cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3 H, t, J = 7.1 H), 1.44 (3 H, t, J = 7.1 Hz), 3.48 (2 H, q, J = 7.2 Hz), 4.49 (2 H, q, J = 7.1 Hz), 5.18 (2 H, s), 7.27-7.51 (8 H, m), 7.70 (1 H, d, J = 2.3 Hz), 8.81 (1 H, s); mass spectrum, m/e (CI, CH_4) 375 (M + 1, 100).

9-Methyl-6-(benzyloxy)-4-ethyl-β-carboline-3-carboxylic Acid Ethyl Ester (9). The β-carboline **8c** (193 mg, 0.516 mmol), NaH (16 mg of an 80% dispersion in oil, 0.568 mmol), and iodomethane (81 mg, 0.568 mmol) was reacted under conditions analogous to the procedure described for the preparation of **3**. Workup and flash chromatography on silica gel (3:1 EtOAc-$CHCl_3$ eluent) afforded the title compound **9** (128 mg, 64%) as a white solid: mp 110-11 °C; IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (3 H, t, J = 7.1 Hz), 1.46 (3 H, t, J = 7.2 Hz), 3.52 (2 H, q, J = 7.2 Hz), 3.95 (3 H, s), 4.50 (2 H, q, J = 7.2 Hz), 8.72 (1 H, s); mass spectrum, m/e (CI, CH_4) 389 (M + 1, 100); high-resolution mass spectrum, m/e 388.1789 ($C_{24}H_{24}N_2O_3$ requires 388.1787). Anal. ($C_{24}H_{24}N_2O_3$) C, H, N.

6-(Benzyloxy)tryptophan Ethyl Ester (12). 5-(Benzyloxy)gramine (5 g, 17.8 mmol) and ethyl nitroacetate (2.61 g, 19.6 mmol) were heated to reflux in anhydrous xylene for 18 h. The solution was cooled, evaporated, and flash chromatographed on silica gel ($CHCl_3$) to afford **11** as a golden yellow oil (6.2 g, 94%), which was used without further purification: IR ($CHCl_3$) 1740, 1550, and 1360 cm^{-1}; mass spectrum, m/e (EI) 368 (M^+, 79.4), 322 (12.9), 277 (100); high-resolution mass spectrum 368.1358 ($C_{20}H_{22}N_2O_5$ requires 368.1372). This material was subjected to hydrogenation over Raney nickel catalyst (15 g) as previously described. Workup and flash chromatography afforded **12** (4.5 g, 75%) as a white solid, which was used without further purification: IR (KBr) 3200-3450, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3 H, t, J = 7.0 Hz), 1.62 (2 H, br s), 3.11 (2 H, ABX, J_{AB} = 14.6, J_{AX} = 7.7 and J_{BX} = 4.4 Hz), 3.78 (1 H, dd, J = 4.7, 8.4 Hz), 4.15 (2 H, q, J = 7.0 Hz), 5.11 (2 H, s), 6.91-7.50 (9 H, m), 8.05 (1 H, br s); mass spectrum, m/e (EI) 338 (M^+, 8.2), 236 (100); high-resolution mass spectrum, m/e 338.1624 ($C_{20}H_{22}N_2O_3$ requires 338.1630).

6-(Benzyloxy)-β-carboline-3-carboxylic Acid Ethyl Ester (13). The amine **12** (2.8 g, 8.3 mmol) and glyoxylic acid monohydrate (0.76 g, 8.3 mmol) were reacted as previously described above for the preparation of **8** followed by oxidation (aromatization) over 10% Pd-C (0.8 g) in mixed xylenes. Flash chromatography on silica gel (4:1 EtOAc-$CHCl_3$, eluent) afforded the β-carboline **13** (230 mg, 8%) as a white solid: mp 260-3 °C (lit.[44] mp 261-3 °C); IR (KBr) 3350-3200, 1735 cm^{-1}; ^1H NMR (d^6-DMSO) δ 1.38 (3 H, t, J = 7.1 Hz), 4.34 (2 H, q, J = 7.0 Hz), 5.22 (2 H, s), 7.25-7.61 (8 H, m), 8.14 (1 H, d, J = 2.3 Hz), 8.91 (1 H, d, J = 2.9 Hz), 10.91 (1 H, br s); mass spectrum, m/e (CI, CH_4) 347 (M + 1, 100); high-resolution mass spectrum, m/e 346.1291 ($C_{21}H_{18}N_2O_3$ requires 346.1307).

