity for $D_4$ but are not selective for $D_4$ over $D_2$. It has been proposed, therefore, that a compound with high affinity and selectivity for the $D_4$ receptor may be an effective antipsychotic without the neurological side effects associated with classical $D_2$ antagonists.

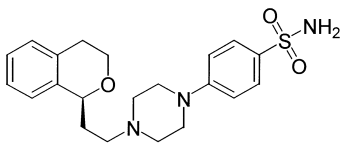
Recent clinical trials have raised doubt about the $D_4$ hypothesis. Three selective $D_4$ anatagonists, NGD-94-1 (**3**),[8] L-745,870 (**4**),[9] and sonepiprazole (**5**)[10] were shown to be ineffective for the treatment of schizophrenia. Clinical results for an additional $D_4$ antagonist, balaperidone (**6**),[11] have yet to be published. In general, more clinical evidence that $D_4$ antagonism is useful for the treatment of schizophrenia or any other disease is required for the hypothesis to be proven.[12]



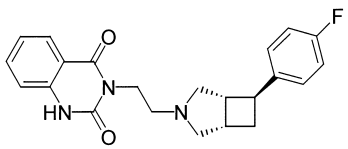
NGD-94-1 (**3**)



L-745,870 (**4**)

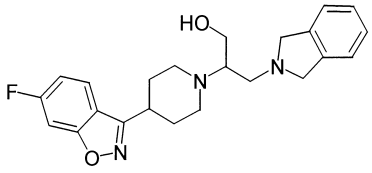


Sonepiprazole (U-101387) (**5**)



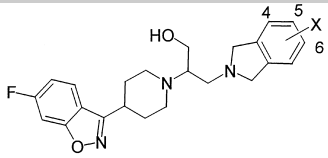
Balaperidone (LU-111995) (**6**)

Screening of our compound collection revealed a potent and selective $D_4$ antagonist, compound **7** (see Table 1). The lead compound (**7**) was racemic and therefore a chiral synthetic route was developed and this method proved amenable to the synthesis of a variety of isoindoline analogues (for examples, see Table 2. Our lead compound was also moderately potent with respect to the $\alpha$-1 adrenoreceptor. Potent antagonists of the $\alpha$-1 receptor are known to cause orthostatic hypotension, which can cause dizziness and fainting spells as a result of a drop in blood pressure.[13] We hoped to avoid this and other side effects by finding a $D_4$ antagonist with at least 100-fold selectivity for $D_4$ over both the $D_2$ and $\alpha$-1 receptors.



**7**

***Table 1.*** *Receptor binding of target isoindolines.[21]*



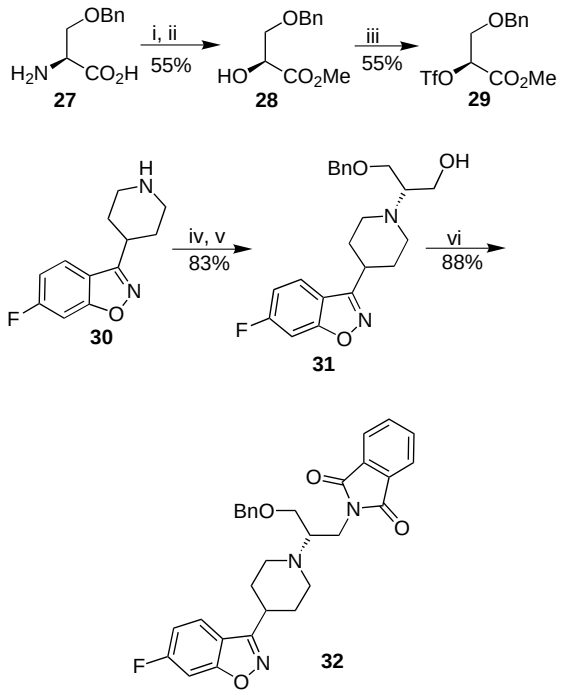
| Compound | X | Chirality | Binding $K_i$ [nM][a] $hD_{4.2}$ | $hD_{2S}$ | rα-1[b] | $D_2/D_4$ | α-1/$D_4$ |
|---|---|---|---|---|---|---|---|
| **7** | H | *R,S* | 1.0 | 496 | 43 | 522 | 45 |
| **8** | H | *S* | 0.5 | 134 | 54.5 | 263 | 107 |
| **9** | H | *R* | 35.4 | 777 | 225 | 22 | 6 |
| **10** | 5-F | *S* | 1.2 | 100 | 92.5 | 81 | 75 |
| **11** | 5-F | *R* | 35.9 | 250 | NT[c] | 7 | |
| **12** | 4-F | *S* | 0.5 | 55.9 | 232 | 116 | 483 |
| **13** | 5-Cl | *S* | 1.2 | 120 | 11.9 | 100 | 10 |
| **14** | 5,6-di-Cl | *S* | 23 | 302 | NT[c] | 13 | |
| **15** | 5-Me | *S* | 4.5 | 188 | NT[c] | 42 | |
| **16** | 4-Me | *S* | 3.7 | 185 | 12.4 | 50 | 3.4 |
| **17** | 5-$CF_3$ | *S* | 19.1 | 501 | 26 | 26 | 1.4 |
| **18** | 5-OMe | *S* | 0.6 | 392 | 20 | 688 | 35 |
| **19** | 5-OMe | *R* | 120 | 3527 | NT[c] | 29 | |
| **20** | 4-OMe | *S* | 1.4 | 203 | 17.5 | 145 | 12.5 |

[a] [$^3$H]Spiperone was used as the ligand for both the $D_{2S}$ and $D_{4.2}$ binding studies. $K_i$ = inhibition constant. [b] [$^3$H]Prazosin was used as the ligand for the rat α-1 cortex membrane binding studies. [c] NT = not tested.

## Results and Discussion

To set the chiral center we elected to use D- or L-*O*-benzyl serine. This approach proved advantageous since both stereoisomers

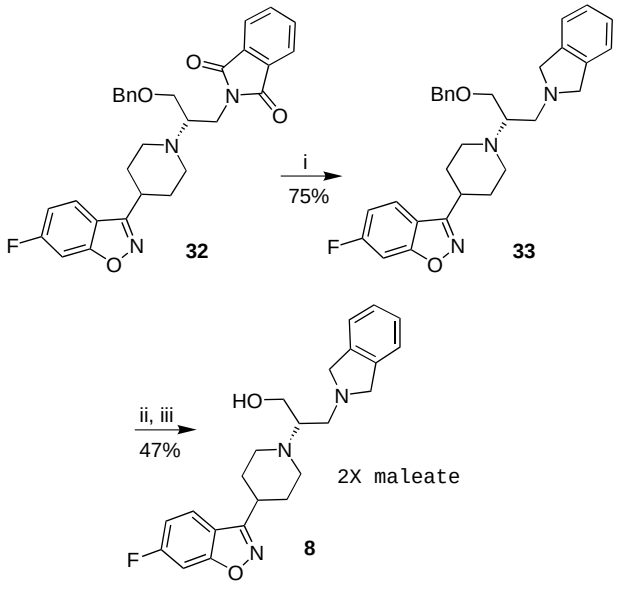
are commercially available in high enantiomeric excess. Diazotization of amino acid **27** (Scheme 1) followed by esterification gave the desired alcohol ester **28** in good yield by the method of




***Scheme 1.*** *Reagents and conditions: i) $NaNO_2$, $H_2SO_4$, 0 °C; ii) MeOH, HCl; iii) triflic anhydride, 2,6-di-*tert*-butyl-4-methylpyridine, $CH_2Cl_2$, 0 °C; iv)* ***29****, $CH_2Cl_2$, 0 °C; v) $LiAlH_4$, $Et_2O$, 0 °C; vi) phthalimide, $Ph_3P$, diethyl azodicarboxylate (DEAD), $CH_2Cl_2$.*

De Witt et al.[14] Conversion of hydroxyester **28** to triflate **29** was achieved in moderate yield. The triflate **29** was coupled without delay to piperidinyl benzisoxazole **30**[15] to give the desired product in good yield with stereochemical inversion by a well-precedented $S_N2$ reaction.[16] This ester was then reduced with lithium aluminium hydride (LAH), which yielded the desired primary alcohol **31**. This alcohol was subsequently subjected to Mitsunobu reaction conditions with phthalic anhydride to give desired phthalimide **32** in good yield as a key intermediate. The synthesis of the *S* enantiomer is shown in Scheme 1.

