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Further evaluation of the tropane analogs of haloperidol

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ABSTRACT

Previous work from our labs has indicated that a tropane analog of haloperidol with potent D_2 binding but designed to avoid the formation of MPP^+-like metabolites, such as 4-(4-chlorophenyl)-1-(4-(4-fluorophenyl)-4-oxobutyl)pyridin-1-ium ($BCPP^+$) still produced catalepsy, suggesting a strong role for the D_2 receptor in the production of catalepsy in rats, and hence EPS in humans. This study tested the hypothesis that further modifications of the tropane analog to produce compounds with less potent binding to the D_2 receptor than haloperidol, would produce less catalepsy. These tests have now revealed that while haloperidol produced maximum catalepsy, these compounds produced moderate to low levels of catalepsy. Compound **9**, with the least binding affinity to the D_2R, produced the least catalepsy and highest Minimum Adverse Effective Dose (MAED) of the analogs tested regardless of their affinities at other receptors including the 5-$HT_{1A}R$. These observations support the hypothesis that moderation of the D_2 binding of the tropane analogs could reduce catalepsy potential in rats and consequently EPS in man.

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Haloperidol is an effective antipsychotic medication that is used to treat schizophrenia; however, it is associated with producing short and long term extrapyramidal side effects (EPS), that is, Parkinsonism-like symptoms. These adverse effects may be due to its potent binding at the D_2 receptor and/or its metabolism into quaternary pyridinium species, such as $BCPP^+$ and $RHPP^+$[1–4] (Fig. 1).

Previous studies in our laboratories have shown that modifications in the butyrophenone and the piperidine moieties of haloperidol significantly altered its binding affinities at the D_2, D_4, and 5-HT_{1A} receptors.[1,5,4] Modifications of the piperidine ring resulting in D_2 receptor binding profiles that are similar or better than haloperidol and which could not form toxic pyridinium metabolites, were also identified.[4,6,7] These studies have indicated that adding an ethylene bridge to the piperidine moiety to form a tropane analog, maintained or increased affinity for the D_2 receptor subtype. It was also observed that replacement of the carbonyl functional group in haloperidol with an oxygen or a sulfur atom retains D_2 binding and increases affinity at the 5-HT_{1A} receptor, indicating that the carbonyl group is not essential for binding at the D_2R but can be replaced with other groups to produce compounds that bind with high affinity to the receptors associated with antipsychotic properties.[8]

While the tropane analog of haloperidol (**5**) appears to have a better binding profile than haloperidol, in vivo studies in our hands have confirmed that its similar potent antagonism at the D_2R subtype resulted in very significant catalepsy in rats.[5,9] Thus, it was of interest in this study, to further test the hypothesis that moderation of the binding affinity at the D_2 receptor could attenuate catalepsy in the tropane analogs of haloperidol. To test this hypothesis, we modified the fluorobutyrophenone moiety while replacing the piperidinol with 3-tropanol to obtain compounds **2**–**10** as shown in Figure 2 and then evaluated their binding affinities at receptors associated with antipsychotic activity, that is, D_1 and D_2-like receptors, 5-$HT_{1A}R$, 5-$HT_{2A}R$ and 5-HT_7R (Table 1). Subsequently, binding affinities at off-target receptors were also evaluated and reported in Table 2.

The syntheses of compounds **2**-**7** were previously reported.[8–10] The alkylating agent, (3-chloropropyl)(4-fluorophenyl)sulfane, was prepared using the procedure in our previously published paper,[8] with slight modification, by refluxing 4-fluorobenzenethiol and 1-bromo-3-chloropropane in the presence of K_2CO_3 in *i*PrOH. The other two alkylating agents were similarly prepared by using the corresponding *n*-fluorobenzenethiol. The target compounds, **8**–**10** were obtained by alkylating 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol, in the presence of K_2CO_3, KI and DME with the appropriate alkylating agent as shown in Scheme 1.

The first modifications to moderate the D_2R binding involve replacement of the carbonyl group in haloperidol and the results

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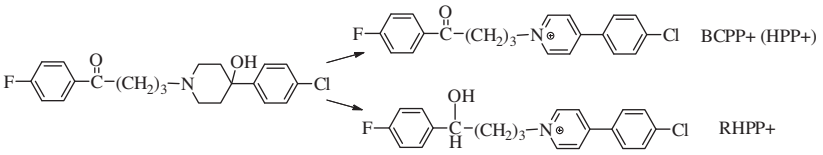


Figure 1. Quaternary pyridinium metabolites of haloperidol.

