Articles

Design, Synthesis, and Evaluation of Metabolism-Based Analogues of Haloperidol Incapable of Forming MPP+-like Species

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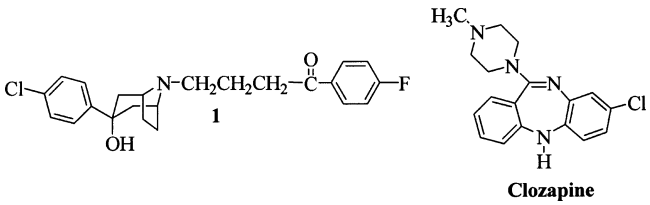
The long-term, irreversible, Parkinsonism-like side effects of haloperidol have been speculated to involve several mechanisms. More recently, it has been speculated that the metabolic transformation to MPP+-like species may contribute to the Parkinsonism-like side effects. Because BCPP+ and its reduced analogue have been shown to possess the potential to destroy dopamine receptors in the nigrostriatum, we have designed new analogues of haloperidol lacking the structural features necessary to form neurotoxic quaternary species but retaining their dopamine-binding capacity. The most potent agent at the D2 receptor, the homopiperidine analogue **11**, was found to be equipotent to haloperidol. It was also of interest to identify analogues with DA binding profiles similar to that of clozapine at the dopamine receptor subtypes. Evaluation of the proposed agents shows that the ratio of D2 to D4 (2) binding of clozapine was mimicked by **7** [K_i(D2) = 33, K_i(D3) = 200, K_i(D4) = 11 nM; K_i(D2)/K_i(D4) = 3] and **9** [K_i(D2) = 44, K_i(D3) = 170, K_i(D4) = 24 nM; K_i(D2)/K_i(D4) = 2]. A preliminary in-vivo testing of compound **7** shows that its behavioral profile is similar to that of clozapine. This profile suggests that there is a need for further evaluation of these two synthetic agents and their enantiomers for efficacy and lack of catalepsy in animal models.

Haloperidol is a widely used antipsychotic[1] whose therapeutic properties have historically been associated with its D2 antagonist activity,[2] based on the so-called dopamine hypothesis.[3] Unfortunately, haloperidol also possesses undesirable short- and long-term extrapyramidal side effects. Although the short-term side effects are troublesome, it is the long-term, debilitating, Parkinsonism-like side effects, including tardive dyskinesia, that have hampered its widespread use.[4] Consequently, haloperidol and other typical antipsychotics are being replaced by atypical antipsychotics possessing minimal extrapyramidal side effects.

Previous studies in several laboratories including ours[5−7] have revealed that haloperidol is converted to a quaternary pyridinium metabolite (BCPP+ or HPP+) that, based on its similarity to MPP+, may possess a potential to cause irreversible, Parkinsonism-like side effects (Chart 1).

Subsequent investigations have confirmed the presence of $BCPP^+$ in the brain of postmortem patients treated with haloperidol[8] as well as its neurotoxic behavior.[9] These results suggest that BCPP+ might contribute to some of the long-term toxicity of haloperidol. Hence, we have hypothesized that agents possessing binding profiles similar to haloperidol but lacking the structural features required to form quaternary pyridinium metabolites can be designed as potential antipsychotic agents.

In a recent publication,[10] we have shown that no significant difference exists between haloperidol and its tropane analogue **1** [K_i(D2) = 0.31 nM, K_i(D4) = 12 nM]



in producing acute catalepsy in rats. Since compound **1** could not form BCPP+-like species, we concluded that BCPP+ may not be responsible for catalepsy during the acute phase of haloperidol use. Therefore, the potent D2 binding of haloperidol may be responsible for acute catalepsy and possibly the acute phase of the extrapyramidal side effects associated with haloperidol use in humans. This observation is consistent with our hypothesis and the occupancy theory of Crocker et al.,[11] which indicates that induction of catalepsy is associated with high D2 occupancy.

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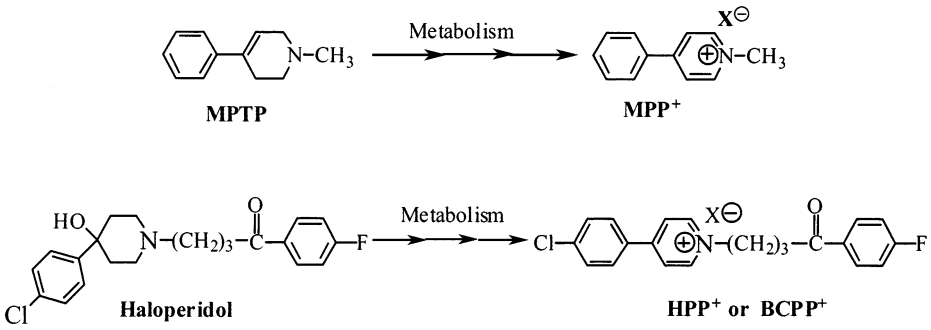
Chart 1



However, metabolism of haloperidol to BCPP+ may contribute to some of the long-term, irreversible, Parkinsonim-like side effects including tardive dyskinesia. On the basis of this hypothesis, we propose the synthesis of new analogues of haloperidol to meet the following criteria: (a) Analogues should have structural features that prevent them from biotransformation to BCPP+-like species. (b) Analogues should fit at least the distance requirements of the Humber pharmacophore model for D2 binding (Figure 1). It is important to note that the model was not constructed to discriminate among the DA subtypes. [12] (c) Analogues should have a clozapine-like D2/D4 affinity ratio i.e., [K_i(D2)/K_i(D4)] > 1[13] and a lower affinity for the D2 receptor subtype, 30 < D2 < 150 (Range of clozapine binding in the literature).

Although there are several hypotheses in the literature describing the mechanism by which clozapine produces its superior therapeutic effects in schizophrenic patients,[14] we were drawn to the D2/D4 binding constant ratio, because there are no effective antipsychotic agents that lack D2 affinity and the most selective D4 ligand was ineffective in clinical trials.[14] Thus, the proposed compounds were also designed to answer specific structure−activity relationship (SAR) questions in a search for a clozapine-like binding profile i.e., K_i(D2)/K_i(D4) > 1. The target compounds proposed are presented in Chart 2.

The first target compound (**2**), is the most obvious design target, since the first step in the metabolic transformation of haloperidol to BCPP+ is dehydration.[6] Thus, compound **2** should help in shedding light on the role played by this hydroxy group on the binding selectivity at the other dopamine receptor subtypes. Compound **3** is the 4-benzyl analogue of haloperidol and is based on the suggestion that a benzyl substituent

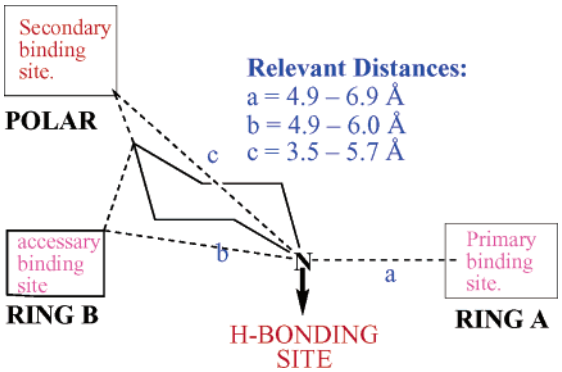
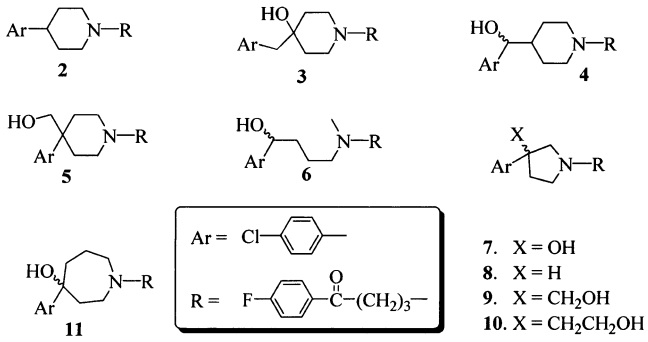


Figure 1. A proposed D2-like pharmacophore model by Humber et al.[14]

Chart 2. Analogues of Haloperidol That Meet the Two Drug-Design Criteria for Synthesis



prevents metabolism to quaternary pyridinium species.[15] Compound **4**, would be expected, if dehydration were to occur, to form an exocyclic double bond in conjugation with the aromatic ring. The resulting olefin would not be expected to undergo further oxidation. Compound **5** takes advantage of a quaternary carbon at the 4-position of the piperidine ring to not only prevent dehydration of the primary alcohol but also aromatization of the piperidine ring, since a double bond cannot be formed at the quaternary carbon. Compound **6** is a ring-opened analogue of **3** and was designed to test the hypothesis that an intact piperidine ring may not be essential for binding to the dopamine receptor subtypes. Compound **7**, a pyrrolidine analogue of haloperidol,[16] was designed on the basis that a five-membered pyrrolidine ring cannot form a quaternary species, even if it undergoes dehydration and a P_{450}-type oxidation similar to haloperidol. However, measurement of the pharmacophoric distances in **7** (Table 2) indicates that distance *c* is shorter than the range proposed in the Humber pharmacophore. Compound **8** is the pyrrolidine analogue of **2**. To extend distance *c* in **7** and bring it in line with the Humber proposal, we also designed and synthesized compounds **9** and **10**. Compound **9** cannot undergo aromatization to a quaternary species and satisfies all the D2-like pharmacophore distance requirements including distance *c* = 4.45 Å (cf. distance *c* = 3.5−5.7 Å for the Humber model).[14] Compound **10** (distance *c* = 5.67 Å) was similarly designed. Replacement of the piperidine ring in haloperidol with the azepine ring, as in **11**, should produce an analogue incapable of forming the pyridinium-type structure yet meet distance requirements of the Humber model (Table 2).