The phthalimide **32** was then reduced to the isoindoline **33**. We found that this reduction could only be achieved with LAH in the presence of aluminum chloride.[17] The literature indicates that isoindoline is unstable[18] and we observed that our isoindolines were prone to oxidation. In order to maximize our yields we did not store the isoindoline intermediates but quickly used them in subsequent steps. The benzyl group was removed with boron tribromide and then the maleic acid salt **8** was formed (Scheme 2). We observed that the solid salt **8** was far more stable to oxidation than the corresponding free base and could be stored for long periods of time without any observable oxidative degradation. The chiral purity of the target was assessed by using chiral HPLC methods. No racemization was observed in the course of the synthesis. The high enantiomeric



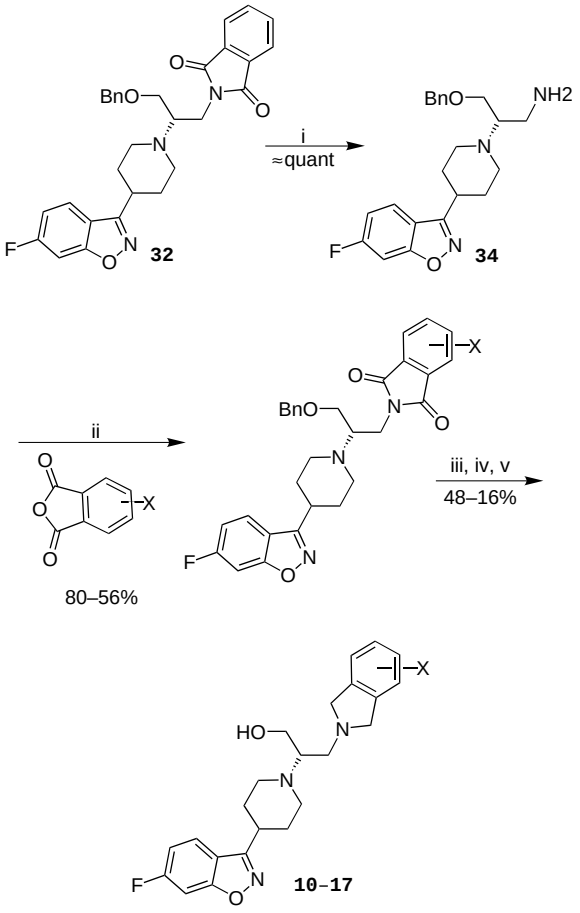

***Scheme 2.*** *Reagents and conditions: i) $LiAlH_4$, $AlCl_3$; $Et_2O$, 0 °C; ii) $BBr_3$, $CH_2Cl_2$; iii) maleic acid, MeOH, $Et_2O$.*

excess of the product appeared to be dependent on the *ee* value of the starting amino acid.

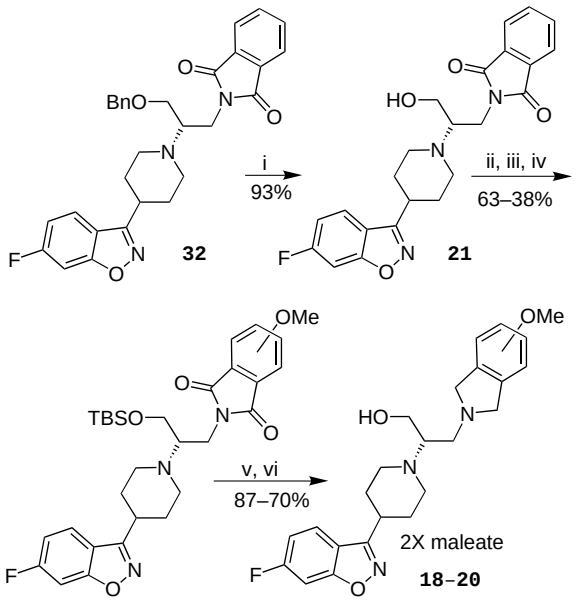
To gain access to substituted isoindolines, phthalimide **32** was quantitatively converted into amine **34** by reaction with hydrazine (Scheme 3). Amine **34** was then reacted with substituted phthalic anhydrides to yield the substituted phthalimides. The substituted phthalimides were reduced, deprotected, and converted into a salt by using the method given above for the synthesis of **8** (method A), to yield the desired substituted isoindolines (**10** – **17**, Scheme 3).

The route shown in Scheme 3 needed to be modified to obtain the methoxy-substituted isoindolines. We were concerned that the methoxy group would be unstable under the $BBr_3$ reaction conditions used for the removal of the benzyl protecting group. Therefore, the benzyl group was replaced by an acid-labile silyl protecting group. The phthalimide alcohol was converted into the methoxy-substituted phthalimides in three steps. The alcohol was protected with a *tert*-butyldimethylsilyl (TBS) group then the phthalimide was converted into the amine in high yield by addition of hydrazine. The amine was then reacted with methoxy phthalic anhydrides to yield the desired methoxy phthalimides. The methoxy phthalimides were reduced and deprotected in a single step with LAH and $AlCl_3$. The product was converted quickly into the more stable salt, which yielded the desired methoxy isoindolines **18** – **20** (Scheme 4).

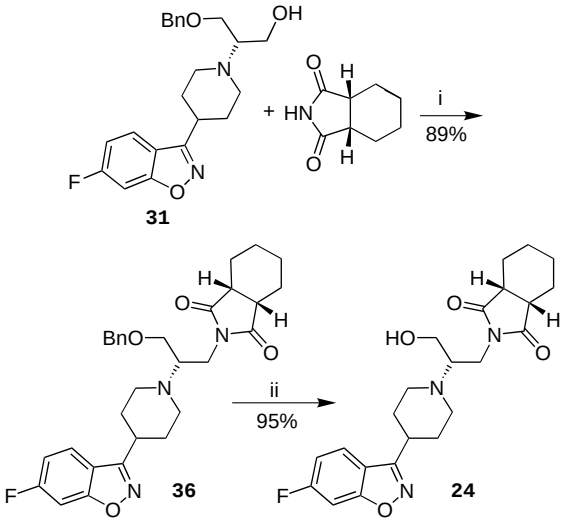
We also wanted to explore alternatives to isoindolines. We synthesized the phthalimide analogue **21** (Scheme 4) by removal of the benzyl protecting group immediately after the Mitsunobu reaction. We also synthesized 4-trifluoromethylphthalimide (**22**) in an analogous manner. The *cis*-hexahydrophthalimide analogues **24** and **25** were synthesized from the alcohol intermediate **31** by a Mitsunobu reaction followed by benzyl deprotection (Scheme 5).




*Scheme 3. Reagents and conditions: i) $H_2NNH_2$, MeOH, reflux; ii) toluene, reflux, Dean – Stark trap; iii) $LiAlH_4$, $AlCl_3$; $Et_2O$, 0 °C; iv) $BBr_3$, $CH_2Cl_2$; v) maleic acid, EtOH, $Et_2O$.*

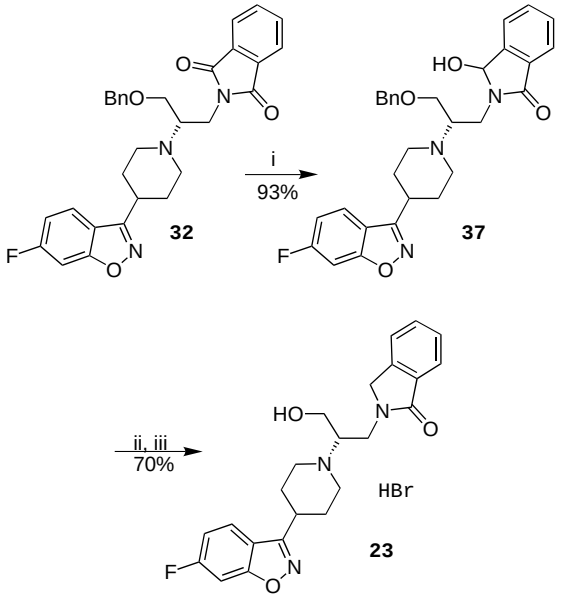



*Scheme 4. Reagents and conditions: i) $BBr_3$, $CH_2Cl_2$; ii) TBS-Cl, $Et_3N$, 4-dimethylaminopyridine, THF; iii) $H_2NNH_2$, MeOH, reflux; iv) 3- or 4-methoxy phthalic anhydride, toluene, reflux, Dean – Stark trap; v) $LiAlH_4$, $AlCl_3$; $Et_2O$, 0 °C; vi) maleic acid, EtOH, $Et_2O$.*



