Bioorganic & Medicinal Chemistry Letters, Vol.3, No.1, pp. 49-54, 1993
Printed in Great Britain

0960-894X/93 $5.00 + .00

SYNTHESIS AND BIOLOGICAL ACTIVITY OF CONFORMATIONALLY CONSTRAINED 4a-PHENANTHRENEAMINE DERIVATIVES AS NONCOMPETITIVE NMDA ANTAGONISTS

Thomas C. Malone*, Daniel F. Ortwine, Graham Johnson[1] and Albert W. Probert, Jr.

Parke-Davis Pharmaceutical Research Division
Warner Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48105

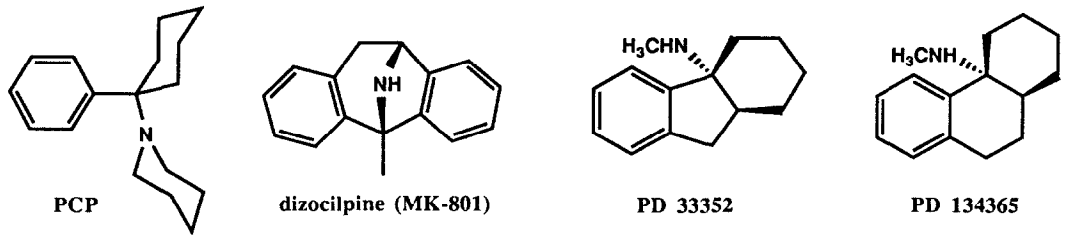
Abstract. *The syntheses, biological activity, and molecular modeling of conformationally constrained derivatives of cis-1,3,4,9,10,10a-hexahydro-N-methyl-4a(2H)-phenanthreneamine (PD 134365), a new conformationally rigid noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, are described.*

Activation of excitatory amino acid receptors by excessive amounts of the central neurotransmitter glutamic acid has been proposed as a key mechanism in a variety of neuropathological conditions. It has been suggested that chronic overactivation of glutamate receptors may be responsible for conditions such as Alzheimer's Disease[2], Parkinsonism[3], Huntington's Disease[4] and Amyotrophic Lateral Sclerosis (ALS)[5], while acute increases in glutamate concentration may be a causative factor for neuronal damage resulting from cerebral ischemia[6] and epilepsy[7]. One attractive target for pharmacological intervention in these neurodegenerative conditions has been the N-methyl-D-aspartate (NMDA) receptor complex.

Several modulatory sites exist on the NMDA receptor[8], and a number of attempts to inhibit NMDA receptor activation through competitive NMDA antagonists, glycine site antagonists, and noncompetitive NMDA receptor antagonists have been reported. Noncompetitive NMDA antagonists exert their effects by blockade of the open state of the receptor operated ion channel in a use-dependant manner[9]. Such antagonists offer several advantages relative to competitive and glycine site antagonists. In contrast to competitive and glycine site antagonists, antagonists such as phencyclidine (PCP) and dizocilpine (MK-801) are lipophilic compounds that can effectively penetrate the CNS (Figure 1). In addition, due to the noncompetitive nature of the ion channel blockade, the compounds need not compete with large amounts of an endogenous ligand (glutamate or glycine) to effect receptor modulation. Unfortunately, these compounds also exhibit behavioral side effects that may limit their eventual usefulness.

As part of a research effort to identify potent and selective noncompetitive NMDA antagonists, a series of 4a-phenanthreneamines was prepared, of which PD 134365[10] showed a favorable pharmacological profile. In an attempt to enhance PCP-site selectivity, a further restriction of the conformational degrees of freedom was envisioned by bridging the nitrogen to the remaining bridgehead carbons in the molecule. To accomplish this, a molecular modeling approach[11,12] has been applied to understand the stereoelectronic requirements at the noncompetitive NMDA receptor. The model was generated by a conformational search and fitting analysis applied to a diverse set of known ligands, including (m-OH)PCP, MK-801, etoxadrol, LY154045, SKF10047, PD 33352 and PD 134365, and refined by including selected PCP, MK-801, PD 33352, and PD 134365

