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Haloperidol: towards further understanding of the structural contributions of its pharmacophoric elements at D2-like receptors

Donald M. N. Sikazwe,[a] Shouming Li,[a] Leroy Mardenborough,[a] Vivian Cody,[b] Brian L. Roth[c] and Seth Y. Ablordeppey[a,*]

[a]*College of Pharmacy and Pharmaceutical Sciences, Florida A & M University, Tallahassee, FL 32307, USA*
[b]*Hauptman–Woodward Medical Research Institute Inc., Buffalo, NY 14203, USA*
[c]*Departments of Biochemistry, Psychiatry and Neurosciences and NIMH Psychoactive Drug Screening Program, Case Western Reserve University Medical School, Cleveland, OH 44106, USA*

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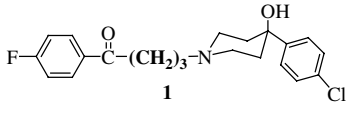
Abstract—An attempt to understand the pharmacophore-relevant position of the alcoholic moiety in haloperidol and the contributions of other pharmacophoric elements led to the re-synthesis of its tropane analogue (compound **2**). An analysis of the binding data suggests that haloperidol binds to the DA receptors with the OH group in the axial position and the OH group, while not essential for binding, enhances binding especially at the D2 receptor. It also became clear that shortening the butyrophenone chain not only reduces binding affinity at the DA receptors but eliminates subtype selectivity.

Haloperidol (**1**) has long been known to be a most effective antipsychotic and until recently a drug of choice in treating schizophrenia.[1,2] Although, so much work has been reported on the structure–activity relationship of haloperidol,[3,4] the preferred conformation and the pharmacological role of its tertiary alcohol group in binding to dopamine receptor subtypes[5] have not been addressed. X-ray crystallographic studies indicate haloperidol's hydroxyl group to be axial,[6,7] however, the pharmacophore-relevant conformation at the D2-like receptors has not been identified.



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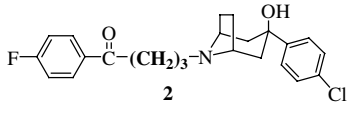
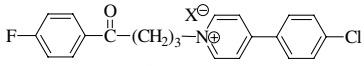


2

The purpose of this study was threefold: to identify the preferred conformation and pharmacophore-relevant position of the alcoholic group at D2-like receptors, to evaluate the contribution of the hydroxyl group to binding at the dopamine receptors, and to explore the contribution of the N to phenyl distance of the butyrophenone for selectivity at the DA D2-family receptor subtypes. Compound **2** was previously synthesized as a haloperidol analogue, which could not undergo metabolism to form the quaternary pyridinium metabolite, BCPP+.[8]



BCPP+ or HPP+

Compound **2** was re-synthesized to ascertain the position of its OH (Scheme 1). In this regard, the carbamate-protected intermediate, **4**, was submitted for X-ray analysis in the laboratory of Dr. V. Cody.[9] The X-ray structure analysis showed that the OH group was fixed in the *endo* position (equivalent to the axial position in haloperidol) as shown below (Fig. 1). Thus, we confirm that Grignard reaction of 4-chlorophenyl magnesium bromide on the tropinone, **3** results in stereoselective synthesis of the carbamate-protected

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* Corresponding author. Tel.: +1 850 599 3834; fax: +1 850 599 3934; e-mail: seth.ablordeppey@famu.edu

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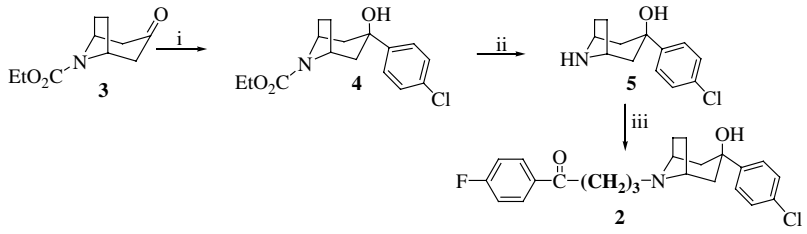


Scheme 1. Reagents and conditions: (i) 4-chlorophenyl magnesium bromide, Et_2O (anhydrous), N_2, reflux, 12 h, 42%; (ii) KOH, ethylene glycol, 150 °C, 73%; (iii) 4-chloro-4-fluorobutyrophenone, KI, K_2CO_3, DME (anhydrous), N_2, reflux, 12 h, 23%.