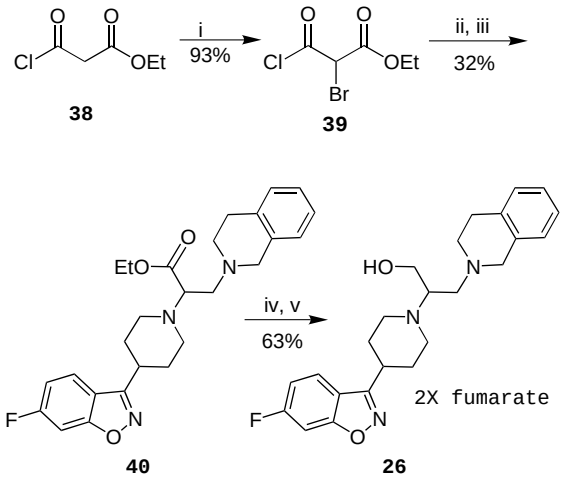

*Scheme 5. Reagents and conditions: i) $Ph_3P$, DEAD, $CH_2Cl_2$; ii) $BBr_3$, $CH_2Cl_2$.*

The synthesis of dihydroisoindolone **23** (Scheme 6) required a mild, two-step reduction of phthalimide **32**. The phthalimide was first partially reduced with sodium borohydride to yield **37**.[19] This compound was further reduced under acidic conditions by treatment with triethylsilane. The benzyl protecting group was then removed to give the desired dihydroisoindolone **23** in good yield.




*Scheme 6. Reagents and conditions: i) $NaBH_4$, MeOH, $CH_2Cl_2$; ii) $Et_3SiH$, trifluoroacetic acid, $CH_2Cl_2$; iii) $BBr_3$, $CH_2Cl_2$.*

Early in the program, the racemic tetrahydroisoquinoline derivative **26** was synthesized by using an alternate route (Scheme 7). First, ethyl malonyl chloride (**38**) was brominated with *N*-bromosuccinimide. The amide was then formed with the addition of the tetrahydroisoquinoline to the acid chloride **39**.




***Scheme 7.*** *Reagents and conditions: i) $Br_2$, $CCl_4$; ii) 1,2,3,4-tetrahydroisoquinoline, $Et_3N$, THF; iii)* ***30****,[15] $Et_3N$, N-methylpyrrolidone (NMP), 50 °C; iv) $LiAlH_4$, $AlCl_3$, THF; v) fumaric acid, EtOH, $Et_2O$.*

The bromide was displaced by benzisoxazole piperidine **30** to form the desired amide ester **40**. This amide ester was subsequently reduced with LAH and $AlCl_3$, followed by the formation of the fumarate salt **26**.

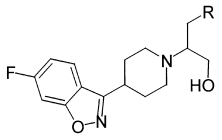
Table 1 shows the binding data for the target isoindolines at the dopamine $D_2$ and $D_4$ receptors and the $\alpha$-1 adrenoceptor. The binding of the racemic unsubstituted isoindoline **7** was strong and very selective for $D_4$ over $D_2$. We hoped to achieve even greater selectivity over the $\alpha$-1 receptor by obtaining the pure enantiomers of the isoindolines. The enantiomers were screened and the data clearly shows that the *S* enantiomer **8** is more potent at the $D_4$ receptor than at either of the other receptors. In addition, the *S* enantiomer has good selectivity for $D_4$ over $D_2$ and improved selectivity over the $\alpha$-1 receptor as compared to both the *R* enantiomer **9** and the racemate **7**. In all cases where both *R* and *S* enantiomers were screened, the *S* enantiomers had greater potency than the *R* enantiomers (**8** – **9**, **10** – **11**, **18** – **19**, **24** – **25**). In fact, no *R* enantiomer had a $D_4$ $K_i$ value more potent than 35 nM.

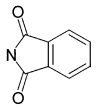
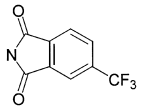
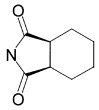
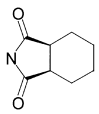
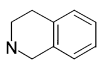
The addition of substituents to the isoindoline ring system produced no significant changes in potency at $D_4$. All the *S* enantiomers were very potent with $K_i$ values of less than 5 nM, with the exception of the 5,6-dichloro derivative **14** and 5-trifluoromethyl derivative **17**, both of which had $K_i$ values of approximately 20 nM. Four of the substituted analogues (**12**, **13**, **18**, and **20**) showed at least 100-fold selectivity for $D_4$ over $D_2$. Potency at the $\alpha$-1 receptor was only disrupted by fluoro substituents at the 3- or 4-position. The 4-fluoro derivative **12** had the weakest affinity at the $\alpha$-1 receptor in this series, with a $K_i$ value of 232 nM, while the 5-fluoro derivative **10** ($K_i = 92.5$ nM) bound slightly better to the $\alpha$-1 receptor than the unsubstituted isoindoline **8**. No other substituted isoindolines produced $\alpha$-1 receptor $K_i$ values greater than 26 nM.

Table 2 shows a series of isoindoline analogues. The phthalimides **21** and **22** showed quite weak binding at $D_4$ ($K_i = > 500$ nM). In contrast, the dihydroisoindolone **23** was quite a potent antagonist at $D_4$ with a $K_i$ value of 5 nM. Unfortunately, compound **23** was equipotent at the $\alpha$-1 receptor. The *S* enantiomer of the *cis*-hexahydrophthalimide **24** was also relatively potent as compared to the phthalimides, with a $D_4$ $K_i$ value of 24 nM. The *R* enantiomer **25** had a $D_4$ $K_i$ value greater than 1 μM. It appears, therefore, that some unsaturation about the phthalimide ring system enhances $D_4$ binding affinity. The racemic tetrahydroisoquinoline derivative **26** had similar potency to the racemic isoindoline derivative **7** but was much less selective and therefore the enantiomers were not separated or synthesized.

Table 3 shows the in vivo activity of the isoindoline analogues in two behavioral assays, the inhibition of apomorphine-induced

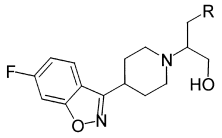
***Table 2.*** *Receptor binding of target isoindoline analogues.*

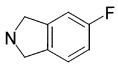
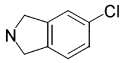
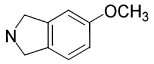
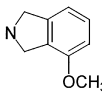
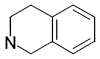


| Compound | R | Chirality | Binding $K_i$ [nM][a] $hD_{4.2}$ | $hD_{2S}$ | rα-1[b] | $D_2/D_4$ | α-1/$D_4$ |
|---|---|---|---|---|---|---|---|
| **21**[22] |  | *S* | 583 | NT[c] | NT[c] | | |
| **22**[22] |  | *S* | 727 | NT[c] | NT[c] | | |
| **23**[22] |  | *S* | 5.3 | 341 | 4.1 | 64 | 0.77 |
| **24**[23] |  | *S* | 24.3 | 6912 | NT[c] | 284 | |
| **25**[23] |  | *R* | > 1000 | > 1000 | NT[c] | | |
| **26**[24] |  | *R,S* | 3.6 | 120 | 19 | 33 | 5.3 |

[a] [$^3$H]Spiperone was used as the ligand for both the $D_{2S}$ and $D_{4.2}$ binding studies. [b] [$^3$H]Prazosin was used as the ligand for the rat $\alpha$-1 cortex membrane binding studies. [c] NT = not tested.

