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Synthesis and Binding Affinity of 2,3,3a,4,9,9a-Hexahydro-9,4-(Iminomethano)-1H-benz[f]indenes. Ligands for the PCP Site of the NMDA Receptor.

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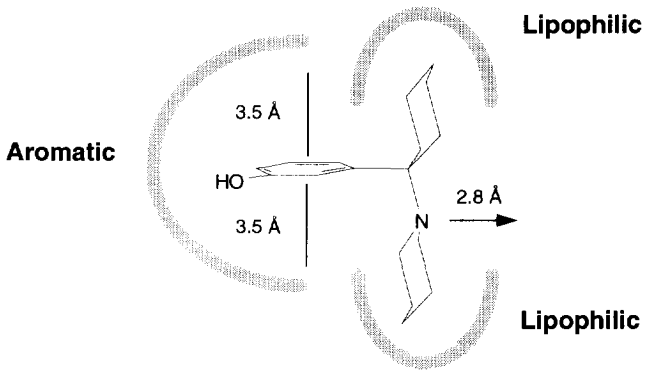
Abstract: A series of 2,3,3a,4,9,9a-hexahydro-9,4-(iminomethano)-1H-benz[f]indenes was prepared and their ability to displace [^{3}H]TCP was measured. The 5-amino derivatives **5** and **12b** were the most potent members of this series with K_i values of 14 nM and 8 nM respectively. The orientation of the cyclopentane ring was crucial for binding potency, with the *endo* isomer **12a** >10 times more potent than the *exo*-isomer **13**.

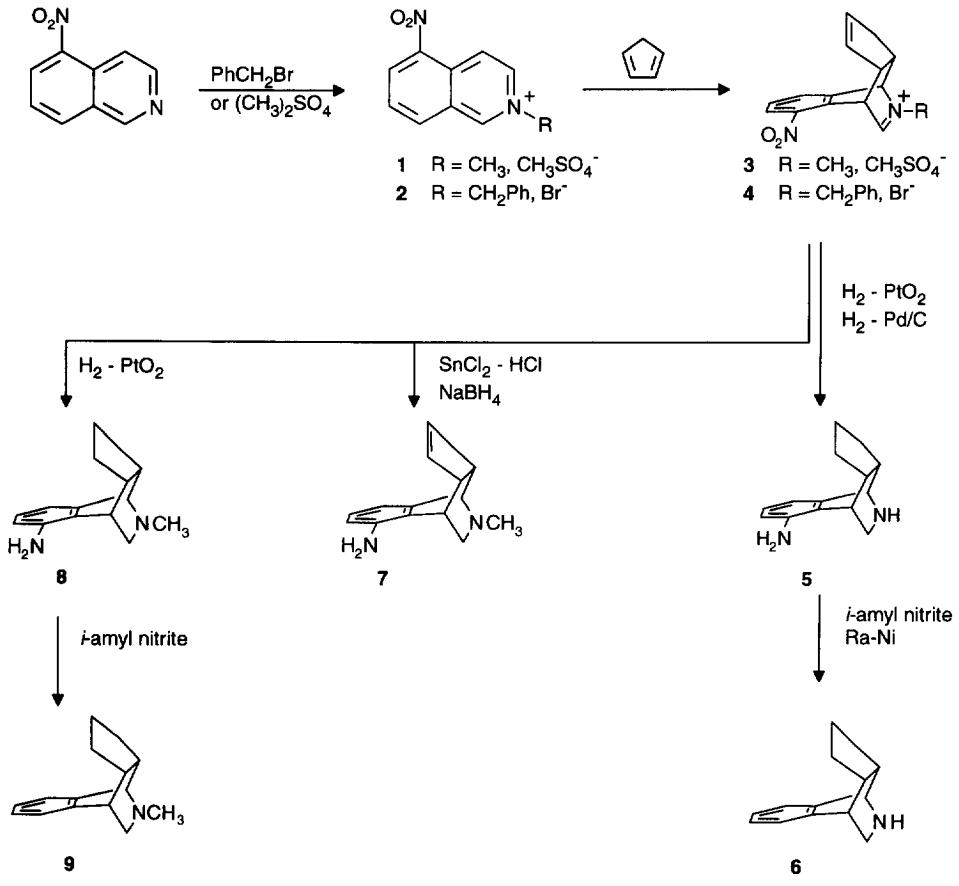
Introduction

Modulation of the NMDA receptor ion channel is of continuing interest for the treatment of a variety of neurological diseases. In particular, a blockade of this ion channel reduces the influx of Ca^{2+} and thus has potential utility in treating epilepsy and cerebral ischemia.[1-7] For our studies, we sought to develop ligands with a high affinity for the PCP site located inside the NMDA receptor ion channel. A recently proposed model of the PCP binding site has a required hydrogen bonding interaction 2.8 Å from the nitrogen atom as well as additional features that include two lipophilic clefts and an additional optional hydrogen bonding site (Figure 1).[8] A series of conformationally fixed dibenzoalkenimines were used to furthur refine this model.[9] Potent PCP ligands include m-hydroxy-PCP, (+)-MK-801, TCP, hexahydrobenzo[b]quinolizidines,[10] and 6,11-ethanobenzo[b]quinolizinium cations.[11] Many of these ligands occupy both lipophilic clefts of the Andrews model.[8] In particular, the hexahydrobenzo[b]quinolizidines[10] clearly occupy all the lipophilic sites of this model. The current series of compounds is an extension of this work in which the lower lipophilic cleft is essentially unoccupied, thus defining some minimal structural requirements for the binding of these classes of compounds to the PCP receptor.