Chemistry

Compound **2** was obtained by reduction of the commercially available **12** to form **13**, which was then

Table 1. Binding Affinity Constants of Synthetic Compounds to Dopamine Receptors

compd[a]	binding data, pK_i ± SEM, nM (n[c]) D2	D3	D4	K_i(D2)/K_i(D4) ratio
haloperidol (**1**)	9.05 ± 0.30 (3)	8.34 ± 0.27 (3)	7.98 ± 0.28 (3)	0.1
2	7.81 ± 0.14 (3)	7.34 ± 0.05 (4)	7.59 ± 0.05 (3)	0.6
3[b]	8.10	8.05	7.23	0.1
4	7.62 ± 0.08 (4)	7.11 ± 0.08 (4)	6.91 ± 0.05 (3)	0.2
5	7.81 ± 0.07 (3)	6.96 ± 0.12 (3)	7.11 ± 0.02 (3)	0.2
6	7.58 ± 0.09 (3)	6.79 ± 0.04 (3)	6.72 (2)	0.1
7	7.48 ± 0.18 (3)	6.70 ± 0.14 (3)	7.98 ± 0.07 (3)	3.0
8	7.81 ± 0.11 (4)	8.00 ± 0.16 (4)	7.82 ± 0.22 (3)	1.1
9	7.36 ± 0.13 (3)	6.78 ± 0.04 (3)	7.62 ± 0.08 (3)	1.8
10	7.64 ± 0.21 (3)	7.49 ± 0.09 (3)	6.71 ± 0.18 (3)	0.1
11	8.96 ± 0.16 (3)	8.07 ± 0.05 (4)	8.09 ± 0.02 (3)	0.1
BCPP+	<6.0	<6.0	<6.0	
clozapine	6.87 ± 0.10 (3)	6.62 ±0.05 (10)	7.27 ± 0.06 (36)	2.4

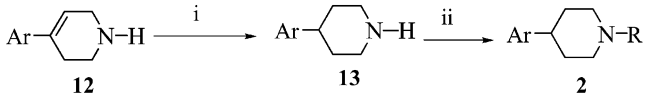
[a] All chiral compounds were synthesized and tested as racemic mixtures. [b] Single determinations. [c] n = number of determinations.

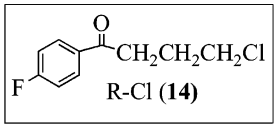
Table 2. Measurement of the Humber Pharmacophore Model Distances for OH-a for Synthesized Pyrrolidine and Homopiperidine Analogues of Haloperidol

compd[a]	distance *a* (4.9−6.9 Å)	distance *b* (4.9−6.0 Å)	distance *c* (3.5−5.7 Å)	lowest energy[b]
haloperidol	6.62	5.76	3.40	5.57
7	6.63	5.11	3.00	11.15
9	6.75	4.66	4.45	13.46
10	6.70	4.47	5.67	14.88
11	6.63	6.19	3.69	16.83

[a] The hydroxyl group was placed in the axial position in the starting geometry. [b] Energy measured in kcal/mol.

Scheme 1[a]



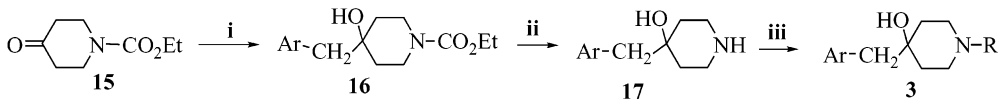


Ar = 4-Chlorophenyl

[a] Reagents: (i) 10% Pd/C, H_2, MeOH; (ii) R−Cl, K_2CO_3, KI, DME.

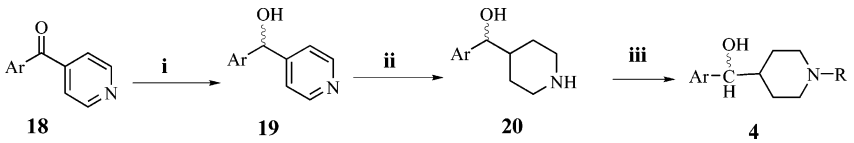
alkylated with **14** (Scheme 1). The key intermediate for the synthesis of **3** was constructed by reacting a freshly generated 4-chlorobenzylmagnesium chloride with a carbamyl-protected ketone, **15**. The resulting alcohol was decarbamylated in an ethanolic KOH and subsequently alkylated in the usual manner (Scheme 2). To obtain compound **4**, pyridine **18** was first reduced to the racemic alcohol **19** using $NaBH_4$ and further reduced by hydrogenation to **20**. Intermediate **20** was alkylated in the usual manner to obtain **4** (Scheme 3). The method of Bercz[17] was employed to obtain the starting material **21** for the synthesis of **5**. Hydrolysis of **21** to form acid **22** followed by esterification and reduction of the ester yielded intermediate **23**. Debenzylation of **23** and subsequent alkylation produced compound **5** in moderate yields (Scheme 4). The synthesis of **6** utilized **25** as starting material as depicted in Scheme 5. The acid was converted to the amide and subsequently reduced with $LiAlH_4$ to the corresponding amino alcohol, **27**. The alcohol was protected with triisopropyl silyl chloride; the amino function was then alkylated in the usual way before deprotection by TBAF to **6**. The synthesis of compound **7** followed the method we previously reported.[16] Compound **8** requires two key intermediates (**33** and **36**). Intermediate **33** was obtained by converting 4-chlorobenzyl cyanide to the diol and mesylating the resulting diol to the desired intermediate, **33**. The other intermediate **36** was obtained by substituting the chloride **34** with an azide to form **35** and then reducing **35** to the primary amine **36**, as shown in Scheme 6. The pyrrolidine ring was constructed by the double alkylation of the primary amine **36** with intermediate **33** to form the protected target compound. Deprotection of the keto group under acidic condition then yielded the desired compound **8**. The key intermediate in synthesizing compound **9**, alcohol **44**, was obtained by ring contraction of the piperidine ring starting with **12**, as shown in Scheme 7. Compound **12** was carbamylated to **37** and converted to epoxide **38**, and the ring was contracted to aldehyde **39** by $BF_3{\cdot}Et_2O$. The aldehyde was reduced to alcohol **40** and deprotected with ethanolic KOH, and the resulting amine **41** was alkylated in the usual manner. Aldehyde **39** in Scheme 7 also served as the starting material for the synthesis of

Scheme 2[a]



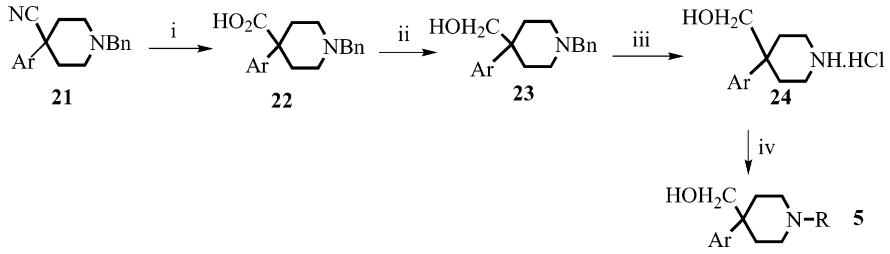
[a] Reagents: (i) $ArCH_2MgBr/Et_2O$. (ii) 20% KOH, EtOH; (iii) R−Cl, K_2CO_3, KI, DME.

Scheme 3[a]



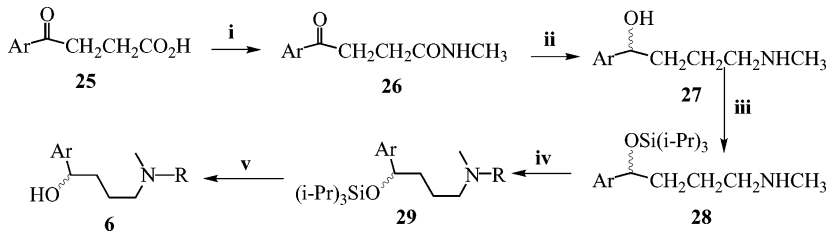
[a] Reagents: (i) $NaBH_4$, EtOH; (ii) PtO_2, H_2; (iii) R−Cl, $KHCO_3$, toluene.

Scheme 4[a]



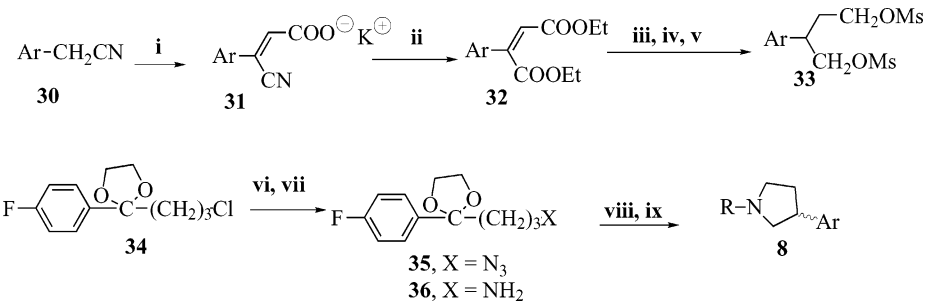
[a] Reagents: (i) dilute H_2SO_4, (ii) (a) H_2SO_4/MeOH, (b) $LiBHEt_3$; (iii) $CH_3CHClOCOCl$, MeOH/reflux; (iv) R−Cl, K_2CO_3, KI, DME.

Scheme 5[a]



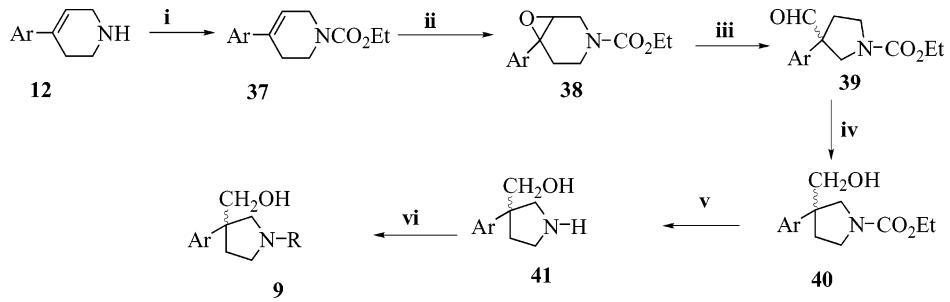
[a] Reagents: (i) $ClCO_2Et$, NEt_3, (ii) $LiAlH_4$/THF; (iii) $(^iPr)_3SiCl_3$, NEt_3, DMAP; (iv) R−Cl, K_2CO_3, KI, DME; (v) TBAF.