***Table 3.*** *In vivo activity of target isoindoline analogues.*




| Compound | R | Chirality | MK-801 Locomotion $ED_{50}$ [mg $Kg^{-1}$] ip[a] | po[a] | CMA@20 mg $Kg^{-1}$ ip |
|---|---|---|---|---|---|
| **7** |  | *R*,*S* | 7.1 (3.94 – 12.72) | 11.4 (6.45 – 20.20) | 50% |
| **8** |  | *S* | 4.4 (2.47 – 7.75) | 5.6 (2.84 – 10.93) | 83% |
| **9** |  | *R* | 9.0 (5.24 – 15.33) | NT[c] | 29% |
| **10** |  | *S* | 3.9 (2.37 – 6.46) | 5.1 (2.71 – 9.64) | $ED_{50}$ = 4.4 mg $Kg^{-1}$ (1.8 – 10.96) |
| **12** |  | *S* | 4.9 (2.89 – 8.26) | NT[c] | $ED_{50}$ = 11.6 mg $Kg^{-1}$ (5.10 – 26.13) |
| **13** |  | *S* | 4.2 (2.70 – 6.59) | NT[c] | $ED_{50}$ = 15.4 mg $Kg^{-1}$ (13.57 – 17.44) |
| **16** |  | *S* | 6.4 (3.79 – 10.70) | NT[c] | 37% |
| **18** |  | *S* | 5.3 (2.84 – 9.86)[b] | 4.3 (1.82 – 9.22) | NT[c] |
| **20** |  | *S* | 5.5 (3.25 – 9.44)[b] | NT[c] | NT[c] |
| **23** |  | *S* | 4.2 (2.54 – 6.85) | NT[c] | $ED_{50}$ = 12.5 mg $Kg^{-1}$ (5.61 – 27.76) |
| **26** |  | *R*,*S* | 0.7 (0.27 – 1.85) | NT[c] | $ED_{50}$ = 0.6 mg $Kg^{-1}$ (0.42 – 0.78) |

[a] ip = intraperitoneally administered, po = orally administered. [b] Subcutaneous administration. [c] NT = not tested.

climbing mouse assay (CMA) and inhibition of MK-801-induced locomotion and falling (MK-801 locomotion). CMA is a traditional in vivo measure of potential antipsychotic activity that tests the ability of a compound to inhibit the effects induced by the administration of a dopamine agonist. In contrast, the compound MK-801 locomotion is an *N*-methyl-D-aspartate receptor antagonist that induces stereotyped behavior. It has been shown that behavior induced by MK-801 is inhibited by clozapine (**1**) at a lower dose than that required to inhibit the apomorphine-induced climbing of mice. It has, therefore, been proposed that MK-801 locomotion is a model that can be used to identify compounds with enhanced efficacy and an atypical profile.[20] We found that, in general, compounds with good selectivity for $D_4$ over $D_2$ were also potent in MK-801 locomotion but weak in CMA. The best example of this behavior is the highly selective unsubstituted isoindoline **8**. This compound was potent in MK-801 locomotion but showed such low activity in CMA that a dose-response curve for CMA could not be obtained in the range of MK-801 locomotion potency. It also appears that CMA potency is dependent on $D_2$ potency and independent of $D_4$ potency. The obvious exception is the tetrahydroisoquinoline **26**, which is very potent in both MK-801 locomotion and CMA but is 30-fold more potent at $D_4$ than at $D_2$. It should also be noted that all four of the compounds dosed orally in MK-801 locomotion experiments showed good activity and were only slightly less potent than when dosed intraperitoneally, which implies good bioavailability in this species.

The isoindolinyl benzisoxazolpiperidines represent a new class of potent and selective $D_4$ antagonists with oral activity. It appears that the optimal structure for $D_4$ potency and selectivity for $D_4$ versus $D_2$ and the $\alpha$-1 adrenoreceptor amongst compounds in this series is the *S* enantiomer at the hydroxymethyl side chain with either an unsubstituted isoindoline (**8**) or a 3-fluoro-substituted isoindoline (**12**). Further studies on the structure – activity relationship of this series of $D_4$ antagonists will be reported in the future and will include considertion of the role of the hydroxymethyl side chain.

## Experimental Section

**Chemistry**: All phthalic anhydrides were purchased from Aldrich except 4-fluorophthalic anhydride (Alfa-Aesar) and 4-methyl- and 4-trifluoromethylphthalic anhydride, which were prepared by literature methods. All reactions were monitored by TLC on Merck glass plates precoated with silica gel (0.25 mm). Chromatographic purification was done with Merck silica gel (230 – 400 mesh). Solvents are reported as % v/v solutions. Melting points were recorded on a Thomas – Hoover capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a Finnegan 4500 spectrometer equipped with an INCOS data system. Proton NMR spectra were recorded on a Brucker 300 or Varian XL-200 spectrometer with tetramethylsilane as an internal standard. Chiral HPLC analysis was performed on a Perkin Elmer 200 system with a 235C diode array detector. Optical rotations were obtained on a Rudolph Research Autopol III polarimeter at wavelength 589 nm (sodium D line) by using a 1.0-decimeter cell with a total volume of 1 mL. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at the specific temperature and concentration (*c*) given in grams per 100 mL of solvent. Combustion analyses were performed by Midwest Microlab, Indianapolis, IN, USA or Robertson Microlit Laboratories, Madison, NJ, USA.

**Methyl-3-benzyloxy-(2*S*)-hydroxypropanoate (28)**:[14] A solution of sodium nitrate (27 g, 380 mmol) in water (350 mL) was added to a 0-°C solution of *O*-benzyl-L-serine (**27**; 50 g, 260 mmol) in $H_2SO_4$ (2.5 N, 520 mL). The resulting mixture was stirred at 0 °C for 2 h and then at room temperature overnight. The mixture was extracted with EtOAc ($3 \times 400$ mL). The combined extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil (34 g). The oil was dissolved in MeOH (430 mL) and treated with a solution of 1 N HCl in $Et_2O$ (17 mL). The resulting solution was stirred overnight then concentrated in vacuo to give an oil (33 g). Purification of the residue by bulb-to-bulb distillation (124 – 134 °C, 0.8 mm Hg) yielded the desired product (27 g, 50 %) as a clear, colorless oil: $^1$H NMR ($CDCl_3$): $\delta = 3.08$ (br s, 1H), 3.78 (m, 2H), 3.79 (s, 3H), 4.35 (m, 1H), 4.57 (ABq, $J = 12.0$, 7.9 Hz, 2H), 7.29 (m, 5H) ppm; CIMS: *m/e*: 211 [$M^+$]; $[\alpha]_D^{20.5}$: found: + 4.22 ($c = 9.16$, $CHCl_3$); literature: + 4.5 ($c = 8.34$, $CHCl_3$).

**Methyl-3-benzyloxy-(2*R*)-hydroxypropanoate**:[14] Synthesized as above from *O*-benzyl-D-serine (20 g, 100 mmol) to yield the desired product (10 g, 46 %) as a clear, colorless oil: $[\alpha]_D^{20.5} = -4.60$ ($c = 9.33$, $CHCl_3$).

**3-(Benzyloxy)-(2*S*)-{[(trifluoromethyl)sulfonyl]oxy}-propanoic acid methyl ester (29)**: A 0-°C solution of triflic anhydride (0.86 mL, 4.8 mmol) in anhydrous $CH_2Cl_2$ (11 mL) was added dropwise to a 0-°C solution of **28** (1.0 g, 4.8 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (990 mg, 4.8 mmol) in anhydrous $CH_2Cl_2$ (7.3 mL). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. The resulting precipitate was removed by filtration and washed with pentane. The filtrate was concentrated in vacuo. The residue was taken up in pentane again and the additional salt that precipitated was removed by filtration. Concentration of the filtrate in vacuo gave the product (1.1 g, 67 %) as a pale yellow oil. The product was not stored but was quickly advanced to the next step. $^1$H NMR ($CDCl_3$): $\delta = 3.81$ (s, 3H), 3.90 (d, $J = 10.0$ Hz, 2H), 4.59 (d, $J = 8.0$ Hz, 2H), 5.30 (t, $J = 5.5$ Hz, 1H), 7.29 (m, 5H) ppm.

**Methyl 3-benzyloxy-2-(*R*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propionate**:[16] A solution of **29** (41.3 g, 121 mmol) in anhydrous $CH_2Cl_2$ (150 mL) was added dropwise to a 0-°C solution of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (**30**;[15] 53.1 g, 240 mmol) in anhydrous $CH_2Cl_2$ (360 mL). The resulting mixture was stirred at 0 °C for 1 h then poured directly onto a flash column and eluted with 3:1 heptane/EtOAc to afford a white solid (70 g). Recrystallization of this product from heptane yielded the desired product (34.2 g, 69 %) as colorless crystals: m.p.: 61 – 62 °C; $^1$H NMR ($CDCl_3$): $\delta = 2.05$ (m, 4H), 2.58 (m, 2H), 3.03 (m, 4H), 3.59 (m, 1H), 3.78 (s, 3H), 3.80 (m, 1H), 4.59 (d, $J = 2.6$ Hz, 2H), 7.03 (dt, $J = 13.1$, 4.1 Hz, 1H), 7.22 (dd, $J = 11.1$, 4.1 Hz, 1H), 7.31 (m, 5H), 7.66 (dd, $J = 13.1$, 11.1 Hz, 1H) ppm; CIMS: *m/e*: 413 [$M^+$]; elemental analysis ($C_{23}H_{25}FN_2O_4$): C, H, N; $[\alpha]_D^{20.5} = +13.40$ ($c = 1.00$, $CHCl_3$).