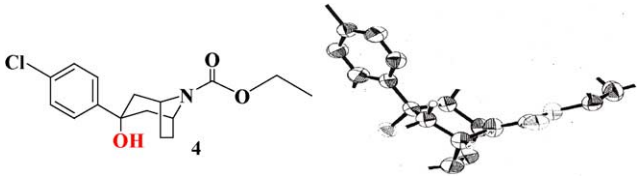
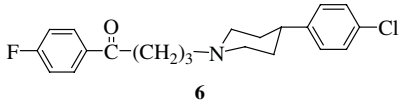


Figure 1. X-ray crystallographic rendering of compound **4**.

endo-alcohol. Subsequent decarbamylation and alkylation of the resulting amine, **5** yielded compound **2** albeit in low yield. Attempts to change the Grignard reaction conditions to obtain the *exo*-alcohol were unsuccessful.

We have previously shown that compound **2** has a higher affinity at the D2 receptor than haloperidol. That being the case, one can conclude that the ethylene bridge in the tropane moiety of **2**, at a minimum, does not distract from binding to the D2 receptors. If the OH in an axial position is the preferred conformation, then compound **2** with the OH in the *endo* position should, at a minimum, be equipotent to haloperidol in binding to DA receptors. On the other hand, if **2** is significantly less potent in binding to the DA receptors then, the *exo*-alcohol must be more potent and hence the OH group must be preferred in the equatorial position in haloperidol. The binding data (Table 1) indicates that **2** is about 3-fold more potent than haloperidol at the D2 receptor subtype and hence suggests that haloperidol binds to the D2 receptor with the OH group in the axial conformation. It was hoped that additional confirmation of the preferred position of the OH would be provided by the synthesis and evaluation of the *exo*-OH of **2** but we were hampered by our inability to obtain the *exo*-OH analogue using the usual synthetic routes.

We have previously reported the synthesis and binding affinity of compound **6**, a deoxygenated analogue of haloperidol, to dopamine receptors (D2, $K_i = 16$ nM; D4, $K_i = 26$ nM).[10] The binding data suggest that deoxygenation results in about 16-fold loss of affinity for the D2 receptor but a less pronounced 2-fold loss of affinity for the D4 receptor.



To further evaluate the contribution of the OH group to binding at the dopamine receptors, it was necessary to obtain compound **9**, the deoxygenated analogue of **2**. In this regard, intermediate **5** was subjected to dehydration conditions to produce **7**, which was subsequently alkylated to obtain **8**. Intermediate **7** was also hydrogenated and then alkylated with the intention of obtaining compound **9** however, subsequent hydrogenation consistently resulted in dechlorination (compound **10**) as well (Scheme 2).

Table 1. Physicochemical data and binding properties of synthetic compounds at dopamine receptors

