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ENHANCEMENT OF BINDING OF QUATERNARY AMMONIUM DERIVATIVES OF CHLORPROMAZINE TO DOPAMINE D-2 RECEPTORS BY THE ADDITION OF A H-BONDING GROUP

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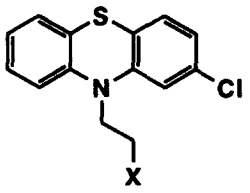
Abstract: Several permanently charged analogs of chlorpromazine were synthesized and evaluated for their binding to dopamine D-2 receptors.

In order to determine the molecular species, charged or uncharged, of dopamine agonists and antagonists that interact with the dopamine receptor, we have previously synthesized and studied permanently charged analogs of dopamine[1] and chlorpromazine (**1**)[2] on D-2 dopamine receptors in the striatum. Our results show that the quaternary ammonium (**2**) and sulfonium (**3**) compounds bind and produce agonist and antagonist activity while the permanently uncharged methyl sulfide analog (**4**) was devoid of either agonist or antagonist activity.

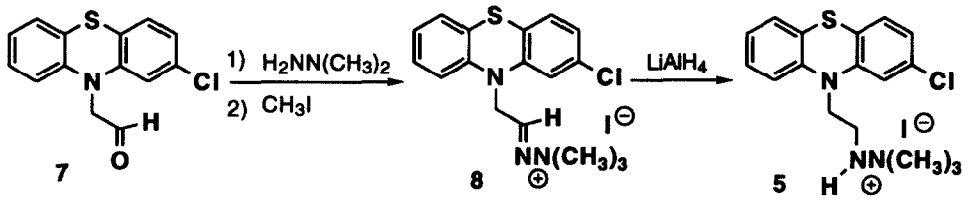


1 X = $CH_2N(CH_3)_2$
2 X = $CH_2\overset{\oplus}{N}(CH_3)_3\ I^{\ominus}$
3 X = $CH_2\overset{\oplus}{S}(CH_3)_2\ I^{\ominus}$
4 X = CH_2SCH_3
5 X = $NH\overset{\oplus}{N}(CH_3)_3\ I^{\ominus}$
6 X = $CH_2\overset{\oplus}{N}(CH_3)_2NH_2\ ^{\ominus}OMes$

However, an interesting observation has been made that, although active, the permanently charged analogs of both agonists and antagonists are less active than the corresponding parent primary, secondary or tertiary amine. One explanation that we have put forth is that permanently

charged agonist or antagonist analogs only bind through an ionic bond with the receptor while protonated amines may bind with the receptor through a reinforced ionic bond (a combination of both an ionic and hydrogen bond) and thus show a higher affinity for the D-2 receptor[3]. We hypothesized that it should be possible to enhance the activity of permanently charged analogs of chlorpromazine by adding a hydrogen bonding functional group in the region of the permanent positive charge. In this paper we report the synthesis of two permanently charged chlorpromazine aza analogs, **5** and **6**, which have the potential for hydrogen bonding, and the comparative binding of these analogs to that of parent chlorpromazine (**1**) and the quaternary salt (**2**) on dopamine D-2 receptors.

The synthesis of the aza analog (**6**) of chlorpromazine had been previously reported in the patent literature by Ruder and Prapas[4]. They treated chlorpromazine with either gaseous chloramine or hydroxylamine O-sulfonic acid. For our investigation, the aza analog **6** was prepared in 66% yield using the improved N-amination method reported by Tamura et. al.[5] which involves the treatment of chlorpromazine (**1**) with O-mesitylenesulfonylhydroxyl amine.