Figure 1 Model for the PCP site of the NMDA receptor.



Scheme 1

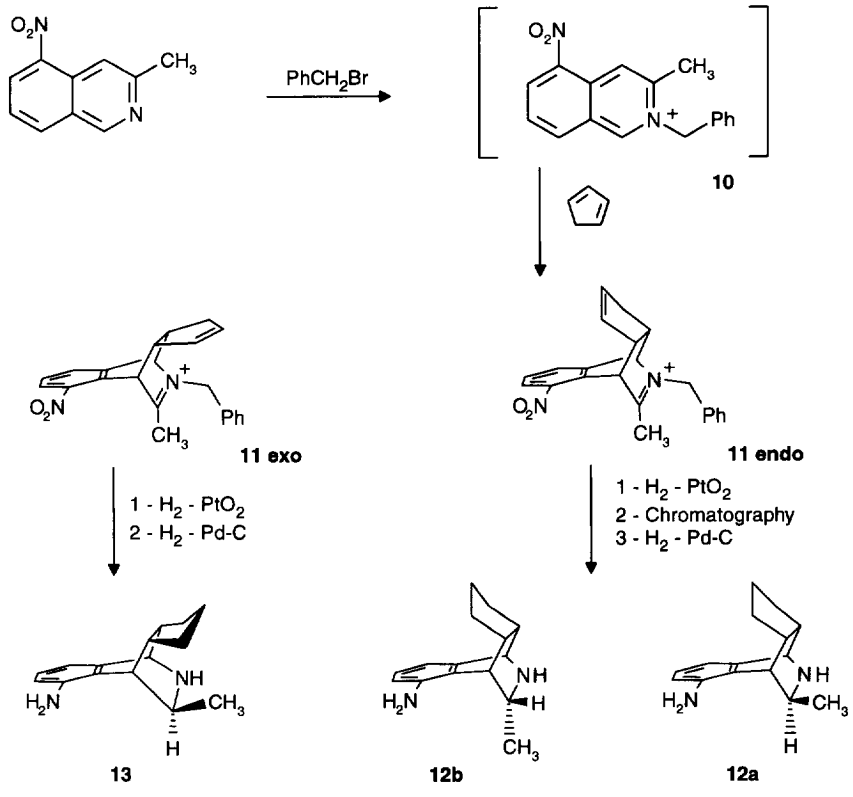


Chemistry

The preparation of the target hexahydro-9,4-(iminomethano)-1H-benz[f]indenes is outlined in Scheme 1. Isoquinolinium salts **1** and **2** were treated with cyclopentadiene to give the Diels-Alder adducts **3** and **4**.[12] The adduct derived from the methylisoquinolinium salt **3** was reduced stepwise with stannous chloride in HCl followed by $NaBH_4$ to give the unsaturated derivative **7**. Hydrogenation of **3** (H_2-PtO_2) effected complete reduction to **8**. When the catalytic hydrogenation was applied to the N-benzyl salts **4**, it was necessary to follow the PtO_2 catalyst with Pd-C in order to effect debenzylation giving derivative **5**. Both **5** and **8** were deaminated using *i*-amyl nitrite in THF or dioxane to give **6** and **9** respectively. This deamination method is believed to involve the formation of an aryl radical which abstracts hydrogen from the reaction solvent.[13] The 11-methyl derivatives **12a**, **12b**, and **13** were obtained (Scheme 2) by treating 3-methyl-5-nitroisoquinoline with benzylbromide in acetonitrile to give **10** (not isolated) followed by cyclopentadiene. Based on the analysis of the isolated product mixture, this [4+2] addition gave a product distribution of 8.4:1 *endo* to *exo*. The endo

isomer of **11** was hydrogenated using PtO_2 to give a mixture of the corresponding isomeric benzyl amines. The isomers were separated and debenzylated (H_2 Pd-C) to give **12a** and **12b**. The *exo* isomer was hydrogenated (H_2-PtO_2, then H_2 Pd-C) to give **13** as the only product. Apparently steric factors influence the facial selectivity in reduction of the *exo* isomer.