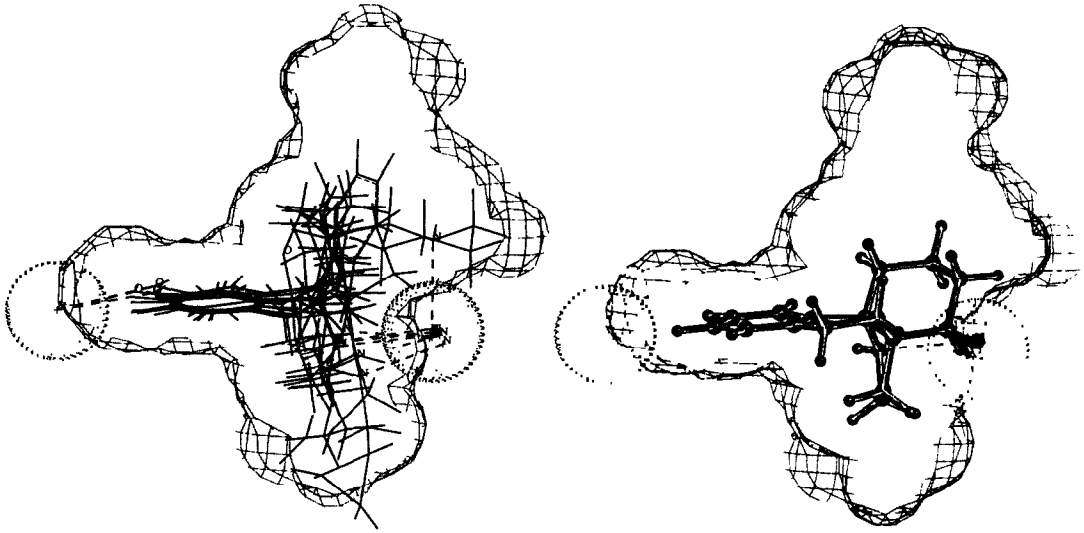
Figure 1. Noncompetitive NMDA Antagonists



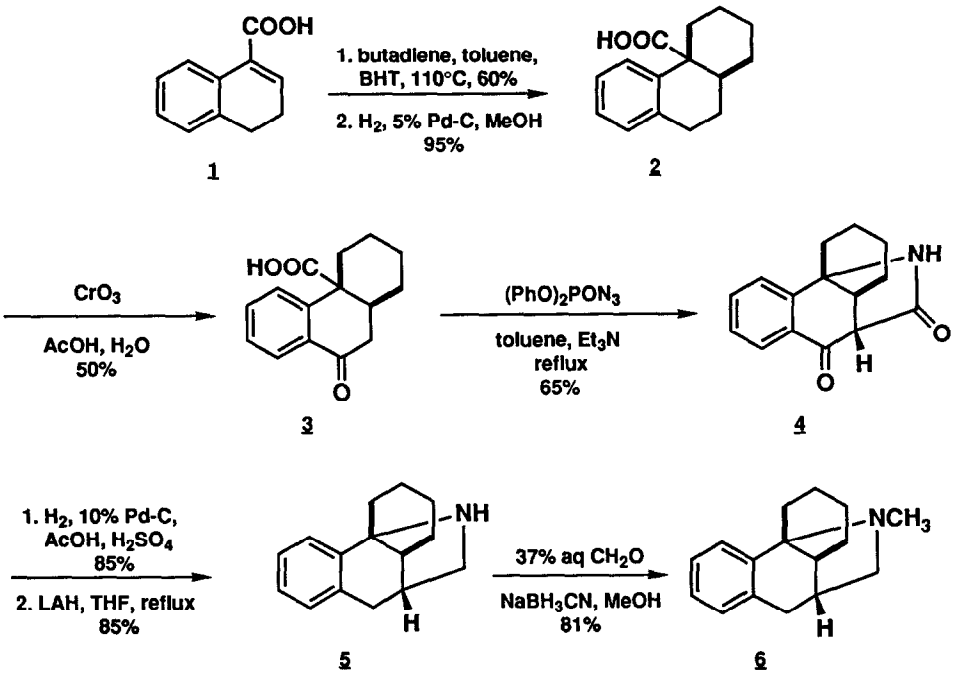
PCP dizocilpine (MK-801) PD 33352 PD 134365

derivatives[13]. The resulting pharmacophore is consistent with published models[14-16], and includes two specific receptor interaction points flanked by regions of excluded volume (Figure 2). Between these points lie areas of lipophilic bulk. Among analogs that fit within the volume confines of the model and interact with the receptor site point(s) at the appropriate angle(s), additional factors such as log P[17,18] play a role in determining affinity. Thus, in general, optimal potency is associated with compounds with a measured log P > 0. The pharmacophore model has provided a rationalization of the SAR observed in the present series, and allowed us to predict which rigid

Figure 2. (left) Superposition of 7 noncompetitive antagonists used in the formation of a pharmacophore model. Two receptor interaction points are included (N atoms surrounded by dots), as is a cut-away view of a portion of the receptor-tolerated volume from the refined model. Consistent with a previous study[15], one of these antagonists (etoxadrol) contains a receptor interaction from a novel angle ("top down", as shown). (right) Fit of **17** in the model. Although it appears that a portion of the cyclohexane ring is projecting into the right-hand binding site region, this is not the case. In the orientation shown, the receptor interaction actually occurs *behind* the lower right portion of the cyclohexane ring.