Scheme 6[a]



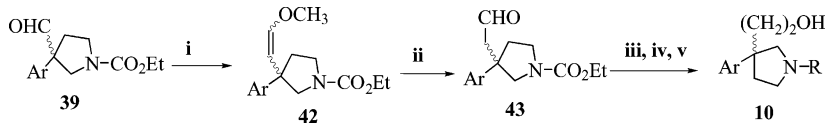
[a] Reagents: (i) glyoxylic acid, K_2CO_3/MeOH; (ii) H_2SO_4/EtOH; (iii) H_2, 10% Pd/C; (iv) $LiAlH_4$; (v) NEt_3, DMAP, MsCl; (vi) KI, NaN_3; (vii) PPh_3/Et_2O; (viii) intermediate **33**; (ix) 2 N HCl, reflux.

Scheme 7[a]



[a] Reagents: (i) $ClCO_2Et$, K_2CO_3, (ii) mCPBA, (iii) BF_3OEt_3/Et_2O; (iv) $NaBH_4$/EtOH; (v) KOH/EtOH, N_2H_4; (vi) R−Cl, K_2CO_3, KI, DME.

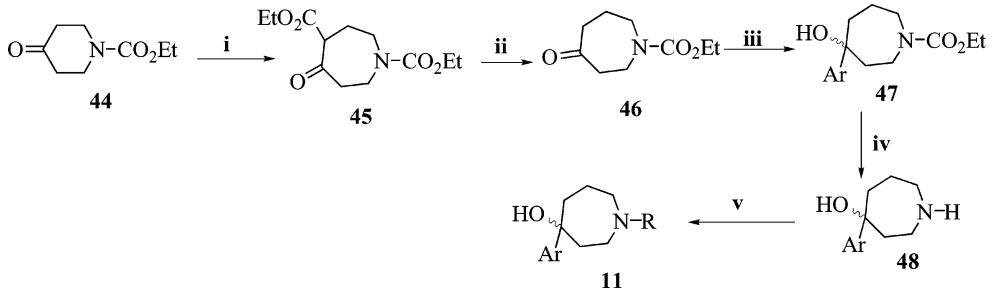
Scheme 8[a]



[a] Reagents: (i) NaHMDS/$Ph_3P^+CH_2OCH_3$; (ii) 4 N HCl; (iii) $NaBH_4$/EtOH; (iv) KOH/EtOH; (v) R−Cl, K_2CO_3, KI, DME.

compound **10**. It was converted to the corresponding enol ether, which under acidic condition was transformed to a new aldehyde (**43**) with one more carbon inserted as shown in Scheme 8. Aldehyde **43** was similarly reduced to the alcohol, its amino function deprotected and alkylated as before to obtain compound **10**. Finally, as depicted in Scheme 9, ketone **46** was obtained using the method of Riley et al.[18] Compound **44** was ring-expanded and then subjected to Grignard reaction to form intermediate **47**. The carbamate-protected alcohol **47** was deprotected to **48** in the usual way and then alkylated as indicated previously (Scheme 9). All chiral compounds were obtained as racemates and tested as such.

Scheme 9[a]



[a] Reagents: (i) $N_3CH_2CO_2Et$, BF_3OEt_2; (ii) 4 N KOH/EtOH; (iii) ^{n}BuLi, 4-chlorophenyl bromide; (iv) 50% KOH/EtOH, N_2H_4; (v) R−Cl, K_2CO_3, KI, DME.

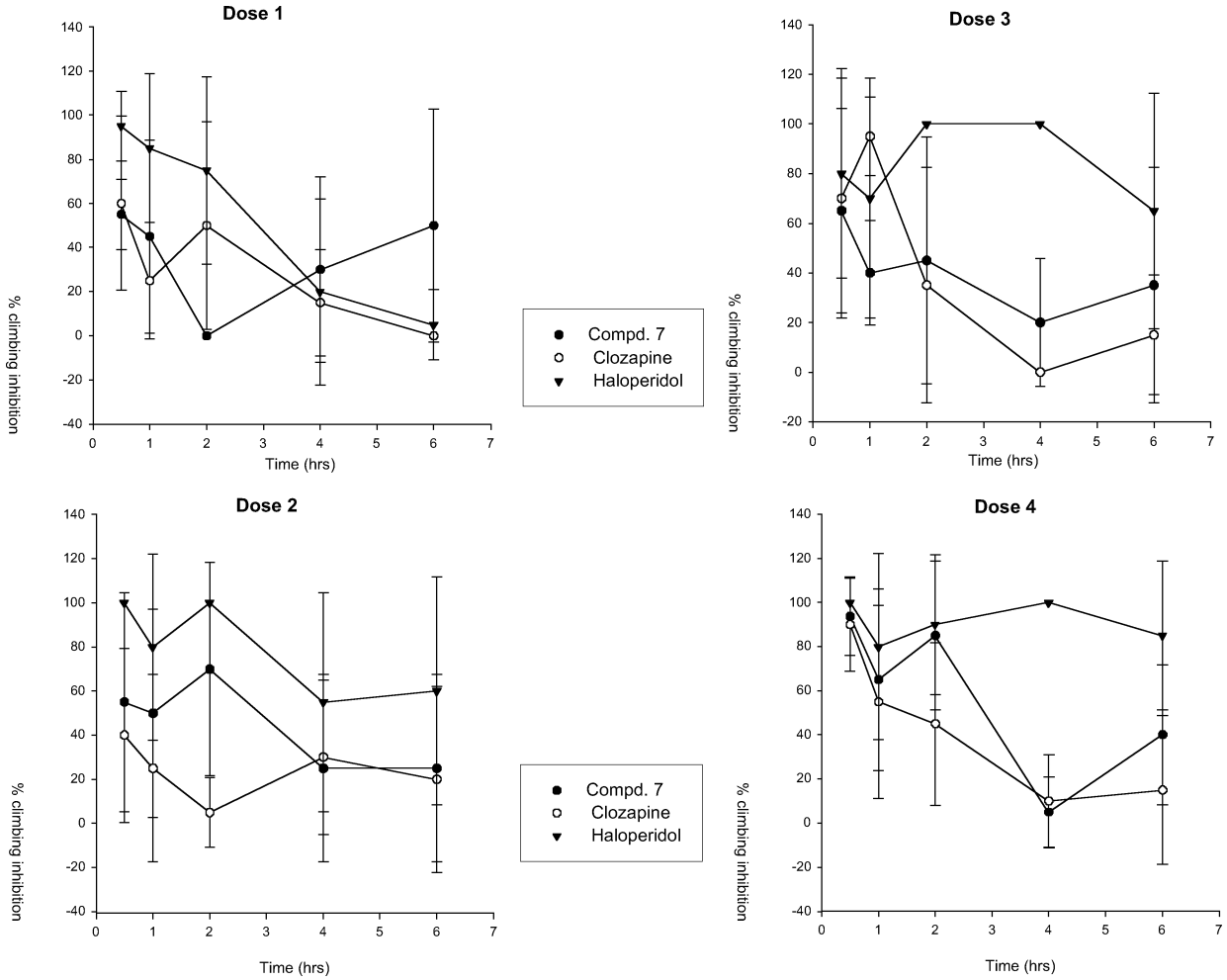


Figure 2. Percent inhibition of apomorphine-induced climbing by compound **7**, clozapine, and haloperidol. Data represents mean values (±SEM) for $n = 10$ mice.

Discussion

Among the binding profiles proposed to have efficacy against positive schizophrenia and a low propensity to induce movement disorders is the clozapine-like binding profile $K_i(D2)/K_i(D4) > 1$.[13] Thus, although they were designed to obviate metabolic transformation to MPP+-like species, the proposed compounds were also designed to answer specific SAR questions in a search for clozapine-like binding profile. Comparing the binding affinity of haloperidol with that of compound **2** reveals that deoxygenation of haloperidol substantially decreases binding at the D2 (18-fold) and D3 receptor (9-fold) subtypes. At the D4 subtype, however, the decrease is less than 3-fold. This observation suggests that the hydroxy group is not essential for binding affinity but does enhance affinity for the D2-like receptors. In addition, the decrease in binding affinity in the absence of the hydroxy group is not uniform at the dopamine receptor subtypes, providing the first clue that varying structural features at the DA receptor subtypes can achieve receptor selectivity.