**3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]-1-propanol (31)**: A solution of methyl 3-benzyloxy-2-(*R*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propionate (33 g, 80 mmol) in diethyl ether (350 mL) was added to a 0-°C solution of LAH (85 mL, 1.0 M solution in $Et_2O$, 85 mmol) in $Et_2O$ (115 mL). After stirring at 0 °C for 1 h, the reaction mixture was sequentially quenched with water (3.2 mL), NaOH (2 N, 3.2 mL), and water (9.7 mL). The resulting suspension was stirred for 30 min at room temperature, then filtered through a pad of celite. The aluminum salts were thoroughly washed with $Et_2O$ and the filtrate was concentrated in vacuo. Recrystallization of the residue from $Et_2O$ yielded the desired product (27 g, 89 %) as colorless crystals: m.p.: 66 – 70 °C; $^1$H NMR ($CDCl_3$): $\delta = 2.08$ (m, 5H), 2.45 (m, 1H), 3.00 (m, 4H), 3.42 (m, 2H), 3.63 (m, 2H), 4.52 (s, 2H), 7.06 (dt, $J = 17.8$, 3.8 Hz, 1H), 7.24 (dd, $J = 13.7$, 3.8 Hz, 1H), 7.35 (m, 5H), 7.66 (dd, $J = 17.8$, 13.7 Hz, 1H) ppm; CIMS: *m/e*: 385 [$M^+$]; elemental analysis ($C_{22}H_{25}FN_2O_3$): C, H, N; $[\alpha]_D^{20.5} = -15.20$ ($c = 1.00$, $CHCl_3$); > 98 % *ee*, as determined by chiral HPLC (12.42 min retention time, Chiralcel OJ, 0.7 mL min$^{-1}$, 1:1 (0.5 % $Et_2NH$ in EtOH)/heptane, 237 nm).

**2-{3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propyl}-isoindole-1,3-dione (32)**: Phthalimide (9.47 g, 64.4 mmol), triphenylphosphine (16.9 g, 64.4 mmol), and diethylazodicarboxylate (10.1 mL, 64.4 mmol) were added to a room temperature solution of **31** (23.6 g, 61.3 mmol) in anhydrous $CH_2Cl_2$ (350 mL). After stirring at room temperature for 1 h, the resulting solution was partitioned between NaOH (1 N, 135 mL) and $Et_2O$ (500 mL). The ether layer was separated and was washed with NaOH (1 N, 135 mL), water (135 mL), and brine (135 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (5 % EtOAc/$CH_2Cl_2$) yielded the desired product (27.7 g, 88 %): $^1$H NMR (DMSO-$d_6$): $\delta = 2.34$ (m, 4H), 3.58 (m, 3H), 3.83 (m, 4H), 4.04 (m, 1H), 4.19 (m, 2H), 4.59 (s, 2H), 7.35 (m, 6H), 7.72 (m, 1H), 7.91 (m, 1H), 8.21 (m, 1H) ppm; CIMS: *m/e*: 514 [$M^+$]; $[\alpha]_D^{20.5} = -11.10$ ($c = 1.00$, MeOH); > 98 % *ee*, as determined by chiral HPLC (22.91 min retention time, Chiralcel OJ, 0.7 mL min$^{-1}$, 1:1 (0.5 % $Et_2NH$ in EtOH)/heptane, 237 nm).

**2-{3-Benzyloxy-2-(*R*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propyl}-isoindole-1,3-dione**: Synthesized by the same method as used to make **32** (73 % yield). > 98 % *ee*, as determined by chiral HPLC (28.29 min retention time, Chiralcel OJ, 0.7 mL min$^{-1}$, 1:1 (0.5 % $Et_2NH$ in EtOH)/heptane, 237 nm).

**Method A:**

**2-{3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propyl}-isoindole (33)**:[17] Aluminum chloride (4.6 g, 34.1 mmol) was added to a 0-°C solution of LAH (98 mL, 1.0 M solution in $Et_2O$, 98 mmol) in anhydrous tetrahydrofuran (THF; 300 mL). The mixture was stirred at 0 °C for 15 min then treated dropwise with a solution of **32** (16 g, 31 mmol) in anhydrous THF (125 mL). After stirring at 0 °C for 2 h, the resulting mixture was sequentially quenched with water (3.8 mL), NaOH (2 N, 3.8 mL), and water (15.2 mL). The resulting suspension was filtered through a pad of celite and the aluminum salts were thoroughly washed with EtOAc. The filtrate was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the

residue by flash chromatography (gradient elution, 30–100% EtOAc/heptane) yielded the product (11 g, 75%) as a yellow oil: $^1$H NMR (DMSO-$d_6$): $\delta = 2.32$ (m, 2H), 3.60 (m, 9H), 4.18 (m, 3H), 4.67 (s, 4H), 4.98 (m, 2H), 7.42 (m, 10H), 7.77 (dd, $J = 12.3$, 2.6 Hz, 1H), 8.20 (dd, $J = 14.2$, 9.4 Hz, 1H) ppm; CIMS: *m/e*: 486 [$M^+$]; $[\alpha]_D^{20.5} = -13.20$ ($c = 0.515$, MeOH).

**3-(2,3-Dihydro-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (8)**: Boron tribromide (76.0 mL, 1.0 M solution in $CH_2Cl_2$, 76.0 mmol) was added to a room temperature solution of **33** (12.1 g, 25.0 mmol) in anhydrous $CH_2Cl_2$ (230 mL). After stirring at room temperature for 20 min, the reaction was quenched with MeOH (110 mL) and the resulting solution was concentrated in vacuo. The residue was redissolved in MeOH (110 mL) and reconcentrated in vacuo. This residue was redissolved in the minimum amount of MeOH and the HBr salt was precipitated by the addition of $Et_2O$. The suspension was filtered and the solid product was thoroughly washed with diethyl ether. The solid was partitioned between NaOH (1 N, 450 mL) and $CH_2Cl_2$ (1.10 L) and separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 1.10 L) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (5% MeOH/EtOAc) yielded the desired product (7.8 g). The solid material was redissolved in a hot solution of MeOH and maleic acid (2 equiv). The solution was allowed to cool to room temperature and the dimaleate salt was triturated by the addition of $Et_2O$. The product was collected by filtration and dried to yield **8** (7.4 g, 47%) as a gray solid: m.p.: 124–126 °C; $^1$H NMR ($CDCl_3$): $\delta =$ 2.04 (m, 4H), 2.90 (m, 1H), 3.24 (m, 7H), 3.75 (m, 2H), 4.41 (s, 4H), 6.12 (s, 4H), 7.35 (m, 5H), 7.71 (dd, $J = 10.8$ Hz, 1H), 8.15 (dd, $J = 15.8$ Hz, 1H) ppm; CIMS: *m/e*: 396 [$M^+$]; elemental analysis ($C_{23}H_{26}FN_3O_2 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{20.5} = -31.04$ ($c = 1.00$, MeOH).

**3-(2,3-Dihydro-1H-isoindol-2-yl)-2-(*R*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (9)**: Synthesized by the method used to make **8** (55% yield): $[\alpha]_D^{20.5} = +30.90$ ($c = 1.00$, MeOH).

**Method B**:

**3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]-1-propylamine (34)**: Hydrazine monohydrate (0.50 mL, 16 mmol) was added to a solution of **32** (5.4 g, 10 mmol) in absolute MeOH (30 mL). The resulting solution was heated at reflux for 2 h. Upon cooling to room temperature, the solution was concentrated in vacuo to give 4.0 g (100%) of the crude product as a yellow solid, which was used in the next reaction without any purification.