Scheme 2

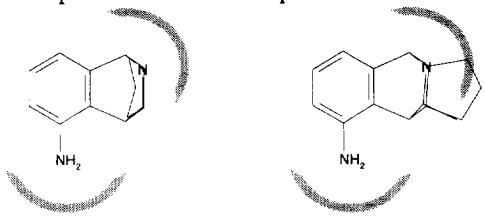


Results and Discussion

The most active member of this series of compounds is **12b** with a K_i of 8 nM (Table 1). This compound contains an amino group to accommodate the proposed additional hydrogen bonding site in the receptor, as well as a methyl group to partially fill the lower lipophilic cleft. The role of the primary amino group in this series of compounds would be to occupy the "optional" hydrogen bonding site in this receptor.[8] When **9** (Table 1) is compared to its amino substituted analog **8**, the binding affinity of the amino derivative is 5 fold greater. Similarly, amine **5** is 3 times more active than its deaminated counterpart **6**. Without a methyl group at the 11-position of this ring system (R_2=R_3=H) as in **6**, binding affinity is only slightly lower suggesting that filling the lower pocket of this site is helpful but not crucial for binding. When the orientation of the methyl group is

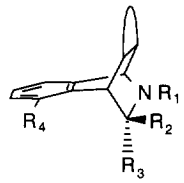
changed with **12a**, the activity drops over 10 fold. Presumably either the methyl group in this orientation is less adequately accommodated by the receptor site or the required H-bonding interaction to the adjacent nitrogen is obstructed (Figure 2). When the cyclopentane ring is in the *exo* orientation (**13**) this situation is exacerbated and binding drops substantially. When the ring nitrogen carries a methyl group, activity is over 15 times lower than their NH counterparts confirming that access to this nitrogen is important.

Figure 2 Comparison of the steric requirements of **12b** and **13**.



12b **13**

Table 1 Binding Affinity of Selected Ligands and Reference Compounds for the PCP Receptor Site[15]



No.[16]	R_1	R_2	R_3	R_4		Ring	K_i nM[17]	± SEM	n
PCP							38	1	53
(+)MK-801							2.2	0.2	5
8	CH_3	H	H	NH_2	endo		226	47	3
7	CH_3	H	H	NH_2	endo		701	194	3
5	H	H	H	NH_2	endo		14	4	3
9	CH_3	H	H	H	endo		1142	204	3
6	H	H	H	H	endo		52	10	3
12b	H	H	CH_3	NH_2	endo		8	3	3
12a	H	CH_3	H	NH_2	endo		89	11	3
13	H	CH_3	H	NH_2	exo		1204	106	3

Conclusion

From the compounds in this study, the optimal structure will occupy *both* lipophilic clefts in a manner consistent with allowing the necessary nitrogen-receptor hydrogen bond. Additionally, the optimized structure will avoid unfavorable steric/lipophilic interactions with the wall of the pockets in this receptor. Ideally, a provision should be made for a group to interact with the additional hydrogen bonding site that appears to be available in this receptor.

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16 Analytical data for new compounds: **3**, mp 133-136.5 °C (lit.[12] oil), Anal. Calc. for $C_{16}H_{18}N_2O_6S$, C - 52.45, H - 4.95, N - 7.65, S - 8.75, found C - 52.80, H - 4.97, N - 7.65, S - 8.43; **4**, mp 210 °C decomp., Anal. Calc. for $C_{21}H_{19}BrN_2O_2$, C - 61.33, H - 4.66, N - 6.81, found C - 60.92, H - 4.36, N - 6.49; **5**, mp 188-190 °C, Anal. Calc. for $C_{14}H_{18}N_2$, C - 78.46, H - 8.46, N - 13.07, found C - 78.27, H - 8.34, N - 13.08; **6**, mp 230-235 °C, Anal. Calc. for $C_{14}H_{17}N{\cdot}HCl$, C - 71.33, H - 7.69, N - 5.94, Cl - 15.04, found C - 70.53, H - 7.75, N - 5.83, Cl - 15.11; **7**, mp 136-137 °C, Anal. Calc. for $C_{15}H_{18}N_2$, C - 79.61, H - 8.02, N - 12.38, found C - 79.46, H - 7.90, N - 12.39; **8**, mp 160-162.5 °C, Anal. Calc. for $C_{15}H_{20}N_2$, C - 78.90, H - 8.83, N - 12.27, found C - 79.10, H - 8.98, N - 12.34; **9**, oil, CIMS (CH_4) m/z 214 [M+H], Anal. Calc. for $C_{15}H_{19}N$, C - 84.46, H - 8.98, N - 6.57, found C - 82.49, H - 8.81, N - 6.52; **12a**, mp 180-181 °C, Anal. Calc. for $C_{15}H_{20}N_2$, C - 78.90, H - 8.83, N - 12.27, found C - 78.90, H - 8.80, N - 12.32; **12b**, mp 140-142 °C, Anal. Calc. for $C_{15}H_{20}N_2$, C - 78.90, H - 8.83, N - 12.27, found C - 78.93, H - 8.85, N - 12.28; **13**, mp 140-143 °C, Anal. Calc. for $C_{15}H_{20}N_2$, C - 78.90, H - 8.83, N - 12.27, found C - 78.96, H - 8.86, N - 12.56.

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