Scheme 1



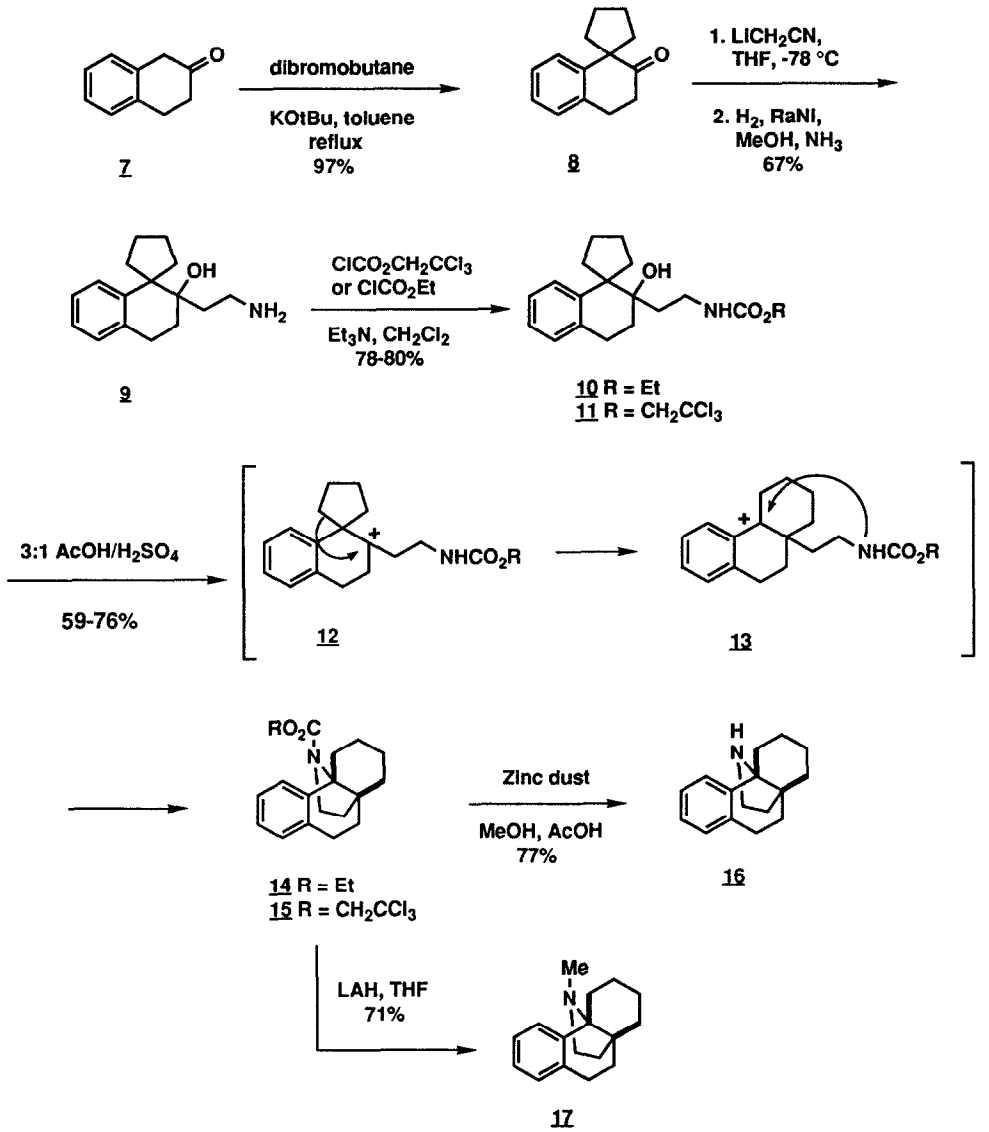
fused ring analogs would be sterically tolerated at the receptor while retaining the basic amine at the appropriate position for optimal interaction with the receptor interaction site point.

Based on synthetic chemistry and modeling considerations, we envisioned that fused ring derivatives such as **6** and **17** would be synthetically accessible while continuing to fit within the confines of the active site region (Figure 2). Moreover, such compounds would be able to present their basic amines in the critical area of space necessary to interact with the receptor atom at an appropriate angle.