According to the Humber pharmacophore (Figure 1), extending distance *b* of haloperidol to form **3**, transposing the alcoholic function to the benzylic position as in **4**, or introducing a quaternary carbon at position 4 as in **5** are changes within the Humber specified distances, yet the binding affinities of **3**−**5** are lower and lack the clozapine-like binding profile. The binding affinity of the

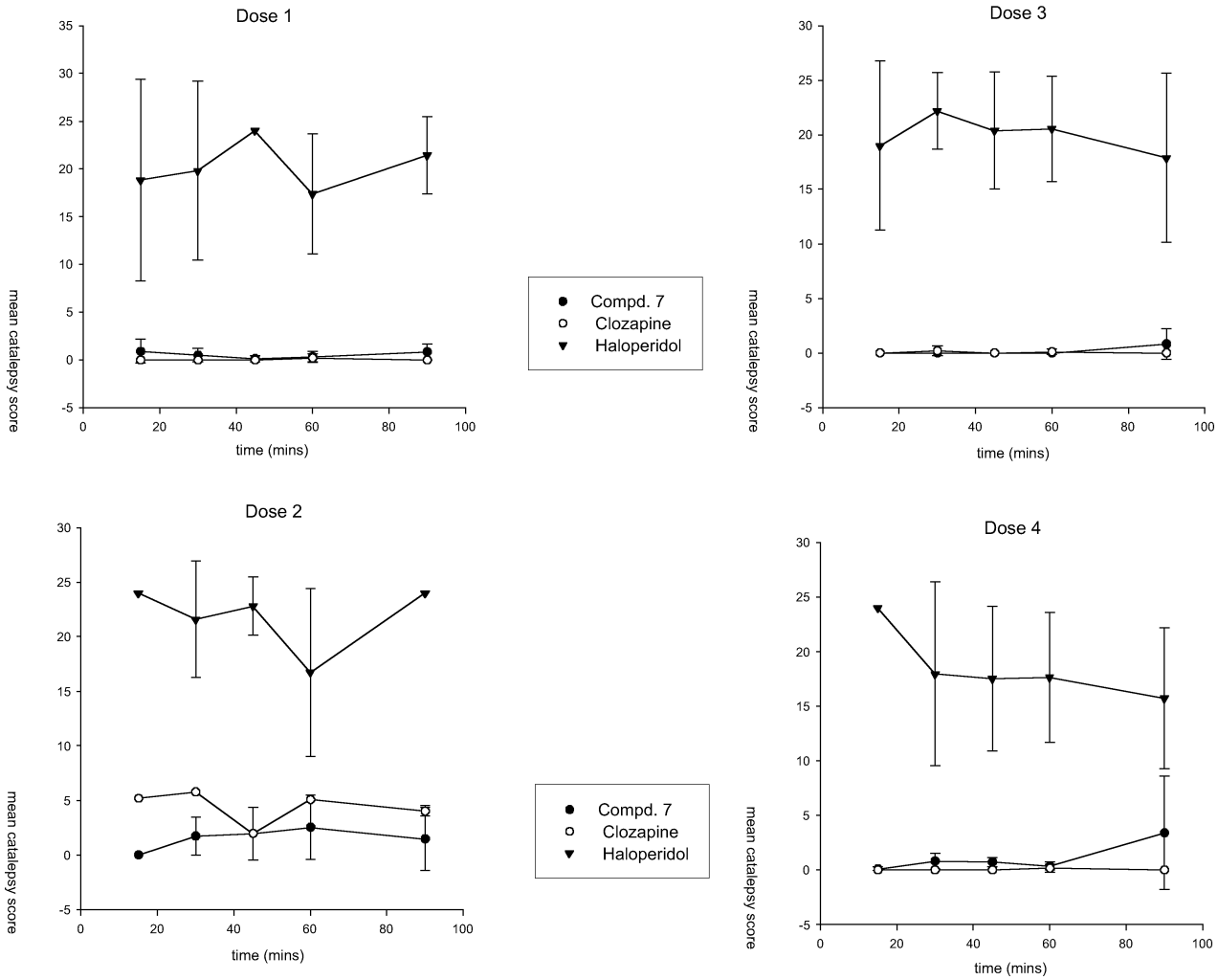


Figure 3. Plots of mean catalepsy scores at various times for haloperidol, compound **7**, and clozapine. Data represents mean values (±SEM) for $n = 5$ rats.

ring-opened analogue of compound **3**, i.e., **6** suggests that the piperidine ring in **4** is not essential for binding at the D2-like receptor subtypes. Ring contraction to pyrrolidine analogue **7** results in a decrease in D2 and D3 binding affinity but essentially no change in D4 binding affinity. Indeed, **7** shows the best selectivity [K_i(D2)/K_i(D4) = 3.0] for the D4 subtype among all the compounds synthesized. Comparing its binding profile with that of clozapine [K_i(D2)/K_i(D4) = 2.4] shows the D2/D4 binding ratio to be similar. In addition, **7** binds with a lower affinity at the D2 receptor subtype as does clozapine, raising the possibility that it may serve as an atypical antipsychotic.[12]

The deoxygenated analogue of **7**, i.e., compound **8**, binds with higher affinity at both D2 and D3 subtypes but has a 3-fold decrease in binding affinity at the D4 subtype, suggesting that the hydroxy group enhances affinity for the D4 receptor subtype in a manner similar to that found in the six-membered ring analogues. This pattern of binding at the dopamine receptor subtypes also shows that the five-membered ring analogues can serve as leads in obtaining selective ligands at the DA subtypes. Extending distance *c* in **7** by inserting one methylene group leads to **9**, with a similar binding affinity ratio [K_i(D2)/K_i(D4) = 1.8] as clozapine. Insertion of an additional methylene group to form **10** shows that further increase in distance *c* produces a decrease in binding affinity, especially at the D4 subtype. In addition, the binding affinity ratio [K_i(D2)/K_i(D4) = 0.1] deviates substantially from the clozapine-like ratio, thus suggesting that further extensions would be unproductive. Ring expansion from six (piperidine) to seven (homopiperidine), to give compound **11** mimics haloperidol binding at the three DA receptor subtypes. Indeed, the binding profile of **11** and that of haloperidol is identical within experimental error. Therefore, we are inclined to suggest that a homopiperidine ring may serve as a bioisostere of a piperidine ring at the D2-like receptor subtypes. Finally, we resynthesized[7] BCPP+ and investigated its binding affinity at the DA receptor subtypes. The results clearly show that BCPP+ does not bind to the D2-like receptors and is therefore unlikely to produce any of its effects through binding at the D2, D3, or D4 receptor subtypes. Overall, although all target compounds satisfy criterion 1 and partially criteria 2 and 3, only compounds **7**−**9** produce the all-important binding affinity ratio [K_i(D2)/K_i(D4) > 1].

An in vivo evaluation was conducted on **7** because of the favorable clozapine-like K_i(D2)/K_i(D4) binding profile. This brief evaluation involves inhibition of apomorphine-induced climbing test in male Swiss mice and catalepsy induction in male Sprague−Dawley rats in a "bar test".[20] Haloperidol and clozapine served as controls in the respective assays. The results are shown in

Figures 2 and 3. Overall, the behavioral profile of **7** mimics the profile of clozapine, while there is a statistically significant difference between **7** and haloperidol in both tests. The fact that **7** mimics clozapine's K_i(D2)/K_i(D4) ratio and does not produce catalepsy in the bar test but blocks apomorphine-induced climbing in a manner similar to clozapine has encouraged us to vigorously pursue more detailed in vivo studies on **7**, its enantiomeric pair, as well as compound **9** and its enantiomers. These experiments are currently ongoing.

Conclusion

In this paper, we have designed and synthesized haloperidol analogues incapable of undergoing metabolism to pyridinium-type metabolites but possess binding affinity at DA receptor subtypes. Since the pyridinium-type metabolites have the potential to contribute to some long-term side effects through the destruction of dopaminergic neurons in the nigrostriatum, these compounds have potential advantage over haloperidol. The fact that compounds **7** and **9** possess D2/D4 binding affinity ratios similar to that of the atypical antipsychotic clozapine is interesting and necessitates further evaluation of these compounds in animal models. The hypothesis that K_i(D2)/K_i(D4) > 1 leads to agents with efficacy against positive schizophrenia and a low propensity to induce movement disorders can be validated using compounds **7** and **9** when their enantiomers are separated. It is necessary to isolate the enantiomers of these compounds so as to evaluate the effect of stereochemistry on the binding affinity of the 5- and 7-membered ring analogues in this paper. After expanded binding profiles of **7**, **9**, and **11** are obtained and enantiomers are separated, we also plan to evaluate their capacity to reverse apormorphine-induced stereotypy and their ability to induce catalepsy in animal models. These experiments are expected to shed more light on the D2/D4 binding hypothesis.

Experimental Section

Chemistry. Column chromatography was performed with silica gel (200−425 mesh) as the stationary phase. Precoated silica gel plates (Analtech F_{254}, 0.25 mm; Merck) were used for TLC analysis. Melting points were determined in open capillaries on Gallenkamp electrothermal apparatus. ^{1}H NMR spectra were recorded either on a Varian EM-300 MHz or on a Bruker AM 270 MHz instrument, with DMSO-d_6 or $CDCl_3$ as the solvent; all values are expressed in δ values (parts per million). The following abbreviations are used: s = singlet, d = doublet, t= triplet, p = pentet, dd = doublet doublet, m = multiplet, and br = broad. Compounds were named using Autonom in Chem Draw version 7.0.1. Elemental analyses (C, H, N) were performed by Atlantic Microlab, Inc.; the analytical results were within ±0.4% of the theoretical values for the formula given.

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(4-fluorophenyl)-butan-1-one (2). Compound **12** (1.30 g, 5.7 mmol) was dissolved in MeOH (110 mL) and the solution was hydrogenated (Parr) over 10% Pd/C (310 mg) at 68 psi for 4 h. The catalyst was removed by filtration (Celite) and the solvent was removed under reduced pressure. The residue was basified using saturated $NaHCO_3$ (pH 12) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a dark yellow oily residue. The residue was converted to the hydrochloride salt **13** (1.3 g, 96.2%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (m, 2H,), 1.77 (d, J = 3.0 Hz, 2H), 2.32 (brs, 1H), 2.56 (m, 1H), 2.72 (t, J = 15 Hz, 2H), 3.20 (d, J = 12 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.23 (d, J = 9 Hz, 2H). A mixture of **13** (140 mg, 0.60 mmol), K_2CO_3 (0.33 g, 2.4 mmol), and KI (15 mg) was stirred in DME (4 mL), and **14** (3.9 ml, 2.4 mmol) was added in a dropwise manner. The reaction mixture was stirred under N_2 at 100 °C overnight and the crude product was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with gradient elution (0−10% MeOH/CH_2Cl_2), to give 160 mg (67% yield) of an oil. The oil was converted to the HCl salt and recrystallized from MeOH/Et_2O to give a solid. Mp: 208.5−209.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.04 (m, 6H), 2.84 (tt, J = 4.1, J = 12.3 Hz, 1H), 3.06 (m, 4H), 3.22 (t, J = 6.1 Hz, 2H), 3.57 (d, J = 12.3 Hz, 2H), 7.26 (d, J = 8.9 Hz, 2H), 7.38 (d, J = 3.2 Hz, 2H), 7.41 (d, J = 3.2 Hz, 2H), 8.07 (dd, J = 2.1, 8.9 Hz, 2H), 10.6 (s, br, 1H). Anal. ($C_{21}H_{24}Cl_2FNO$): C, H, N.