**2-{3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propyl}-5-fluoro-isoindole-1,3-dione**: 4-Fluorophthalic anhydride (1.20 g, 7.28 mmol) was added to a room-temperature solution of **34** (2.73 g, 7.13 mmol) in anhydrous dimethylformamide (20 mL). The solution was warmed to 80 °C and stirred for 3 h. Upon cooling to room temperature, the mixture was partitioned between water (20 mL) and EtOAc (50 mL). The organic layer was washed with water (20 mL) and brine (10 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc/heptane) to afford the desired product (5.76 g). Recrystallization of the product from pentane yielded a colorless solid (5.33 g, 75%): m.p.: 75–78 °C; $^1$H NMR (DMSO-$d_6$): $\delta =$ 1.59 (m, 2H), 1.91 (m, 2H), 2.40 (m, 1H), 2.78 (m, 2H), 3.03–3.23 (m, 3H), 3.57–3.91 (m, 4H), 4.29 (s, 2H), 7.30 (m, 6H), 7.65 (m, 1H), 7.78 (m, 3H), 7.96 (m, 1H) ppm; CIMS: *m/e*: 532 [$M^+$]; elemental analysis ($C_{30}H_{27}F_2N_3O_4$): C, H, N; $[\alpha]_D^{20} = -67.25$ ($c = 0.51$, MeOH).

**3-(2,3-Dihydro-5-fluoro-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo-[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (10)**: Reduction of the phthalimide, deprotection of the alcohol, and formation of the salt was carried out by method A. 37% yield from **32**, off-white solid: m.p.: 121–123 °C; $^1$H NMR (DMSO-$d_6$): $\delta = 2.19$ (m, 4H), 3.19 (m, 2H), 3.40 (m, 6H), 3.79 (m, 2H), 4.35 (m, 4H), 6.15 (s, 4H), 7.29 (m, 2H), 7.37 (m, 2H), 7.75 (dd, $J = 10.8$, 2.5 Hz, 1H), 8.15 (dd, $J = 15.8$, 9.4 Hz, 1H) ppm; CIMS: *m/e*: 414 [$M^+$]; elemental analysis ($C_{23}H_{25}F_2N_3O_2 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{20} = -27.77$ ($c = 1.00$, MeOH).

**3-(2,3-Dihydro-5-fluoro-1H-isoindol-2-yl)-2-(*R*)-[4-(6-fluorobenzo-[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (11)**: Synthesized by method B. 30% yield from **32**, off-white solid: m.p.: 118–120 °C; elemental analysis ($C_{23}H_{25}F_2N_3O_2 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{20} = +26.1$ ($c = 1.00$, MeOH).

**3-(2,3-Dihydro-4-fluoro-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo-[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dibromide (12)**: Synthesized by method B. 29% yield from **32**, off-white solid: m.p.: –165 °C dec; $^1$H NMR (DMSO-$d_6$): $\delta = 2.38$ (m, 4H), 3.60 (m, 6H), 4.02 (m, 4H), 4.80 (m, 4H), 7.38 (m, 4H), 7.75 (dd, $J = 10.8$, 2.4 Hz, 1H), 8.15 (dd, $J = 15.8$, 9.4 Hz, 1H) ppm; CIMS: *m/e*: 414 [$M^+$]; elemental analysis ($C_{23}H_{25}F_2N_3O_2 \cdot 2HBr$): C, H, N; $[\alpha]_D^{20} = -7.81$ ($c = 1.05$, MeOH).

**3-(2,3-Dihydro-5-chloro-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo-[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (13)**: Synthesized by method B. 26% yield from **32**, white solid: m.p.: 134–137 °C; $^1$H NMR (DMSO-$d_6$): $\delta = 2.19$ (m, 4H), 3.19 (m, 2H), 3.40 (m, 6H), 3.79 (m, 2H), 4.22 (s, 4H), 6.15 (s, 4H), 7.37 (m, 3H), 7.42 (s, 1H), 7.75 (dd, $J = 10.8$, 2.5 Hz, 1H), 8.15 (dd, $J = 15.8$, 9.4 Hz, 1H) ppm; CIMS: *m/e*: 430 [$M^+$]; elemental analysis ($C_{23}H_{25}ClFN_3O_2 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = -28.1$ ($c = 1.00$, MeOH).

**3-(5,6-Dichloro-2,3-dihydro-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (14)**: Synthesized by method B. 36% yield from **32**, off-white solid: m.p.: 135–137 °C; $^1$H NMR (DMSO-$d_6$): $\delta = 2.20$ (m, 4H), 3.10 (m, 2H), 3.42 (m, 6H), 3.80 (m, 2H), 4.15 (s, 4H); 6.15 (s, 4H), 7.38 (dt, $J = 16.2$, 1.6 Hz, 1H), 7.62 (s, 2H), 7.75 (dd, $J = 10.8$, 2.4 Hz, 1H), 8.15 (dd, $J =$ 15.8, 9.4 Hz, 1H) ppm; CIMS: *m/e*: 464 [$M^+$]; elemental analysis ($C_{23}H_{24}Cl_2FN_3O_2 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = -26.97$ ($c = 1.00$, MeOH).

**3-(2,3-Dihydro-5-methyl-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo-[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol maleate (15)**: Synthesized by method B. 15% yield from **32**, off-white solid: m.p.: 169–170 °C; $^1$H NMR (DMSO-$d_6$): $\delta = 2.11$ (m, 1H), 2.28 (m, 3H), 2.85 (m, 1H), 3.28 (m, 6H), 3.50 (m, 1H), 3.74 (m, 2H), 4.40 (s, 4H), 6.15 (s, 2H), 7.20 (m, 4H), 7.70 (dd, $J = 10.8$, 2.1 Hz, 1H), 8.15 (dd, $J = 15.8$, 9.5 Hz, 1H) ppm; CIMS: *m/e*: 410 [$M^+$]; elemental analysis ($C_{24}H_{28}FN_3O_2 \cdot C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = -44.2$ ($c = 1.00$, MeOH).

**3-(2,3-Dihydro-4-methyl-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo-[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (16)**: Synthesized by method B. 30% yield from **32**, white solid: m.p.: 136 °C dec; $^1$H NMR (DMSO-$d_6$): $\delta = 2.15$ (m, 4H), 2.29 (s, 3H), 2.98 (m, 1H), 3.33 (m, 7H), 3.78 (m, 2H), 4.40 (d, $J = 8.1$ Hz, 4H), 6.15 (s, 4H), 7.20 (m, 4H), 7.70 (dd, $J = 10.8$, 2.1 Hz, 1H), 8.15 (dd, $J = 15.8$, 9.4 Hz, 1H) ppm; CIMS: *m/e*: 410 [$M^+$]; elemental analysis ($C_{24}H_{28}FN_3O_2 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = -27.8$ ($c = 1.00$, MeOH).

**3-(2,3-Dihydro-5-trifluoromethyl-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (17)**: Synthesized by method B. 20% yield from **32**, off-white solid: m.p.: 134–136 °C; $^1$H NMR (DMSO-$d_6$): $\delta = 2.21$ (m, 4H), 3.45 (m, 8H), 4.28 (s, 4H), 6.15 (s, 4H), 7.38 (dt, $J = 16.2$, 5.4 Hz, 1H), 7.62 (m, 4H), 8.15 (dd, $J = 15.8$, 9.5 Hz, 1H) ppm; CIMS: *m/e*: 464 [$M^+$]; elemental analysis ($C_{24}H_{25}F_4N_3O_2 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = -21.9$ ($c = 1.00$, MeOH).

**Method C**:

**2-{2-(*S*)-[4-(6-Fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-3-hydroxypropyl}-isoindole-1,3-dione (21)**: Boron tribromide (6.30 mL,

1.0 M solution in $CH_2Cl_2$, 6.30 mmol) was added to a 0 °C solution of **32** (650 mg, 1.27 mmol) in anhydrous $CH_2Cl_2$ (8.0 mL). After stirring at 0 °C for 1 hour, the reaction was quenched with MeOH (20 mL). The mixture was partitioned between $CH_2Cl_2$ (50 mL) and NaOH (5%, 20 mL) and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/$CH_2Cl_2$) yielded the desired product (583 mg). Recrystallization of the product from MeOH yielded colorless crystals (500 mg, 93%): m.p.: 178–180 °C; $^1$H NMR ($CDCl_3$): $\delta = 2.10$ (m, 4H), 2.71 (m, 1H), 2.92 (m, 1H), 3.14 (m, 4H), 3.65 (m, 3H), 3.98 (dd, $J = 13.8$, 6.0 Hz, 1H), 7.03 (dt, $J = 8.9$, 2.0 Hz, 1H), 7.21 (dd, $J = 8.5$, 1.8 Hz, 1H), 7.63 (m, 1H), 7.75 (m, 2H), 7.84 (m, 2H) ppm; CIMS: *m/e*: 424 [$M^+$]; elemental analysis ($C_{23}H_{22}FN_3O_4$): C, H, N; $[\alpha]_D^{20} = -52.4$ ($c = 1.06$, $CHCl_3$).