Synthesis

The preparation of bridged tetracyclic phenanthrene derivatives **5** and **6** is illustrated in Scheme 1. Diels Alder cyclization of 3,4-dihydronapthalene carboxylic acid (**1**) with butadiene followed by hydrogenation provided the tricyclic carboxylic acid **2**. Benzylic oxidation[19] of **2** with chromium trioxide in acetic acid and water gave tricyclic keto-acid **3**. The key one pot sequence to establish the tetracycle involved treatment of **3** with diphenylphosphorylazide in refluxing toluene and triethylamine resulting in a Curtius rearrangement followed by intramolecular capture of the intermediate isocyanate to give the tetracyclic ketoamide **4**. Removal of the benzylic ketone followed by reduction with lithium aluminum hydride resulted in the tetracyclic amine **5**. Reductive amination of **5** with formaldehyde yielded the N-methyl derivative **6**.

Scheme 2



The synthesis of the alternatively bridged azapropellane type derivatives **16** and **17** relied upon a modification of chemistry originally described by Belleau[20] for the preparation of morphinans (Scheme 2). Spiroalkylation of 2-tetralone (**7**) with dibromobutane provided ketone **8**. Cyanomethylation of **8** with lithioacetonitrile in THF at -78 °C gave the hydroxynitrile, which was reduced to the aminoalcohol **9** with Raney nickel and hydrogen. Treatment of **9** with 2,2,2-trichloroethylchloroformate or ethylchloroformate yielded the

carbamates **10 or 11**. Subsequent treatment with 3:1 acetic acid/sulfuric acid (v/v) resulted in a Wagner-Meerwein rearrangement followed by intramolecular capture of the rearranged carbonium ion **13** by the carbamate nitrogen and established the desired azapropellane ring system. Removal of the trichloroethylcarbamate functionality with zinc dust in methanol and acetic acid provided the amine **16**. Lithium aluminum hydride reduction of **14** gave the N-methylamine **17**.

Table 1. Summary of Biological and Physical Results

Compound	[^{3}H]TCP[21] IC_{50} (nM)	NMDA Lethality[22] (ED_{50} mg/Kg)	Ataxia (ED_{50} mg/Kg)	Log P (shake-flask, pH 7.4)
MK-801	3.0	0.34	0.1-0.3	2.1
PD 134365	14.7	0.54	0.44	1.1
5	86.0	3.5	3.2	-0.10
6	137	1.8	3.0	0.94
16	151	3.5	3.2	
17	16.8	0.72	0.3	0.53

Biology and Discussion

The compounds were tested for [^{3}H]TCP 1-[1-(2-thienyl)cyclohexyl]piperidine inhibition in whole rat brain homogenate according to the procedure of Largent et al[21]. To measure NMDA antagonism in vivo, the compounds were assessed for their ability to prevent lethality in mice due to injection of NMDA. Simultaneously, their ataxic liability was determined using a rotorod measurement[22]. Relative to PD 134365, compounds **5, 6,** and **16** demonstrated an approximate 7 to 10-fold decrease in receptor binding affinity. This decrease in affinity was also reflected in the ability of the compounds to protect against NMDA lethality in mice. The reduced affinity may be due excluded volume occupation of the additional fused ring, low log P (compound **5**), and in the case of **6**, the N-Me group, which projects into a unique area of space when this analog is fit to the pharmacophore model[13]. Interestingly, N-methyl derivative **17** was approximately equipotent with PD 134365 in both receptor binding and in the NMDA lethality assay. When fit to the pharmacophore[13], the N-Me of **17** superimposed closely onto the 5-Me of MK-801, a group known to be critical for high potency within that series[23]. Thus, it appears that there is a hydrophobic pocket in this area of the receptor, which, when unoccupied (as in **16** and the des-5-Me MK-801 analog[23]), results in a 10-fold loss in affinity.

While the bridged compounds described herein retained significant affinity for the noncompetitive NMDA receptor, they also produced ataxia at or near the dose that protected mice against the lethal effects of intravenously administered NMDA. The separation of ataxic liability from receptor affinity remains a challenge in the development of a clinically useful noncompetitive NMDA antagonist.