4-[4-(4-Chlorobenzyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one (3). Into a three-necked flask equipped with a mechanical stirrer, a nitrogen inlet, an addition funnel, and a reflux condenser with a drying tube was added magnesium turnings (3.1 g, 0.129 g-atom), and dry ether (200 mL). A solution of 4-chlorobenzyl chloride (23.0 g, 120 mmol.) in anhydrous Et_2O (100 mL) was added portionwise and the resulting mixture was refluxed for 2 h to produce 4-chlorobenzylmagnesium chloride. A solution of 4-oxopiperidine-1-carboxylic acid ethyl ester (13.3 g, 0.085 mol.) in dry THF (100 mL) was rapidly added to the Grignard reagent produced and the resulting mixture refluxed for 24 h. The mixture was cooled and 30% NH_4Cl solution was added until all solids dissolved. The aqueous phase was separated and extracted with ether (3 × 100 mL). The combined organic phase was shaken with cold 1 N HCl (100 mL) quickly and then with brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed to afford a yellowish brown oil (13.7 g, 60.1%). The oil was further purified by column chromatography on silica gel (70−230 mesh) to afford a colorless product. A mixture of the product (2.5 g, 16 mmol) in absolute EtOH (70 mL) and 20% aqueous KOH (21 mL) was refluxed under nitrogen for 12 h. The solution was cooled, solvent was removed in vacuo, and water (100 mL) was added. The resulting mixture was extracted with chloroform (3 × 100 mL) and the combined chloroform extract was washed with water (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to afford the deprotected amino alcohol **17** (1.55 g, 84.6%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.49 (d, J = 13.5 Hz, 2H), 1.65 (dt, J = 13.8 Hz, J = 4.7 Hz, 2H), 2.69 (s, 2H), 2.98 (m, 4H), 4.83 (s, −OH), 7.23 (part of AA′BB′ system, 2H), 7.33 (part of AA′BB′ system, 2H), 7.84 (br, −NH). A mixture of **17** (1.5 g, 7.6 mmol), **14** (6.0 g, 30 mmol) in DME (35 mL), K_2CO_3 (3 g), and KI (100 mg) in DME (40 mL) was refluxed for 7 h and monitored by TLC for the formation of product. The mixture was cooled to room temperature, diluted with H_2O (100 mL), and extracted with Et_2O (3 × 100 mL). After drying over anhydrous Na_2SO_4, solvent was removed and the resulting oil was chromatographed over silica gel to afford a yellowish oil which solidified on standing. Crystallization from MeOH/Et_2O afforded **3** as white crystals (2.7 g, 83%). Mp: 79−80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (m, 6H), 2.79 (m, 6H), 3.56 (m, 3H), 4.48 (d, J = 3.2 Hz, 1H), 7.06 (m, 2H), 7.25 (m, 4H), 7.91 (m, 2H), 11.29 (br, 1H). Anal. ($C_{22}H_{25}ClFNO_2 \cdot 0.4H_2O$): C, H, N.

(4-Chlorophenyl)pyridin-4-ylmethanol (19). A mixture of $NaBH_4$ (2.4 g, 62 mmol) and **18** (10 g, 46 mmol) in absolute EtOH (200 mL) at room temperature was stirred for 1.5 h and then refluxed for 30 min. To the mixture was added H_2O (20 mL), 10% HCl (75 mL) on ice, and 20% NaOH (40 mL) to form a precipitate. The precipitate was recrystallized from 80% MeOH−H_2O to give 8.1 g (80%) of product **19**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 1H), 3.56 (br, −OH), 7.34 (m, 6H), 8.46 (m, 2H)

(4-Chlorophenyl)piperidin-4-ylmethanol (20). A mixture of **19** (0.76 g, 3.5 mmol) and PtO_2 (76 mg) in EtOH (3.5 mL), H_2O (2.7 mL), and concentrated HCl (0.54 mL) was

hydrogenated at 3 atm for 30 min. The catalyst was filtered and the filtrate was concentrated to form a solid. A 20% NaOH (1 mL) was added to the solution in hot water to precipitate the product. The white precipitate was recrystallized with 50% aqueous MeOH to yield 0.59 g (76%) of **20**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (m, 3H), 1.46 (m, 1H), 1.65 (m, 1H), 2.07 (s, 1H), 2.29 (m, 2H), 2.85 (m, 2H), 4.24 (d, J = 7 Hz, 1H), 7.27 (m, 2H), 7.35 (m, 2H).

4-{4-[(4-Chlorophenyl)hydroxymethyl]piperidin-1-yl}-1-(4-fluorophenyl)butan-1-one HCl (4). A mixture of **20** (0.68 g, 3.0 mmol), **14** (0.78 g, 3.9 mmol), $KHCO_3$ (1.2 g), KI (60 mg), and toluene (30 mL) was allowed to reflux for 48 h. The mixture was filtered to remove any undissolved materials and washed with EtOAc, and solvent was removed under reduced pressure. The residue was chromatographed over silica gel using EtOAc−MeOH gradient elution to obtain **4** (0.7 g, 60%), which was then converted to the HCl salt. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (m, 3H), 1.84 (m, 6H), 2.32 (t, J = 7.3 Hz, 2H), 2.84 (m, 2H), 2.91 (t, J = 7.3 Hz, 3H), 4.32 (d, J = 7.3 Hz, 1H), 7.17 (m, 6H), 7.96 (m, 2H). Anal. ($C_{22}H_{26}Cl_2FNO_2$): C, H, N.

4-(4′-Chlorophenyl)-4-carboxy-1-phenylpiperidine (22). A mixture of H_2O (1 mL) and sulfuric acid (2 mL) was added to compound **21**[17] (2 g), and the resulting mixture was refluxed overnight. Solvent was removed under vacuum to produce a residue, the residue was dissolved in MeOH (20 mL), and concentrated sulfuric acid (3 mL) was added. The resulting mixture was stirred under reflux overnight, cooled to room temperature, neutralized with Na_2CO_3, and extracted with EtOAc (3 × 30 mL). The pooled organic solution was washed with saturated Na_2CO_3 and brine, dried over sodium Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over silica gel with hexane/EtOAc (2/1) to give **22** (1.04 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (m, 9H), 3.65 (m 3H), 3.45 (s, 2H), 2.78 (d, 2H), 2.50 (d, 2H), 2.15 (t, 2H), 1.92 (t, 2H).

4-(4′-Chlorophenyl)-4-methylenehydroxy-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidine Hydrogen Oxalate (5). To a solution of **22** (0.22 g, 0.67 mmol) in THF (4 mL) was added Superhydride (1.5 mL) and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated Na_2CO_3 and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude product **23**. To a solution of the above crude product **23** (202 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added 2-chloroethyl chloroformate (0.14 mL), and the resulting mixture was stirred at 60 °C for 2 h. The solvent was removed and MeOH (4 mL) was added. After the mixture was refluxed for 3 h, it was cooled to room temperature, solvent was removed, and the residue was converted to the HCl salt **24**. A mixture of **24** (0.34 g, 1.3 mmol), K_2CO_3 (0.6 g), KI (0.1 g), and **14** (0.51 g, 2.5 mmol) in DME (10 mL) was stirred at 90 °C overnight and then cooled to room temperature. EtOAc (30 mL) was added, and the mixture was washed with brine, dried over Na_2SO_4, concentrated in vacuo, and chromatographed over silica gel to give the desired crude product (0.14 g, 23%), which was subsequently converted to the oxalate salt **5**. The resulting colorless, soft solid could not crystallize and was thus submitted for analysis and testing as such. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, J = 5.4, 3.4 Hz, 2H), 7.32 (m, 4H) 7.13 (t, J = 8.8 Hz, 2H), 3.56 (s, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.64 (m, 2H), 2.36 (t, J = 6.8 Hz, 2H), 2.50 (m, 3H), 1.90 (m, 3H), 1.70 (m, 2H). Anal. ($C_{24}H_{27}ClFNO_6$): C, H, N.

***N*-Methyl-3-(4-chlorobenzoyl)propionic Amide (26).** Compound **25** (6.4 g, 30 mmol) was stirred in CH_2Cl_2 (80 mL) at room temperature until all the solid had dissolved. The resulting solution was cooled to 0 °C (ice-NaCl bath), Et_3N (4.4 mL, 31.5 mmol) and ethyl chloroformate (3.00 mL, 31.5 mmol) in 20 mL of CH_2Cl_2 were added, and the mixture was stirred for 40 min. Keeping the temperature at 0 °C with an ice bath, CH_3NH_2 (15.8 mL, 31.5 mmol) (2 M solution in THF) was added portionwise. The reaction mixture was stirred at that temperature for 2 h, quenched with water, and the crude product was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The filtrate was chromatographed on silica gel eluting with a 0−15% MeOH/CH_2Cl_2 gradient that afforded compound **26** as a white solid (5.48 g, 81%) yield. Recrystallization from EtOAc−hexane provided an analytical sample. Mp 123−124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (t, J = 5.4 Hz, 2H), 2.79 (s, 3H), 3.31 (t, J = 5.4 Hz, 2H), 5.81 (m, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.1 Hz, 2H).

***N*-Methyl-*N*-4-(4′-chlorophenyl)-4-hydroxybutylamine (27).** Amide **26** (4.2 g, 19.8 mmol) was dissolved in THF (150 mL) then added dropwise to a cooled (0 °C) solution of 2 M LAH in THF (119 mL, 118.8 mmol) and warmed to room temperature under N_2 atmosphere. The reaction mixture was stirred for 20 h at room temperature, poured onto ice, and basified with 1 M NaOH. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, and the residue was chromatographed on silica gel eluting with a 20−50% MeOH/CH_2Cl_2 (0−15% NH_4OH) gradient that afforded 1.89 g (48% yield) of intermediate **27** as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (m, 2H), 1.31 (m, 2H), 1.97 (s, 3H), 2.19 (m, 2H), 4.18 (dd, J = 4.7, 7.3 Hz, 1H), 6.94 (m, 4H).