**3-(2,3-Dihydro-5-methoxy-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (18)**: *tert*-Butyldimethylsilyl chloride (3.51 mL, 1.0 M solution in THF, 3.51 mmol), triethylamine (5.00 mL, 35.9 mmol) and 4-dimethylaminopyridine (121 mg, 1.00 mmol) were added to a room-temperature solution of **21** (1.35 g, 3.19 mmol) in anhydrous $CH_2Cl_2$ (30 mL). After stirring at room temperature for 4 hours, the reaction mixture was partitioned between EtOAc (75 mL) and water (25 mL). The organic layer was washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (10% EtOAC/heptane) afforded 2-{(*S*)-3-(*tert*-butyl-dimethyl-silanyloxy)-2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propyl}-isoindole-1,3-dione (1.29 g, 75%) as a yellow oil.

The phthalimide was then converted into (*S*)-3-(*tert*-butyl-dimethyl-silanyloxy)-2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propylamine by using the same procedure as used in the preparation of **34**, to give a quantitative yield of a viscous yellow oil.

The amine was reacted with methoxy phtalic anhydride by using the same procedure used in the preparation of 2-{3-benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propyl}-5-fluoro-isoindole-1,3-dione to yield 79% 2-{(*R*)-3-(*tert*-butyl-dimethyl-silanyloxy)-2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propyl}-5-methoxy-isoindole-1,3-dione as a yellow foam.

The methoxy phthalimide was reduced to the target **18** by the procedure used in the preparation of **33** (method A) to give 34% yield of a white solid from **32**: m.p.: 135–137 °C; $^1$H NMR (DMSO-$d_6$): $\delta = 2.10$ (m, 4H), 2.82 (m, 1H), 3.25 (m, 9H), 3.79 (m, 3H), 4.40 (d, $J = 11.8$ Hz, 4H), 6.15 (s, 4H), 6.90 (m, 1H), 6.99 (m, 1H), 7.30 (m, 2H), 7.75 (dd, $J = 14.0$, 2.1 Hz, 1H), 8.15 (dd, $J = 15.8$, 9.5 Hz, 1H) ppm; CIMS: *m/e*: 426 [$M^+$]; elemental analysis ($C_{24}H_{28}FN_3O_3 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = -35.88$ ($c = 0.485$, MeOH); >98% *ee*, as determined by chiral HPLC (Chiralcel OJ, 0.7 mL min$^{-1}$, 1:1 (0.5% $Et_2NH$ in EtOH)/heptane, 237 nm).

**3-(2,3-Dihydro-5-methoxy-1H-isoindol-2-yl)-2-(*R*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (19)**: Synthesized by method C. 33% yield of a white solid from **32**: m.p.: 135–138 °C; CIMS: *m/e*: 426 [$M^+$]; elemental analysis ($C_{24}H_{28}FN_3O_3 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = +35.25$ ($c = 0.505$, MeOH).

**3-(2,3-Dihydro-4-methoxy-1H-isoindol-2-yl)-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]propan-1-ol dimaleate (20)**: Synthesized by method C. 32% yield of a white solid from **32**: m.p.: 138 °C dec; $^1$H NMR (DMSO-$d_6$): $\delta = 2.19$ (m, 4H), 3.38 (m, 8H), 3.76 (m, 2H), 3.81 (m, 2H), 4.36 (d, $J = 21.0$ Hz, 4H), 6.15 (s, 4H), 6.96 (d, $J = 17.5$ Hz, 2H), 7.35 (m, 2H), 7.70 (dd, $J = 15.0$, 2.3 Hz, 1H), 8.15 (dd, $J = 16.2$, 9.2 Hz, 1H) ppm; CIMS: *m/e*: 426 [$M^+$]; elemental analysis ($C_{24}H_{28}FN_3O_3 \cdot 2C_4H_4O_4$): C, H, N; $[\alpha]_D^{21} = -28.90$ ($c = 1.00$, MeOH).

**2-{2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]-3-hydroxypropyl}-5-trifluoromethyl-isoindole-1,3-dione hydrochloride hemihydrate (22)**: As described above for the preparation of **21**, but the synthesis started from 2-{3-benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propyl}-5-trifluoromethyl-isoindole-1,3-dione (83% yield). M.p.: 128–130 °C; $^1$H NMR (DMSO-$d_6$): $\delta = 2.27$ (m, 4H), 4.05–3.70 (m, 8H), 4.19 (m, 1H), 5.61 (m, 1H), 7.30 (m, 1H), 7.63 (m, 1H), 8.10 (m, 1H), 8.27 (m, 3H), 10.55 (br s, 1H) ppm; CIMS: *m/e*: 492 [$M^+$]; elemental analysis ($C_{24}H_{21}F_4N_3O_4 \cdot HCl \cdot 0.5H_2O$): C, H, N; $[\alpha]_D^{21} = -25.3$ ($c = 1.00$, MeOH); >98% *ee*, as determined by chiral HPLC (Chiralcel OJ, 0.7 mL min$^{-1}$, 1:1 (0.5% $Et_2NH$ in EtOH)/heptane, 237 nM).

**Method D**:

**2-{(*S*)-3-Benzyloxy-2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propyl}-*cis*-hexahydro-isoindole-1,3-dione (36)**: See preparation of **32**, but *cis*-hexahydroisoindole-1,3-dione was utilized in place of phthalimide (57% yield). $^1$H NMR (DMSO-$d_6$): $\delta = 1.38$ (m, 4H), 1.60 (m, 2H), 1.75 (m, 2H), 2.30 (m, 3H), 2.51 (s, 4H), 2.97 (m, 2H), 4.48–4.85 (m, 7H), 4.58 (s, 2H), 7.38 (m, 6H), 7.75 (m, 1H), 8.10 (m, 1H) ppm; CIMS: *m/e*: 519 [$M^+$]; elemental analysis ($C_{30}H_{34}FN_3O_4 \cdot HBr \cdot 1/2H_2O$): C, H, N; $[\alpha]_D^{21} = -6.4$ ($c = 4.50$, 1:4 MeOH/$CHCl_3$).

**2-{(*S*)-(-)-2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]-3-hydroxy-propyl}-*cis*-hexahydro-isoindole-1,3-dione (24)**: See preparation of **21** (89% yield). $^1$H NMR (DMSO-$d_6$): $\delta = 1.43$ (m, 4H), 1.78–2.13 (m, 8H), 2.59 (t, $J = 20.8$ Hz, 1H), 2.87 (m, 3H), 3.04 (m, 4H), 3.50 (m, 3H), 3.79 (dd, $J = 24.8$ Hz, 1H), 7.03 (dt, $J = 14.2$ Hz, 1H), 7.20 (m, 1H), 7.63 (dd, $J = 16.7$ Hz, 1H) ppm; CIMS: *m/e*: 430 [$M^+$]; elemental analysis ($C_{23}H_{28}FN_3O_4$): C, H, N; $[\alpha]_D^{23} = -24.4$ ($c = 1.00$, $CHCl_3$).

**2-{(*R*)-(-)-2-[4-(6-Fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]-3-hydroxy-propyl}-*cis*-hexahydro-isoindole-1,3-dione hydrochloride hydrate (25)**: See preparation of **24** (method D; 91% yield). CIMS: *m/e*: 429 [$M^+$]; elemental analysis ($C_{23}H_{28}FN_3O_4 \cdot HCl \cdot H_2O$): C, H, N; $[\alpha]_D^{23} = +8.4$ ($c = 0.50$, MeOH).

**Method E**:

**2-{3-Benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazole-3-yl)-piperidin-1-yl]-propyl}-3-hydroxy-dihydroisoindol-1-one (37)**:[19] Sodium borohydride (0.4 g, 10 mmol) was added to a room temperature solution of **33** (2.0 g, 4.0 mmol) in 7:1 MeOH/$CH_2Cl_2$ (40 mL). After stirring at room temperature for 16 h, the reaction mixture was quenched with water (~1 mL), diluted with brine (250 mL), and extracted with $CH_2Cl_2$ (3 × 250 mL). The organic layers were dried ($Na_2SO_4$), combined, and concentrated in vacuo to give 1.9 g (93%) of alcohol **37** as an approximately 2:1 mixture of diastereomers, which were used in the next reaction without any purification.