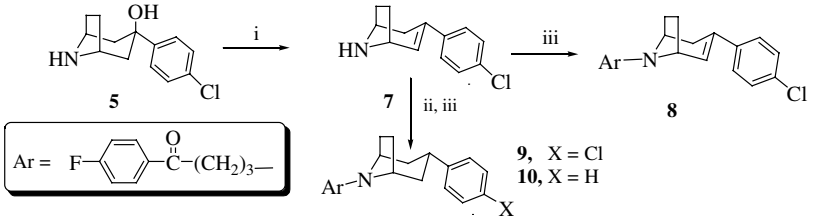
	Recrystallization solvent	% Yield	Mp (°C)	Empirical[a] formula	D2 K_i (nM)[b]	D3 K_i (nM)[b]	D4 K_i (nM)[b]	K_i D2/K_i D4
1[c]	—	—	—		1.1 ± 0.7	5.5 ± 3.0	12.7 ± 7.2	0.1
2[b]	MeOH/Et_2O	23	237–238	$C_{23}H_{26}NO_2Cl_2F{\cdot}0.5H_2O$	0.31 ± 0.04	0.81 ± 0.4	12.1 ± 3.3	0.03
6[d]	MeOH/Et_2O	67	209–210	$C_{21}H_{24}NOCl_2F$	16.3 ± 5.1	46.0 ± 5.3	25.9 ± 3.0	0.6
8	MeOH/Et_2O	34	216–217	$C_{23}H_{24}NOCl_2F{\cdot}0.1H_2O$	189.8 ± 31.6	222.3 ± 45	345.3 ± 48.7	0.6
10	MeOH/Et_2O	11	183–184	$C_{23}H_{27}NOClF{\cdot}0.4H_2O$	124.4 ± 16.5	51.4 ± 9.0	176.8 ± 36.0	0.7
12	None	33	128–129	$C_{23}H_{26}NO_2F{\cdot}0.25H_2O$	2.3 ± 0.28	3.2 ± 1.4	19.1 ± 2.3	0.12
13	MeOH/Et_2O	54	142–143	$C_{20}H_{24}N_2OCl_3F{\cdot}0.2H_2O$	253.5 ± 38.9	403.9 ± 66.0	17.5 ± 1.98	14.5
14	MeOH/Et_2O	44	257–258	$C_{21}H_{22}NO_2Cl_2F{\cdot}0.2H_2O$	1231 ± 144.8	>10,000	789 ± 363	1.6
15	MeOH/Et_2O	59	110–111	$C_{20}H_{22}NOCl_2F{\cdot}0.25H_2O$	1050 ± 209.3	172.4 ± 33	1015 ± 178.9	1.03

[a] All compounds reported are HCl salts and each passed CHN analysis within 0.4% of the theoretical values.

[b] Radioligand binding studies were conducted by NIMH DPSP and reported here as mean K_i ± SEM of four determinations. For compounds **1**, **2**, and **6**, data previously reported.

[c] Data previously reported in Ref. 8.

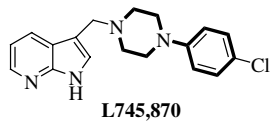
[d] Data previously reported in Ref. 10. Dopamine receptor binding assays were performed using cloned receptor preparations as previously described.[12]



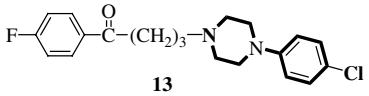
Scheme 2. Reagents and conditions: (i) AcOH (17.4 M), HCl (12 M), reflux, 2.5 h, 100%; (ii) 10% Pd/C, H_2 (65 psi), MeOH, 1.5 h, rt, 100%; (iii) 4-chloro-4-fluorobutyrophenone, KI, K_2CO_3, DME (anhydrous), N_2, reflux, 12 h, yields (**8** = 34%, **10** = 11%).

Hence, we synthesized compound **12** using the same approach as indicated above for **2** (Scheme 3), to provide the baseline for comparison of the deoxygenated analogues, **8** and **10**. The physicochemical characterization and binding data of **8**, **10**, and **12** are recorded in Table 1.