***N*-Methyl-*N*-4-(4′-chlorophenyl)-4-triisopropylsilyloxybutylamine (28).** A mixture of alcohol **27** (2.2 g, 10.41 mmol), DMAP (0.12 g, 1 mmol), and NEt_3 (1.9 mL, 13.5 mmol) was stirred in CH_2Cl_2 (70 mL) at room temperature. TIPSCl (2.9 mL, 13.5 mmol) was added to the resulting solution and stirred 20 h under N_2 atmosphere. The reaction mixture was quenched with water and the crude product extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The filtrate was chromatographed on silica gel eluting with a 10−50% MeOH−CH_2Cl_2 (5−15% NH_4OH) gradient to give 2.8 g of compound **28**. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.96 (m, 21H), 1.37 (p, J = 6.83 Hz, 2H), 1.71 (p, J = 6.35 Hz, 2H), 2.35 (s, 3H). 2.49 (t, J = 8.1 Hz, 2H), 4.76 (t, J = 8.1 Hz, 1H), 7.24 (m, 4H).

***N*-[4-(4-Fluorophenyl)-4-oxobutyl]-*N*-4-(4′-chlorophenyl)-4-triisopropylsilyloxybutylamine (29).** A mixture of **28** (2.80 g, 7.57 mmol), 4-chloro-4-flourobutyrophenone (3.72 mL, 22.7 mmol), K_2CO_3 (3.08 g), and KI (0.22 g) in DME (60 mL) was refluxed 24 h. The reaction mixture was quenched with water and the product extracted EtOAc (3 × 100 mL. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel and gradient elution with 0−15% MeOH−EtOAc afforded of **29** (2.09 g, 51%) as a light yellow residue. ^{1}H NMR (270 MHz $CDCl_3$): δ 0.98 (m, 21H), 1.33 (p, J = 7.33 Hz, 2H), 1.84 (p, J = 7.33 Hz, 4H), 2.13 (s, 3H), 2.26 (t, J = 7.32 Hz, 2H), 2.34 (t, J = 7.32 Hz, 2H), 2.91 (t, J = 7.33 Hz, 2H), 4.75 (t, J = 5.86 Hz, 1H), 7.09 (dd, J = 8.30, 8.79 Hz, 2H), 7.22 (m, 4H), 7.94 (dd, J = 5.37, 8.54 Hz, 2H).

***N*-[4-(4-Fluorophenyl)-4-oxobutyl]-*N*-4-(4′-chlorophenyl)-4-hydroxybutylamine (6).** A mixture of **29** (2.0 g, 3.74 mmol) and TBAF (5.2 μL, 5.23 mmol) was stirred in THF (12 mL) under N_2 at room temperature for 24 h. The reaction mixture was poured into H_2O (50 mL) and then extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification on silica gel eluting with 0−15% MeOH/CH_2Cl_2 gradient afforded the target compound as a yellowish oil that was converted into the HCl salt **6** (1.2 g, 84%). Recrystallization from MeOH/Et_2O provided an analytical sample. Mp: 109−112 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.65 (m, 4H), 1.99 (t, J = 7.33, 2H), 2.71 (s, 3H), 3.03 (m, 4H), 3.18 (t, J = 6.84 Hz, 2H), 4.57(s, 1H), 7.35 (m, 6H), 8.05 (dd, J = 8.79, 5.86, 2H). Anal. ($C_{21}H_{26}Cl_2FNO_2 \cdot 0.2H_2O$): C, H. N.

2-(4-Chlorophenyl)buten-2-dioic 1,4-Diethylate (32). A mixture of **30** (10 g, 66 mmol), glyoxylic acid monohydrate (12.1 g, 13.2 mmol), and K_2CO_3 (35.9 g, 26 mol) and MeOH (100 mL) was refluxed for 24 h to give a thick suspension, which was filtered, stirred with $CHCl_3$ (50 mL) overnight, and filtered again. The white crude solid (**31**) was used without purification. A mixture of **31**, concentrated H_2SO_4 (20 mL), and EtOH

(80 mL) was refluxed for 6 h. After removing solvent in vacuo, saturated aqueous $NaHCO_3$ (150 mL) was added, the mixture was extracted with $CHCl_3$ (3 × 200 mL), and the organic phase was dried over Na_2SO_4. The solvent was removed to give **32** (13.5 g, 72%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 4.21 (q, 7.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 6.24 (s, 1H), 7.37 (m, 4H).

2-(4-Chlorophenyl)butane-1,4-dimesylate (33). A solution of **32** (13.5 g, 47.8 mmol) in EtOH (50 mL) was stirred with 10% Pd/C (1 g) at room temperature for 2.5 days. After removing catalyst and solvent, 2-(4-chlorophenyl)succinic acid diethyl ester (11.6 g, 85%) was obtained as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (m, 6H), 2.63 (dd, J = 16.8, 5.3 Hz, 1H), 3.16 (dd, J = 16.8, 10.1 Hz, 1H), 4.10 (m, 5H), 7.27 (m, 4H). A mixture of $LiAlH_4$ (7.73, 0.203 mmol) and the diethyl ester (11.6 g, 40.8 mmol) was stirred in THF (150 mL) and refluxed overnight. The reaction was quenched by dropwise addition of H_2O (20 mL) in an ice bath. The mixture was extracted with CH_2Cl_2 (2 × 200 mL) and washed with saturated aqueous NaCl (75 mL). The organic phase was dried over Na_2SO_4 and removed in vacuo to give the alcohol (6.9 g, 85.77%) as an oil. The crude oil was used without further purification. To a solution of the alcohol (6.87 g, 34.96 mmol), Et_3N (10.59 g, 115.36 mmol), and DMAP (1.28 g, 10.5 mmol) was added methane sulfonyl chloride (12.88 mL, 13.21 g, 115.37 mmol) at room temperature. Stirring was continued at room temperature overnight. Reaction was diluted with CH_2Cl_2 (100 mL) and washed with aqueous NH_4Cl solution. The organic phase was dried over Na_2SO_4 and removed in vacuo. The crude product was purified on column (silica gel) with EtOAc/hexane to give **33** as a colorless oil (11.2 g, 89.8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (m, 1H), 2.32 (m, 1H), 2.84 (s, 3H), 2.90 (s, 3H), 3.21 (m, 1H), 4.01 (m, 1H), 4.19 (m, 1H), 4.32 (ddd, J = 18.4, 10.0 & 7.0 Hz, 2H), 7.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.85, 36.87, 41.26, 67.23, 72.69, 76.58, 127.63, 127.74, 128.81, 138.23.

2-(3-Azidopropyl)-2-(4-fluorophenyl)[1,3]dioxolane (35). A mixture of 2-(3-chloropropyl)-2-(4-fluorophenyl)[1,3]dioxolane (**34**) (10 g, 40.9 mmol), NaN_3 (10.62 g, 16.4 mmol), and KI (3 g) in DMF (80 mL) was heated to 130 °C and stirred overnight. The reaction mixture was extracted with EtOAc (3 × 200 mL) and washed with saturated NaCl (150 mL). The organic phase was dried over Na_2SO_4 and removed in vacuo to produce a residue. The crude material was purified on column (silica gel, 9:1 hexane:EtOAc) to give **35** as an oil (10 g, 97.4%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (m, 2H), 1.91 (m, 2H), 3.24 (t, J = 6.9 Hz, 2H), 3.75 (m, 2H), 3.96 (m, 2H), 6.99 (m, 2H), 7.39 (m, 2H).

2-(3-aminopropyl)-2-(4-fluorophenyl)[1,3]dioxolane (36). To a solution of azide **35** (10 g, 39.8 mmol) in Et_2O (100 mL) was added PPh_3 (18.8 g, 71.6 mmol) in a portionwise manner at 0 °C. After gas evolution, the reaction was stirred at room temperature for 3 h and subsequently overnight after the addition of H_2O (10 mL). The reaction mixture was extracted with ether (2 × 200) and washed with saturated aqueous NaCl (20 mL), and the organic phase was dried over Na_2SO_4. After solvent was evaporated under reduced pressure, the crude product was chromatographed over silica gel with 9:1:1 CH_2Cl_2:MeOH:NH_4OH to give **36** (7 g, 78%) as a white solid. Mp: 116−117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.87 (m, 2H), 2.63 (t, J = 7.0 Hz, 2H), 3.72 (m, 2H), 3.96 (m, 2H), 6.98 (m, 2H), 7.39 (m, 2H).

4-[3-(4-Chlorophenyl)pyrrolidin-1-yl]-1-(4-fluorophenyl)butan-1-one (8). A mixture of dimesylate **33** (1 g, 2.8 mmol) and amine **36** (3 g, 13.2 mmol) was heated at 150 °C for 24 h. The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and aqueous NaCl (50 mL). The organic phase was dried over $NaSO_4$ and the solvent was removed under reduced pressure. The crude product was purified on a column (silica gel) with 7:3 EtOAc:MeOH to give the dioxalane-protected ketone an oil (1 g, 91.7%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (m, 2H), 1.85 (m, 4H), 2.41 (m, 5H), 2.77 (m, 1H), 2.97 (t, J = 8.3 Hz, 2H), 3.31 (m, 2H), 3.74 (m, 2H), 3.99 (m, 2H), 6.98 (m, 2H), 7.22 (m, 4H), 7.40 (m, 2H). A mixture of the protected ketone (1 g, 2.5 mmol) in acetone (5 mL) and 2 N HCl (50 mL) was refluxed overnight. The reaction mixture was neutralized by adding 2 M NaOH and then extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified by column chromatography on silica gel with 8:2 EtOAc:MeOH to yield **8** as an oil (0.77 g, 86%). The free base **8** was converted to the oxalate salt. Mp: 143.0−143.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (m, 1H), 1.97 (m, 2H), 2.27 (m, 1H), 2.68 (m, 6H), 3.03 (t, J = 8.3 Hz, 2H), 3.32 (m, 1H), 7.13 (m, 6H), 7.99 (m, 2H). Anal. ($C_{20}H_{21}ClFNO\cdot0.4C_2H_2O_4$): C, H, N.