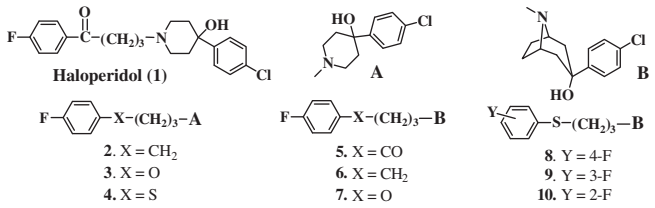


Figure 2. Structures of compounds evaluated.

are reported in Table 1. Deoxygenation (**2**), replacement with oxygen (**3**) or sulfur (**4**) resulted in significant improvements in binding to the 5-HT_{1A}, D_1 and D_4 receptors. Affinity however, was decreased at the 5-HT_7R while binding to the D_2 and 5-HT_{2A} receptors remained about the same except for the deoxygenated compound (**2**) which had a 27-fold decrease at the D_2 receptor (K_i = 24 nM, haloperidol K_i = 0.89 nM). The next compounds (**5**–**8**), the tropane analogs of haloperidol and compounds **2**–**4**, were also screened at the same receptors and the results are also presented in Table 1. The methylene (**6**) and the oxygen (**7**) analogs had similar binding across all 7 receptors of interest (Table 1); however, their affinities were significantly lower than those of the previously reported carbonyl analog (**5**). The binding affinities of compound **8**, the sulfur analog of **6** and **7**, turned out to be generally more potent at the primary receptors of interest, that is, D_2, 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors. Thus, compound **8** was selected for further investigation.

Having been aware that replacement of the fluorine atom on the butyrophenone moiety with other substituents resulted in significant changes in binding affinities,[8] we synthesized the other

Table 1
Binding affinities expressed as mean K_i ± SEM (nM) of the analogs at CNS receptors[22]

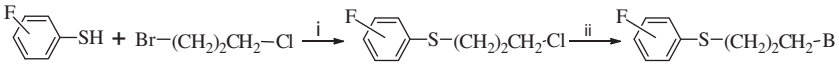
Compound	Binding affinities (K_i ± SEM) in nM at relevant CNS receptors							
	5-HT_{1A}	5-HT_{2A}	5-HT_7	D_1	D_2	D_3	D_4	D_5
Haldol (**1**)	3600	120	ND	120	0.89	2.5	10	ND
2	658 ± 50	302 ± 23	1042 ± 45	130 ± 11.0	24 ± 2.0	668 ± 39	1.5 ± 0.1	414 ± 34
3	317 ± 29	72±7	656 ± 29	22.0 ± 1.0	8.8 ± 1.0	49.0 ± 1.7	4.3 ± 0.2	103 ± 5
4	74.0 ± 6.0	93 ± 10	1044 ± 52	27.0 ± 2.0	5.3 ± 0.3	182 ± 22	2.4 ± 0.1	113 ± 9
5[a]	27.7 ± 8.0	30.9 ± 6.0	ND	ND	0.31	0.71	12.0	ND
6	102 ± 0.7	317 ± 2	472 ± 5	>10K	33 ± 0.26	9.7 ± 0.1	9.4 ± 0.1	>10K
7	123 ± 2	236 ± 1	420 ± 4	>10K	22 ± 0.17	4.10 ± 0.03	49.0 ± 0.5	>10K
8	20.0 ± 0.2	89.0 ± 1.4	97.0 ± 1.0	347 ± 5	2.9 ± 0.31	0.70 ± 0.00	8.9 ± 0.04	MT
9	13.0 ± 0.1	509 ± 7	917 ± 11	MT	27 ± 0.36	11.0 ± 0.1	28.0 ± 0.3	MT
10	8.2 ± 0.1	115 ± 1	882 ± 9	4093 ± 68	4.8 ± 0.04	1.3 ± 0.01	27.0 ± 0.2	MT
Olanzapine[b]	2100	3.3	NA	52	20	45	50	NA

ND = not determined; NA = not available; MT = missed assay threshold of 50% inhibition.
[a] Previously reported in Ref. 9 except at 5-HT_{1A}R and 5-HT_{2A}R.
[b] Data from Ref. 12.

Table 2
Binding affinities expressed as mean K_i ± SEM (nM) for the compounds at off-target receptors[22]

Compound	Binding affinities (K_i ± SEM) in nM						
	5-HT_{2B}	5-HT_{2C}	H_1	M_1–M_3	DAT	NET	SERT
Haldol (**1**)	NA	4700	440	ND	ND	5500	1800
2	723 ± 65	MT	128.5 ± 17.5	MT	MT	1225 ± 87	1867 ± 146
3	1622 ± 134	>10K	698.6 ± 91.7	MT	>10K	3959 ± 471	2228 ± 187
4	790 ± 68	MT	115.0 ± 9.7	MT	497 ± 28	2249 ± 239	160 ± 24
5	ND	872 ± 178	8780 ± 1625	ND	ND	ND	ND
6	1381 ± 23	2434 ± 44	1719 ± 30	MT	778 ± 10	MT	414 ± 6
7	898	MT	4149 ± 14	MT	620 ± 9	1791 ± 28	255 ± 2
8	1057 ± 14	1498 ± 26	977 ± 16	MT	1081 ± 11	1409 ± 19	316 ± 4
9	270 ± 2	1861 ± 20	1207 ± 16	MT	285 ± 4.38	510 ± 5	227 ± 3
10	520 ± 5	1122 ± 15	1009 ± 10	MT	354 ± 11	462 ± 5	102 ± 0.6

ND = not determined; MT = missed assay threshold of 50% inhibition.
Ki values without the associated SEM, are within 20% of the mean value.



Scheme 1. Reagents and conditions: (i) *i*PrOH, K_2CO_3, reflux 12 h; (ii) 3-(4-chlorophenyl)-8-azabicyclo[3.2.1]octan-3-ol (B), DME, KI, K_2CO_3, 100 °C, reflux, 12 h.