**2-{3-Hydroxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-propyl}-2,3-dihydroisoindol-1-one hydrobromide hemihydrate (23)**: Triethylsilane (0.45 mL, 2.8 mmol) was added to a room temperature solution of **37** (0.91 g, 1.8 mmol) and trifluoroacetic acid (3.4 mL, 44 mmol) in $CH_2Cl_2$ (20 mL) and the resulting solution was stirred at room temperature for 48 h. The mixture was poured into water (200 mL), neutralized to pH 7–8 with $NaHCO_3$, and extracted with $CH_2Cl_2$ (3 × 200 mL). The organic layers were dried ($Na_2SO_4$), combined, and concentrated in vacuo to give an orange oil. Purification of the residue by flash chromatography (10–50% MeOH/EtOAc) afforded 2-{3-benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d] isoxazol-3-yl)-piperidin-1-yl]-propyl}-dihydroisoindol-1-one (0.85 g, 97%) as a yellow oil. A 0.25-g aliquot of the product was dissolved in EtOAc, cooled to 0 °C, and acidified with 1.0 N HCl in $Et_20$. After dilution of the solution with $Et_2O$, the resulting precipitate was filtered, washed with $Et_2O$, and dried in vacuo. Recrystallization of the product from MeOH/$Et_2O$ gave the HCl salt/hemihydrate (0.20 g,

72%) as a tan powder: m.p.: 180–184 °C; IR (KBr) 3410 (br s), 2910 (w), 2360 (m), 1680 (vs), 1610 (s), 1455 (m), 1410 (m), 1110 (m) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 2.22$ (m, 2H), 2.60 (m, 2H), 3.50 (m, 3H), 3.72–4.15 (m, 7H), 4.59 (m, 4H), 7.26–7.47 (m, 6H), 7.52 (dd, $J = 7.6$, 3.6 Hz, 1H), 7.63 (s, 2H), 7.73 (d, $J = 7.6$ Hz, 2H), 8.31 (dd, $J = 8.4$, 5.4 Hz, 1H), 11.38 (br s, 1H); CIMS: *m/e*: 500 [$M^+$]; $[\alpha]_D^{20} = -23.54^\circ$ ($c = 0.50$, MeOH); elemental analysis ($C_{30}H_{31}ClFN_3O_3 \cdot 1/2\,H_2O$): C, H, N. Boron tribromide (5.0 mL, 1.0 M solution in $CH_2Cl_2$, 5.0 mmol) was added to a −78-°C solution of 2-{3-benzyloxy-2-(*S*)-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-propyl}-dihydroisoindol-1-one (0.55 g, 1.0 mmol) in $CH_2Cl_2$ (12 mL). The resulting solution was allowed to warm to room temperature overnight. The reaction mixture was recooled to −78 °C, quenched with MeOH (~1 mL), allowed to warm to room temperature, and concentrated in vacuo. Repeated (3×) dissolution of the residue with MeOH followed by concentration in vacuo removed the volatile $B(OCH_3)_3$ byproduct. The residue was redissolved in a minimum of MeOH, and the HBr salt **23** was precipitated by trituration with $Et_2O$. The precipitate was filtered, washed with $Et_2O$, and dried in vacuo. Recrystallization of the product from MeOH/$Et_2O$ gave a tan powder (0.39 g, 72%): m.p.: 258–260 °C; IR (KBr) 3390 (s), 2945 (m), 2660 (m), 1660 (s), 1400 (s), 1290 (m) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): $\delta = 2.15–2.46$ (m, 4H), 3.45–3.68 (m, 3H), 3.69–4.05 (m, 6H), 4.17 (m, 1H), 4.63 (s, 2H), 5.60 (br s, 1H), 7.37 (td, $J = 9.5$, 2.0 Hz, 1H), 7.52 (m, 1H), 7.66 (d, $J = 3.8$ Hz, 2H), 7.74 (d, $J = 7.3$ Hz, 2H), 8.11 (dd, $J = 8.9$, 5.4 Hz, 1H), 9.34 (br s, 1H) ppm; CIMS *m/e*: 410 [$M^+$]; $[\alpha]_D^{23} = -46.03^\circ$ ($c = 1.00$, MeOH); elemental analysis ($C_{23}H_{25}BrFN_3O_3 \cdot 1/2\,H_2O$): C, H, N.

**Method F**:

**2-Bromo-2-chlorocarbonyl-acetic acid ethyl ester (39)**: Bromine (8.8 mL, 0.17 mmol) was added to a room temperature solution of chlorocarbonyl acetic acid ethyl ester (**38**; 26 g, 170 mmol) in carbon tetrachloride (25 mL). The resulting solution was stirred at room temperature for 2 h. The solution was concentrated and purified by bulb-to-bulb distillation (b.p.: 48–55 °C) to yield 37 g (93%) of the desired bromide as a clear, colorless oil, which was quickly advanced to the next step.

**3-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-3-oxo-propionic acid ethyl ester (40)**: A solution of **39** (3.97 g, 17.3 mmol) in THF (10 mL) was added to a 0-°C solution of 1,2,3,4-tetrahydroisoquinoline (2.31 g, 17.3 mmol) and triethylamine (2.65 mL, 19.0 mmol) in THF (50 mL). After stirring at room temperature for 2 hours, the solution was poured into water (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (20% EtOAc/heptane) yielded 2-bromo-3-(3,4-dihydro-1*H*-isoquinolin-2-yl)-3-oxo-propionic acid ethyl ester (3.38 g, 60%) as a yellow oil.

A solution of **30** (2.30 g, 10.4 mmol), triethylamine (1.70 mL, 11.9 mmol), and 2-bromo-3-(3,4-dihydro-1*H*-isoquinolin-2-yl)-3-oxo-propionic acid ethyl ester (3.38 g, 10.4 mmol) in NMP (30 mL) was heated at 50 °C for 4 h. The resulting solution was poured into water (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (30–40% EtOAc/heptane) to give a white solid (2.95 g). Recrystallization of the solid from aq MeOH yielded the desired product (2.61 g, 54%): m.p.: 138–142 °C; $^1H$ NMR ($CDCl_3$): $\delta = 1.27$ (m, 3H), 2.18 (m, 3H), 2.86–3.18 (m, 7H), 3.24 (m, 1H), 3.73 (m, 1H), 4.08 (m, 1H), 4.24 (m, 2H), 4.39 (s, 1H), 4.6 (dd, $J =$ 27.7, 15.0 Hz, 1H), 5.00 (dd, $J = 30.8$, 11.0 Hz, 1H), 7.02 (m, 1H), 7.15 (m, 4H), 7.48 (m, 1H), 7.62 (m, 1H) ppm; CIMS: *m/e*: 465 [$M^+$]; elemental analysis ($C_{26}H_{28}FN_3O_4$): C, H, N.

**3-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-piperidin-1-yl]-propan-1-ol dimaleate (26)**: See the preparation of **33**. 51% yield of a white powder: m.p.: 133–135 °C dec; $^1H$ NMR (DMSO-$d_6$): $\delta = 2.19$ (m, 4H), 2.98 (m, 2H), 3.28 (m, 4H), 3.41 (m, 4H), 3.75 (m, 2H), 4.02 (s, 2H), 6.15 (s, 4H), 7.20 (m, 4H), 7.34 (m, 1H), 7.72 (dd, $J = 15.8$, 2.2 Hz, 1H), 8.05 (dd, $J = 16.0$, 9.5 Hz, 1H). CIMS: *m/e*: 410 [$M^+$]; elemental analysis ($C_{24}H_{28}FN_3O_2 \cdot 2\,C_4H_4O_4$): C, H, N.

**Pharmacology**: All dopamine $D_{4.2}$ and $D_{2S}$ receptor binding was performed at NPS Allelix Corp by the methods previously described.[25] All rat α-1 adrenoceptor binding was performed by Hugo M. Vargas, Karen M. Brooks, and Lynn Laws-Ricker by the method previously described.[26] All $K_i$ values were determined from concentration–displacement curves with triplicate determinations for each concentration. The triplicate values generally had errors of less than 20%.

**In Vivo Pharmacology**: All MK-801 locomotion and CMA studies were performed by Thomas J. Corbett and Sharon Kafka according to methods previously described.[20]

*The authors would like to dedicate this paper to the memory of our dear friend and colleague Thomas J. (Roy) Corbett.*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