4-(4-Chlorophenyl)-1,2,3,6-tetrahydropyridine-1-carboxylic Acid Ethyl Ester (37). A mixture of ClCOOEt (68.1 g, 0.43 mol), **12**·HCl (6.9 g, 30.0 mmol), and K_2CO_3 (60 g, 0.63 mol) in acetone (150 mL) was refluxed overnight under an atmosphere of N_2. The mixture was filtered to remove solid materials and the solution was concentrated in vacuo. An excess amount of ClCOOEt was quenched by the addition of 4% NaOH (100 mL) in methanol. After evaporating off MeOH, the residue was extracted with ethyl acetate (3 × 100 mL) and 100 mL of saturated NaCl solution. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified on column chromatography (silica gel) to yield **37** (6.7 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.0 Hz, 3H), 2.45 (m, 2H), 3.63 (m, 2H), 4.04 (m, 2H), 4.12 (m, 2H), 5.73 (brs, 1H), 7.25 (m, 4H).

6-(4-Chlorophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylic Acid Ethyl Ester (38). A mixture of **37** (0.7 g, 2.60 mmol) and 0.59 g of mCPBA in 7.8 mL of CH_2Cl_2 was stirred for 16 h. After addition of another 0.59 g of mCPBA, the mixture was stirred for 2 h before the addition of Na_2SO_3 (30 mL). The organic phase was exhaustively extracted, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography over silica gel (1:1 EtOAc: hexane) to yield 0.58 g (79%) of epoxide **38**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (m, 3H), 3.22 (m, 1H), 3.56 (m, 2H), 4.05 (m, 2H), 4.15 (m, 2H), 4.30 (m, 2H), 7.39 (m, 3H), 7.85 (m, 1H).

3-(4-Chlorophenyl)-3-formylpyrrolidine-1-carboxylic Acid Ethyl Ester (39). A mixture of $BF_3\cdot Et_2O$ (7.7 g, 54.5 mmol) and epoxide **38** (0.45 g, 1.6 mmol) in 4 mL of anhydrous Et_2O under an atmosphere of N_2 was refluxed for 5 h, 5 N NaOH (20 mL) was added, and the reaction vessel was allowed to cool to ice-bath temperature. The mixture was then extracted with Et_2O (3 × 30 mL) and dried over Na_2SO_4. After removing solvent in vacuo, crude material was purified on a column (silica gel, 3:7 EtOAc:hexane) to yield aldehyde **39** (0.4 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (m, 3 H), 2.14 (m, 1H), 2.76 (m, 1H), 3.54 (m, 2H), 4.12 (m, 2H), 4.35 (t, J = 10.4 Hz, 1H), 7.10 (m, 2H), 7.33 (m, 2H), 9.93 (s, 1H).

3-(4-Chlorophenyl)-3-hydroxymethylpyrrolidine-1-carboxylic Acid Ethyl Ester (40). A mixture of $NaBH_4$ (0.75 g, 19.9 mmol) and aldehyde **39** (2.8 g, 10 mmol) in EtOH (20 mL) was stirred for 1.5 h and then refluxed for 30 min. H_2O (10 mL) was added to the reaction and solid material was removed. The filtrate was concentrated in vacuo and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried over Na_2SO_4 and removed in vacuo. The crude product was separated on a column (silica gel, 1:9 MeOH:EtOAc) to yield alcohol **40** (2.6 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.0 Hz, 3H), 2.06 (m, 1H), 2.35 (m, 1H), 3.55 (m, 3H), 3.59 (m, 2H), 3.85 (d, J = 10.9 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 7.14 (m, 2H), 7.33 (m, 2H).

4-[3-(4-Chlorophenyl)-3-hydroxymethylpyrrolidin-1-yl]-1-(4-fluorophenyl)butan-1-one (9). To a solution of **40** (1.1 g, 3.9 mmol) in EtOH (50 mL) were added 50% NaOH (20 mL) and hydrazine (5 mL). The reaction mixture was refluxed for 2 days. H_2O (100 mL) was added to the resulting mixture and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried over Na_2SO_4 and solvent was removed in vacuo. The crude material was purified on column (silica gel, 9:1:1 MeOH: CH_2Cl_2:NH_4OH) to yield the free amine **41**. A mixture of **41** (1 g, 4.73 mmol), 4-chloro-4-flourobutyrophenone (3.8 g, 18.9 mmol), K_2CO_3 (2.61 g, 18.9 mmol), and KI (0.2 g) in DME (10 mL) was refluxed overnight under an atmosphere of N_2. The

excess DME was removed in vacuo and residue was extracted with CH_2Cl_2 (3 × 50 mL) and saturated NaCl (50 mL). The pooled organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified on a column (silica gel) with 8:2 EtOAc:MeOH to yield of **9** (1.2 g, 68%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99 (m, 2H), 2.11 (m, 6H), 3.01 (dt, J = 7.1, 1.3 Hz, 2H), 3.21 (dt, J = 8.3, J = 3.0 Hz, 1H), 3.42 (t, J = 10.0 Hz, 2H), 3.63 (d, J = 10 Hz, 1H), 7.26 (m, 6H), 7.87 (m, 2H). An analytical compound was obtained by converting the oil to the **9**·HCl salt (68%). Mp: 120−122 °C. Anal. ($C_{21}H_{24}Cl_2FNO_2$): C, H, N.

3-(4-Chlorophenyl)-3-(2-oxoethyl)pyrrolidine-1-carboxylic Acid Ethyl Ester (42). A solution of NaHMDS in THF (1 M, 14.3 mL) was added to a solution of (methoxymethyl)triphenylphosphonium chloride (5.14 g, 15 mmol) in THF (15 mL) at −78 C. After 1 h, a solution of aldehyde **39** (1.92 g, 6.82 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at −78 C for 2 h and then quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried over $MgSO_4$ and solvent removed in vacuo. The crude product was purified on a column (silica gel, 1:1 EtOAc:hexane) to afford 1.497 g (71%) colorless liquid. The mixture of (*E*)/(*Z*)-enol ether **42** was used without characterization.

To a solution of **42** (1.5 g, 4.8 mmol) in THF (35 mL) was added 4 M HCl (22 mL) and the mixture stirred at ambient temperature overnight. Thereafter, the reaction was quenched with saturated aqueous $NaHCO_3$ and solvent was removed under reduced pressure. The crude product was taken up in aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel with elution solvent, 1:1 EtOAc:C_6H_{12}) to afford a colorless liquid, **43** (1.33 g, 93.2%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 3H), 2.24 (m, 1H), 2.74 (m, 3H), 3.47 (br, 2H), 3.70 (t, J = 10.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 7.18 (m, 2H), 7.30 (m, 2H), 9.47 (t, J = 2.2 Hz, 1H).

4-[3-(4-Chlorophenyl)-3-(2-hydroxyethyl)pyrrolidin-1-yl]-1-(4-fluorophenyl)butan-1-one (10). To a solution of **43** (0.57 g, 1.9 mmol) in EtOH (20 mL) at 0 °C was added $NaBH_4$ (0.15 g, 3.8 mmol). The reaction mixture was stirred for 3 h and then quenched with H_2O. EtOH was removed in vacuo and organic crude material was extracted with CH_2Cl_2 (3 × 50 mL) and washed with brine (50 mL). The pooled organic phase was dried over Na_2SO_4 and the solvent removed. The crude product was purified on a Chromatotron (2 mm, silica gel) using 9:1 EtOAc:MeOH to afford the protected amino alcohol (320 mg, 56%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 2H), 2.06 (m, 5H), 3.47 (m, 4H), 3.70 (t, J = 10.5 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 7.24 (AA′BB′ system, 4H). A mixture of the carbamate-protected amino alcohol (0.32 g, 1.1 mmol) in EtOH (30 mL) and 50% aqueous NaOH (30 mL) was refluxed for 17 h. H_2O (100 mL) was added to the reaction mixture and extracted with (3 × 100 mL) CH_2Cl_2. The organic phase was dried over Na_2SO_4 and solvent was removed in vacuo to give a quantitative yield of free amine which was used without further purification. A mixture of free amine (0.24 g, 1.1 mmol), **14** (0.42 g, 2.1 mmol), K_2CO_3 (0.6 g, 4.2 mmol), and KI (100 mg) in DME (10 mL) was refluxed under N_2 overnight. The excess DME was removed in vacuo and the residue was extracted with CH_2Cl_2 (3 × 50 mL) in NaCl (50 mL). The pooled organic phase was dried over $MgSO_4$ and removed under reduced pressure. The crude product was purified on a Chromatotron (4 mm, silica gel) with 8:2 EtOAc:MeOH to afford compound **10** (74 mg, 15%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (dt, J = 15.2, J = 3.4 Hz, 1H), 1.91 (m, 1H), 2.01 (m, 2H), 2.24 (m, 2H), 2.60 (m, 4H), 3.02 (td, J = 7.1, J = 1.2 Hz, 2H), 3.45 (m, 4H), 3.68 (td, J = 10.0, J = 2.9 Hz, 1H), 7.10 (m, 4H), 7.24 (m, 2H), 7.97 (m, 2H). The free base was converted to the HCl salt. Mp: 142−143 °C. Anal. (C_{23} $H_{26}Cl_2FNO$): C, H, N.

