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6,7,8,9-TETRAHYDRO-3-HYDROXY-1*H*-1-BENZAZEPINE-2,5-DIONES VIA A DIELS–ALDER REACTION:ANTAGONISTS WITH A NON-PLANAR HYDROPHOBIC REGION FOR NMDA RECEPTOR GLYCINE SITES

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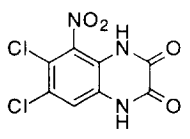
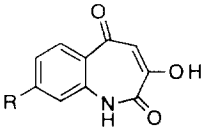
Abstract: Benzazepines **10a**, **10b** and **12** were prepared via a Diels-Alder reaction of dienes **5a** and **5b** with **6** followed by a Schmidt reaction on **9a**, **9b** and **11** then demethylation. The potencies of **10b** and **12** for NMDA receptor glycine sites demonstrate binding site tolerance to antagonists with a non-planar hydrophobic region.

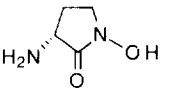
Antagonists for NMDA receptor glycine sites such as **1**[1] and **2a**[2] are of interest as potential drugs for the treatment of stroke. With the exceptions of R-(+)-HA-966 (**3**), its analogs,[3] and the recently reported 5,6,7,8-tetrahydroquinolones as exemplified by **4**,[4] a common structural feature of such antagonists is an aromatic ring system fused to a heterocycle. This confers planarity to the carbon skeleton in the hydrophobic region. To investigate these receptors' tolerance to non-planarity in this region,[5] we prepared three tetrahydro analogs of **2** (i.e., **10a**, **10b** and **12**) and determined their glycine binding site potencies.



1



2a R = Cl, **2b** R = H



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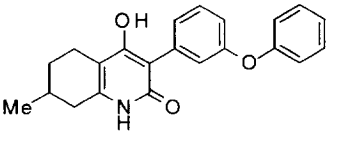
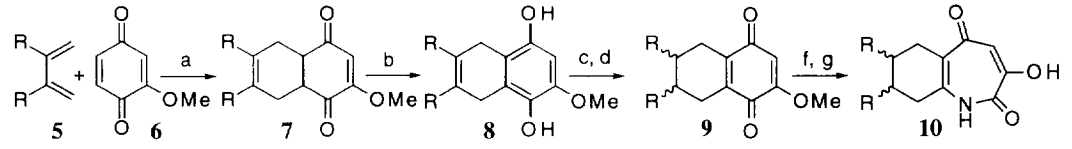


4

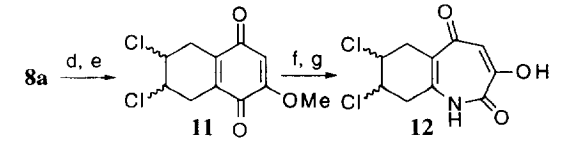
Synthetic flexibility was obtained by employing a Diels-Alder strategy. Thus, reaction of **6**[6] with 1,3-butadienes **5a** and **5b** gave adducts **7a** and **7b**. Enolization to hydroquinones **8a**[7] and **8b**[8] followed by hydrogenation and subsequent oxidation gave tetrahydronaphthoquinones **9a**[9] and **9b**. Alternatively, oxidation of **8a** followed by chlorination gave the dichloroquinone **11**. A Schmidt reaction on **9a**, **9b** and **11** followed by demethylation of the resulting enol ethers gave the desired benzazepines **10a**, **10b** and **12**.[10] The accompanying stereo representation derived from a single crystal X-ray analysis of **10a** illustrates the non-planar nature of the tetrahydrobenzene moiety. NMR analysis indicates that compound **10b** is a diastereomeric mixture while compound **12** is diastereomerically pure.



5 **6** **7** **8** **9** **10**

a R = H, **b** R = Me

Key: a: toluene, Δ; b: K_2CO_3, MeOH under N_2 then HCl/H_2O; c: H_2, Pd/C, MeOH; d: $NaIO_4$, $H_2O/CHCl_3$; e: Cl_2, $CHCl_3$; f: NaN_3, H_2SO_4 or CF_3SO_3H; g: BBr_3, CH_2Cl_2.



11 **12**

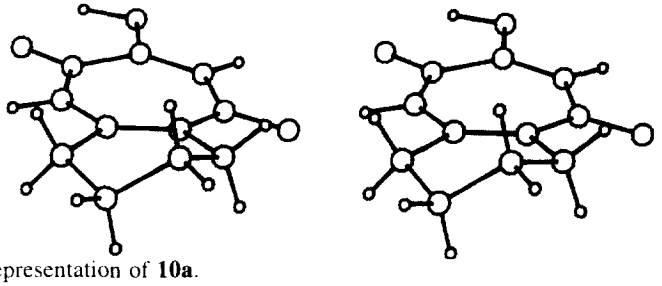


Figure 1. Stereo Representation of **10a**.

Binding potencies were obtained using a [^{3}H]5,7-dichlorokynurenic acid (DCKA) competitive binding assay (three determinations).[11] The IC_{50} value of **10a** (3,205 ± 257 nM) was considerably poorer than that of **2a** (13 ± 2 nM) and **2b**[12] (827 ± 60 nM). However, the addition of substituents as in **10b** and **12** improves the binding potency (IC_{50} values of 228 ± 37 nM and 131 ± 12 nM, respectively). The enhanced binding potency of **10b** and **12** relative to **10a** correlates with the structure-activity relationship observed for benzazepine antagonists such as **2a**, **2b** and other reported analogs.[2,12] The binding data for **10b** and **12** demonstrate receptor tolerance for benzazepine antagonists with a non-planar hydrophobic region.

Additional derivatives with further modifications in the tetrahydrobenzene portion are being prepared. The Diels-Alder route allows for modification through the use of substituted and cyclic 1,3-dienes, and by various derivatizations of the double bond formed as a result of the cycloaddition reaction. A full account of our research will be presented in a future publication.

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9. mp of **9a**: 167.5-168.5 °C. An earlier synthesis (Cunningham, J.; Haslam, E.; Haworth, R. D. *J. Chem. Soc.* **1963**, 2875; mp 172 °C) employed a high pressure hydrogenation of the naphthalene ring system.
10. Physical and spectral properties. **10a**: mp 237-238 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.43-1.62 (m, 4 H), 2.23-2.31 (m, 2 H), 2.40-2.50 (m, 2 H), 6.30 (s, 1 H), 10.14 (s, 1 H), 10.83 (s, 1 H). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74, N, 7.25. Found: C, 62.23; H, 5.62; N, 7.26. **10b**: mp 242-243 °C (dec); ^{1}H NMR (DMSO-d_6) δ 0.72-0.96 (m, 6 H), 1.69-1.90 (m, 2 H), 1.98-2.65 (m, 4 H) 6.29 (s, 1 H), 10.15 (bs, 1 H), 10.82 (s, 1 H). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83, N, 6.33. Found: C, 65.47; H, 6.87; N, 6.32. **12**: mp 246-248 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.70 (dd, J = 18 and 5.6 Hz, 1 H), 2.91 (dd, J = 19 and 5.4 Hz, 1 H), 3.06 (dd, J = 18 and 4.8 Hz, 1 H), 3.26 (dd, J = 19 and 4.6 Hz, 1 H), 4.50-4.69 (m, 2 H), 6.34 (s, 1 H), 10.46 (s, 1 H), 11.11 (s, 1 H). Anal. Calcd for $C_{10}H_9Cl_2NO_3$: C, 45.83; H, 3.46, N, 5.34. Found: C, 46.02; H, 3.54; N, 5.26.
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