The binding data show that deoxygenation of **12** (D2, K_i = 2.3 nM; D4, K_i = 19.1 nM) as expected resulted in significant loss of activity (**10**, D2, K_i = 124.4 nM; D4, K_i = 176.8 nM). The significant contribution of the alcoholic function in these compounds suggests that there may be an interaction (e.g., hydrogen bonding) between the OH group and the dopamine receptor sites. To further explore this possibility, the C–OH group was replaced by a nitrogen atom. Compound **13** was synthesized by simply alkylating the commercially available 4-(4-chlorophenyl)piperazine with the appropriate alkyl halide as previously indicated. Evaluation of the binding affinity of **13** indicates a substantial decrease in affinity (D2, K_i = 254 nM; D4, K_i = 17 nM) at the D2 receptor but not at the D4 receptor. The resulting decrease confirms the lack of the N-atom's capacity to participate in a similar interaction at the D2 receptor subtype. Comparison between **13** and the Merck compound L745,870 shows that the shorter 7-azaindole methylene moiety confers a more significant D4 selectivity.[11]



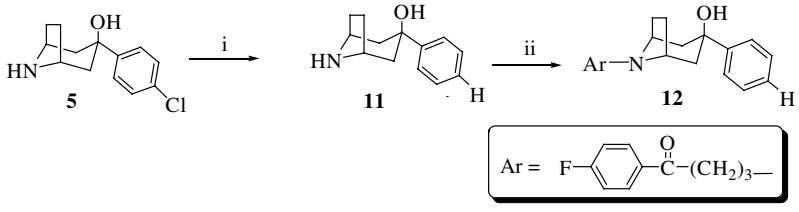
L745,870
D2Ki = 960 nM
D4Ki = 0.43 nM



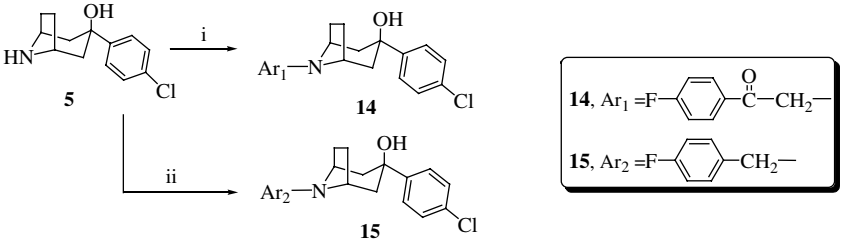
13
D2Ki = 254 nM
D4Ki = 17 nM

Thus, it was of interest to shorten the butyrophenone chain in compound **2** to explore the possibility that D4 selectivity might be conferred on the tropane analogues as well (Scheme 4). Compounds **14** and **15** were synthesized to accomplish this goal according to Scheme 4 below.

Binding affinity at the dopamine receptors[11,12] (Table 1) shows that shortening of the butyrophenone chain length not only resulted in decrease in affinity for both



Scheme 3. Reagents and conditions: (i) 10% Pd/C, H_2 (65 psi), MeOH, 2 h, rt, 88%; (ii) 4-chloro-4-fluorobutyrophenone, KI, K_2CO_3, DME (anhydrous), N_2, reflux, 18 h, 33%.



Scheme 4. Reagents and conditions: (i) 2-chloro-4-fluoroacetophenone, KI, K_2CO_3, DME (anhydrous), N_2, reflux, 18 h, 44%; (ii) 4-fluorobenzylbromide, KI, K_2CO_3, DME (anhydrous), N_2, reflux, 18 h, 59%.

D2 and D4 receptors but also did not result in D4 selectivity. Thus, the physicochemical characteristics of the azaindole methylene moiety rather than the phenyl to N distance may be a contributing factor in the affinity and selectivity of L745,870 for the D4 receptor.

In summary, our data suggest that the pharmacophore-relevant conformation of the alcoholic function in haloperidol is axial, and the OH group while not essential for binding at the D2 receptor enhances binding affinity in a significant manner. With the limited data available, one is led to suggest that the azaindole methylene moiety appears to confer D4 binding selectivity to an appropriate phenyl amine moiety such as the phenylpiperazine moiety in L,745,870.

Acknowledgements

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