5-Oxoazepane-1,4-dicarboxylic Acid Diethyl Ester (45). Solutions of BF_3·Et_2O (3.23 g, 22.8 mmol) and ethyl diazoacetate (3.0 g, 26.3 mmol) in anhydrous Et_2O (6 mL) were simultaneously added over a 20 min period to a solution of **44** (3.0 g, 17.3 mmol) in anhydrous Et_2O (20 mL) maintained at −25 to −30 °C (dry ice−iPrOH bath). After the additions were completed, the reaction was maintained at −25 to −30 °C for 1 h and then allowed to warm to room temperature. The solution was washed with 30% K_2CO_3 (100 mL) and extracted with EtOAc (3 × 100 mL). The organic phase was separated, dried on Na_2SO_4, and concentrated in vacuo to give a crude orange oil, which was purified on silica gel column eluted with 30% EtOAc/hexane to give **45** (4.0 g 88.8%). ^{1}H NMR (Bruker AM 270 MHz, $CDCl_3$) δ 1.25 (m, 6H), 2.02 (m, 2H), 2.66 (m, 2H), 3.44 (m, 2H), 3.69 (t, J = 6.8 Hz, 1H), 3.80 (m, 2H), 4.16 (m, 4H).

4-Oxoazepane-1-carboxylic Acid Ethyl Ester (46). To a solution of intermediate **45** (1.0 g, 3.9 mmol) in EtOH (75 mL) was added 4 M KOH (75 mL) and the mixture was stirred at room temperature for 24 h. The mixture was extracted with EtOAc (3 × 75 mL) and the organic phase was separated, dried (Na_2SO_4), and concentrated in vacuo to yield a residue. The residue was chromatographed on silica gel to give a clear oil (606 mg, 84%). ^{1}H NMR (Varian 300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 3H), 1.77 (m, 2H), 2.62 (m, 4H), 3.61 (m, 4H), 4.10 (q, J = 7.1 Hz, 2H).

4-(4-Chlorophenyl)-4-hydroxyazepane-1-carboxylic Acid Ethyl Ester (47). A solution of 4-chlorophenyl bromide (310.5 mg, 1.6 mmol) in anhydrous THF (8 mL) was cooled to −78 °C and a 1.6 M *n*-Butyllithium (35 mL, 2.2 mmol) in THF was added with stirring for 2 h. Then a solution of 1-carbethoxyperhydroazepin-4-one (200 mg, 1.08 mmol) in THF (2 mL) was added at −78 °C. The reaction mixture was allowed to warm to room temperature and then stirred for an additional 1 h, quenched with saturated NH_4Cl (40 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The organic solvent was pooled and evaporated under reduced pressure. The resulting residue was chromatographed and purified on silica gel column to give product (186 mg, 64.3%). ^{1}H NMR (Bruker AM270 MHz, $CDCl_3$): δ 1.24 (m, 3H), 1.84 (m, 6H), 3.28 (m, 2H), 3.68 (m, 2H), 4.13 (q, J = 6.8 Hz, 2H), 7.32 (m, 4H).

4-[4-(4-Chlorophenyl)-4-hydroxyazepan-1-yl]-1-(4-fluorophenyl)butan-1-one Hydrogen Oxalate (11). A mixture of compound **47** (232 mg 7.8 mmol), hydrazine (3 mL), EtOH (5 mL), and 50% KOH (5 mL) was refluxed overnight. The mixture was allowed to cool to room temperature and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic portion was washed with H_2O (50 mL) and dried (MgSO4) and solvent was evaporated under reduced pressure. The residue was separated by column chromatography on silica gel and the desired compound **48** was obtained in good yield (130 mg, 73.8%). ^{1}H NMR (Bruker AM270 MHz, $CDCl_3$): δ 1.96 (m, 6H), 2.91 (m, 2H), 3.22 (m, 2H), 7.24 (m, 2H), 7.39 (m, 2H). A mixture of compound **48** (276 mg, 1.2 mmol), **14** (990 mg, 4.9 mmol), K_2CO_3 (680 mg, 4.9 mmol), and KI (300 mg) in DME (10 mL) was refluxed with stirring under an atmosphere of N_2 for over 12 h. The solvent was removed under reduced pressure, brine (50 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The pooled organic phase was dried ($MgSO_4$), solvent removed under reduced pressure, and the residue chromatographed over silica gel. Elution with EtOAc/MeOH (7:3) yielded the desired product as an oil (300 mg, 63%) and was converted to the oxalate salt. Mp 172−174 °C). ^{1}H NMR (Varian 300 MHz, $CDCl_3$) δ 1.91 (m, 8H), 2.50 (m, 1H), 2.57 (t, J = 7.1 Hz, 2H), 2.66 (m, 1H), 2.89 (m, 2H), 3.00 (t, J = 7.1 Hz, 2H), 7.13 (t, J = 8.4 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.98 (dd, J = 2.1, 8.4 Hz, 2H). Anal. ($C_{22}H_{27}ClFNO_6$): C, H, N.

Molecular Modeling. Measurements of the pharmacophoric distances for haloperidol and synthesized compounds were conducted using SYBYL 6.8 (Tripos Associates, Inc., St Louis, MO.). The X-ray crystal structure of haloperidol was used as the initial structure. The structures of synthetic compounds were built from SYBYL SKETCH with the chair conformation for pyrrolidine and an axial hydroxyl group as starting geometry. This structure was minimized by the Powell

method with 0.001 kcal/(mol Å) as the termination method. The minimized structure was then subjected to a systematic search for possible allowed conformations. The distance between the center of ring A and the nitrogen was constrained by the range allowed within the Humber pharmacophore model, i.e., 4.9−6.9 Å. The conformation with the lowest energy from the search results was used for measuring the distances reported in Table 1. For compounds **9** and **10,** an additional distant constraint was imposed using the *b* distant range (4.9−6.0 Å) given in the Humber Model.

Biology. Receptor Binding Studies. Radioligand binding studies were performed according to standard receptor binding procedures.[19] Briefly, an appropriate weight of frozen cell paste expressing human dopamine D2, D3, or D4 receptors was homogenized using a Brinkman Polytron model PT3000 (setting 15 000 rpm, 15 s) in 50 mM Tris HCl buffer pH 7.4 containing 2 mM $MgCl_2$. The homogenate was centrifuged for 10 min at 40 000*g*, washed, and recentrifuged. The final pellet was resuspended in 50 mM Tris HCl buffer pH 7.4 containing 100 mM NaCl and 1 mM $MgCl_2$ for the D2 cell homogenate; 50 mM Tris HCl buffer pH 7.4 containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 5 mM $MgCl_2$ for the D3 cell homogenate; and 50 mM Tris HCl buffer pH 7.4 containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$ for the D4 cell homogenate. Incubations were initiated by the addition of tissue homogenate to wells of 96-well plates containing [^{3}H]spiperone (0.20 nM, 0.10 nM, for D2 and D4 assays, respectively) or 3H-7OH-DPAT (0.40 nM, for D3 assays) and varying concentrations of test compound, buffer, or (+)-butaclamol in a final volume of 250 μL. Nonspecific binding was defined as the radioactivity remaining in the presence of a saturating concentration of a known inhibitor (10 μM (+)-butaclamol). After a 15 min incubation at 37 °C for D2 and D3 receptor assays or a 45 min incubation at 30°C for D4 receptor assays, assay samples were filtered onto GF/B filtermats that had been presoaked in 0.5% polyethylenimine, using a Skatron cell harvester (Molecular Devices) and washed with ice-cold 50 mM Tris buffer pH 7.4. Radioactivity was quantified by liquid scintillation counting (Betaplate, Wallac Instruments). The IC_{50} value (concentration at which 50% inhibition of specific binding occurs) was calculated by linear regression of the concentration−response data. K_i values were calculated according to the Cheng−Prusoff equation, where $K_i = IC_{50}/(1 + (L/K_d))$, where L is the concentration of the radioligand used in the experiment and the K_d value is the dissociation constant for the radioligand (determined previously by saturation analysis).

Apomorphine-Induced Climbing Stereotypy. A modified climbing test by Needham et al. was used.[20] Swiss male mice (20−25 g, $N = 125$) in groups of five per time point (30 min and 1, 2, 4, and 6 h) were injected ip with 0.1 mL/kg of vehicle (0.1% lactic acid and 0.9 of saline) or increasing moles/kilogram equivalent doses of dopamine antagonists haloperidol, compound **7** (i.e., 5.3×10^{-7}, 1.9×10^{-6}, 3.2×10^{-6}, 5.3×10^{-6}), and clozapine (3.1×10^{-5}, 9.2×10^{-5}, 1.5×10^{-4}, 2.4×10^{-4}). Animals were then challenged with 2.8×10^{-6} mol/kg of the agonist apomorphine placed in cylindrical wire cages (12 cm in diameter, 14 cm in height) and observed for climbing behavior at 10 and 20 min postdose. Climbing behavior was assessed as follows: 4 paws on the cage floor = 0 score; 2 or 3 paws on the cage = 1 score; 4 paws on the cage = 2 scores. Scores were expressed as mean percent climbing inhibition and are plotted in Figure 2.

Bar Test for Catalepsy. A modified bar test by Needham et al. was used.[20] Male SD rats (200−300 g, $N = 100$) were injected subcutaneously with 1 mL/kg of vehicle (<0.005% acetic acid in H_2O) or increasing moles/kilogram equivalent doses of haloperidol, compound **7** (i.e., 5.3×10^{-7}, 1.9×10^{-6}, 3.2×10^{-6}, 5.3×10^{-6}), and clozapine (3.1×10^{-5}, 9.2×10^{-5}, 1.5×10^{-4}, 2.4×10^{-4}). Catalepsy severity was assessed immediately at various time points (15, 30, 45, 60, and 90 min) postinjection, by scoring how long the rat maintained both forepaws motionless on a horizontal metal bar (1.1 cm in diameter, 10 cm above the benchtop in a box). A score of 1 was given for every 5 s (2 min maximum) the animal remained on the bar. Mean scores from five animals per time point were recorded for catalepsy (Figure 3).

Statistical Analysis. The Student's *t*-test was used to compare the three compounds used in the animal behavioral tests. Results were considered significant at $p < 0.05$.

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