References

1. Current Address: Bristol-Myers Squibb, 5 Research Parkway, Wallingford, Ct. 06492-7660
2. Collingridge, G.L. ; Sawyer, W. *TIPS.* **1990**, *11*, 290.
3. Klockgether, T.; Turski, L. *Ann Neurology* **1990**, *28*, 529.
4. Young, A B.; Greenamyre, J.T.; Hollingsworth, Z.; Albin, R.I.; D'Amato, C.; Shoulson, I.; Penny, J.B. *Science* **1988**, *241*, 981.
5. Rothstein, J.D.; Martin, L.J.; Kuncl, R.W. *New Eng. J. Med.* **1992**, *326*, 1464.
6. Zivin, J.A.; Choi, D.W. *Scientific American* **1991**, July, 56.
7. Dingledine, R.; McBain, C.J.; McNamara, J.O. *TIPS* **1990**, *11*, 334.
8. Wong, E.H.F.; Kemp, J.A. *Annu. Rev. Pharmacol. Toxicol.* **1991**, *31*, 401.
9. Johnson, K. M.; Jones, S.M. *Annu. Rev. Pharmacol. Toxicol.* **1990**, *30*,, 707.
10. Bigge, C.F.; Johnson, G.; Hays, S.J.; Malone, T.C.; Ortwine, D.F.; Boxer, P.A.; Marcoux, F.W.; Coughenour, L.L. *Multiple Sigma and PCP Receptor Ligands: Mechanisms for Neuromodulation and Neuroprotection?* ; J.-M. Kamenka and E.F. Domino, Eds.; NPP Books: Ann Arbor, MI, 1992, pp 1-20.
11. Marshall, G.R.; Barry, C.D.; Bosshard, H.E.; Dammkoehler, R.A.; Dunn, D.A. *ACS Symp. Ser. #112: Computer-Assisted Drug Design* ; Olson, E.C.; Christofferson, R.E. Eds.; American Chemical Society, 1979, 205-226.
12. SYBYL version 5.3.2 (Tripos Associates, Inc., 1699 S. Hanley Road, St. Louis, MO 63144), operating on a VAX 6430, was used for the calculations.
13. Since it has been shown[10] that the 4a(R) enantiomers of PD 134365 and 33352 are more potent at the non-competitive NMDA receptor, they were modeled in this form, as were the related analogs described herein.
14. Mannalack, D.T.; Wong, M.G.; Costa, M.; Andrews, P.R.; Beart, P.M. *Molec. Pharm.* **1988**, *34*, 863-879.
15. Thurkauf, A.; Zenk, P.C.; Balster, R.L.; May, E.L.; George, C.; Carroll, F.I.; Mascarella, S.W.; Rice, K.C.; Jacobsen, A.E.; Mattson, M.V. *J. Med. Chem.* **1988**, *31*, 2257-2263.
16. Leeson, P.D.; Carling, R.W.; James, K.; Smith, J.D.; Moore, K.W.; Wong, E.H.F.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1296-1305.
17. Inami, Y.; Tomita, T.; Terada, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1426-1429.
18. Hays, S.J.; Novak, P.M.; Ortwine, D.F.; Bigge, C.F.; Colbry, N.L.; Johnson, G.; Lescosky, L.J.; Malone, T.C.; Michael, A.; Reily, M.D.; Coughenour, L.L.; Brahce, L.J.; Shillis, J.L.; Probert, A. *J. Med. Chem.*, submitted.
19. Rangarajan, R.; Eisenbraun, E.J. *J. Org. Chem.* **1985**, *50*, 2435.
20. a) Belleau, B. *J. Amer. Chem. Soc.* **1953**, *75*, 1159. b) Monkovic, I.; Conway, T.T.; Wong, H.; Perron, Y.G.; Pachter, I.J.; Belleau, B. *J. Amer. Chem. Soc.* **1973**, *95*, 7910.
21. Largent, B.L.; Gundlach, A.L.; Snyder, S.H. *J. Pharmacol. Exp. Ther.* **1990**, *30*, 707.
22. Lethal seizures were produced in CF-1 mice by intravenous injection NMDA. Mice weighing 22-28 g were injected behind the lateral aspect of the right eye (retrobulbar) with an appropriate dose of the test agent or vehicle control, five minutes prior to NMDA injection. Ataxia assessments were made immediately prior to NMDA injection using an inverted-screen technique. NMDA (25 mg/kg) dissolved in saline was then administered as a bolus via left eye retrobulbar injection. Untreated controls developed seizures 10-25 s in duration immediately following NMDA administration. Seizures were terminated by expiration of the animals. Test agents were assessed for their ability to prevent lethality following NMDA injections. ED_{50} values were determined from dose-response curves constructed from at least three doses at half-log intervals, using ten mice per dose.
23. Monn, A.J.; Thurkauf, A.; Mattson, M.V.; Jacobson, A.E.; Rice, K.C. *J. Med. Chem.* **1990**, *3*, 1069.