The target compound **5** was prepared from the aldehyde **7** previously reported by Corral et al.[6] Treatment of **7** with dimethylhydrazine in absolute ethanol at reflux for three hours gave a quantitative yield of the hydrazone. The formation of the trimethylhydrazonium analog **8** was very sensitive to solvent effects. Treatment of the hydrazone with methyl iodide in acetone at room temperature overnight gave a 69% yield of the desired product **8** (mp 139-140). Use of methyl iodide alone or methyl iodide in ethanol at room temperature or at reflux gave very low yields (<7%) of the desired trimethylhydrazonium salt.Treatment of **8** with 2 equivalents of $LiAlH_4$ in refluxing diethyl ether gave a 48% yield of **5** (mp 189 °C).

In the present study we have compared the potency of the permanently charged aza analogs, **5**

and **6**, and the permanently charged trimethylammonium analog (**2**) with chlorpromazine (**1**) in inhibiting the binding of [^{3}H]-spiperone to the D-2 receptors in rat striatal membranes as shown in Table 1. Since the aza analogs are permanently charged and bind to the D-2 receptor, these observations show further support for the concept that it is the charged form of antagonists that bind to the dopamine D-2 receptor.

Table 1

Effect Of Chlorpromazine (**1**) and Analogs (**2, 5** and **6**) On the Binding Of [^{3}H]-Spiperone To D-2 Dopaminergic Receptors

DRUG	N	[^{3}H]-Spiperone Binding (Ki) μM
1	4	0.05±0.01
2	3	8.57±0.52
5	3	4.88±0.16
6	4	0.82±0.06

Values are the mean ± S.E.M. and N is the number of experiments

Both of the aza analogs which have an additional amine group incorporated into the molecule for intermolecular hydrogen bonding to the receptor were more active than **2** in binding to the dopamine D-2 receptor (Figure 1). Thus, we propose that a combination ionic and hydrogen bond occurs with the aza analogs, **5** and **6**, in their interaction with the D-2 receptor, while only an ionic bond takes place with **2**. Since chlorpromazine was more active than the analogs, this strongly suggests that the optimal binding takes place when the proton involved in hydrogen bonding and the permanent positive charge are on the same nitrogen atom. These results suggest that both ionic and hydrogen bonding are important in the interaction with the aspartic acid residue found on the dopamine D-2 receptor[7].

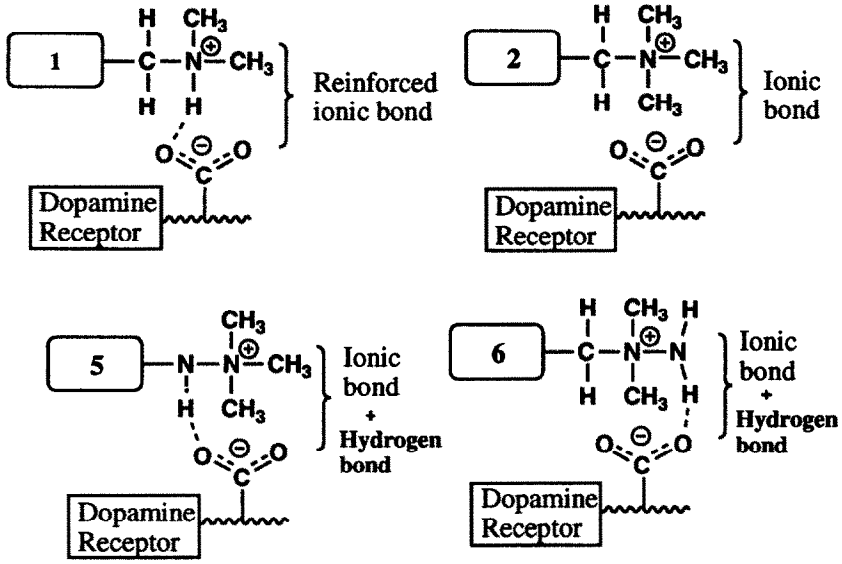


Figure 1. Illustration of possible H-bonding with Chlorpromazine (**1**) and analogs **2**, **5** and **6** with a carboxylic acid from aspartic acid on the dopamine D-2 receptor.

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