9-Methyl-6-(benzyloxy)-β-carboline-3-carboxylic Acid Ethyl Ester (14). The β-carboline (177 mg, 0.51 mmol), NaH (19 mg of a 60% dispersion in oil, 0.56 mmol), and iodomethane (80 mg, 0.56 mmol) was reacted together as described above. Chromatography on silica gel (9:1 $CHCl_3$-Et_2O, eluent) gave **14** as a white solid (120 mg, 65%) which was homogeneous by TLC (9:1 $CHCl_3$-Et_2O): mp 180-2 °C; IR (KBr) 1725 cm^{-1}; mass spectrum, m/e (CI, CH_4) 361 (M + 1, 100); ^1H NMR ($CDCl_3$) δ 1.48 (3 H, t, J = 7.5 Hz), 3.98 (3 H, s), 4.52 (2 H, q, J = 7.5 Hz), 5.20 (2 H, s), 7.40-7.55 (7 H, m), 7.70 (1 H, d, J = 2.5 Hz), 8.81 (1 H, s), 8.92 (1 H, s); mass spectrum, m/e (CI, CH_4) 389 (M + 1, 100). The partition coefficients were either determined experimentally[45] or calculated from tabulated fragmentation constants:[24,25] log P(octanol/water) = 3.97 (**1**), 1.44 (**2**); 2.10 (**8a**), 1.88 (**8b**), 5.79 (**8c**), 4.53 (**13**).

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Registry No. 1, 83910-44-5; **2**, 96136-88-8; **3**, 124563-47-9; **4a**, 1006-94-6; **4b**, 120-72-9; **4c**, 1215-59-4; **5a**, 87824-17-7; **5b**, 104586-20-1; **6a**, 124563-48-0; **6c**, 124563-49-1; **7a**, 124563-50-4; **7b**, 124601-04-3; **7c**, 124563-51-5; **8a**, 83910-32-1; **8b**, 83910-28-5; **8c**, 96136-56-0; **9**, 124563-52-6; **10**, 1453-97-0; 11, 124563-53-7; **12**, 124563-54-8; **13**, 91164-52-2; 14, 124563-55-9; $OHCCO_2H$, 298-12-4; O_2NCH_2COOEt, 626-35-7.

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Synthesis and Structure-Activity Relationship of C5-Substituted Analogues of (±)-10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine [(±)-Desmethyl-MK801]: Ligands for the NMDA Receptor-Coupled Phencyclidine Binding Site

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A series of eight C5-substituted analogues of (±)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (**1**) have been prepared by the directed lithiation-alkylation (and acylation) of its (±)-N-*tert*-butylformamidinyl derivative **2** followed by formamidine solvolysis. An additional 10 analogues were prepared by elaboration of the C5-ethyl ester derivative. Analogues possessing large (e.g. propyl and larger) lipophilic substituents displace [^3H]-1-(1-thienylcyclohexyl)piperidine ([^3H]TCP) from the high-affinity phencyclidine (PCP) binding site in rat brain homogenates only at high concentrations (K_i > 1000 nM); however, the presence of a polar amino functionality (e.g. 2-aminoethyl) offsets this effect (K_i = 20 nM). Thus, the boundary condition for lipophilic substituents larger than ethyl appears to be polar in nature. Interaction of the 11 relatively small (MR < 14) C5-substituted analogues of **1** with the high-affinity PCP binding site associated with the *N*-methyl-D-aspartate (NMDA) receptor is best described by the equation log $(1/K_i) = -5.83\mathcal{F} + 0.64\pi + 7.41$ (r = 0.90).

The *N*-methyl-D-aspartate (NMDA) subclass of the excitatory amino acid (EAA) glutamate receptor has been the focus of a considerable amount of multidisciplinary research in the field of neuroscience.[1-4] Much, if not all of the interest in the NMDA receptor is due to its postulated involvement in such diverse central nervous system

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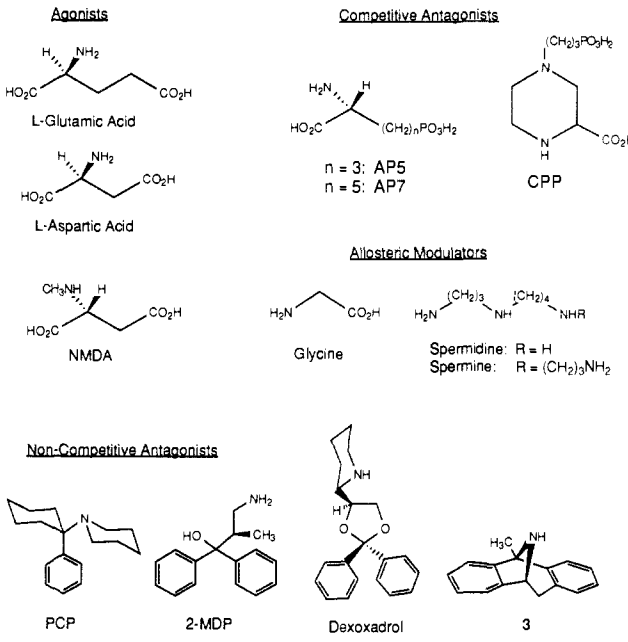
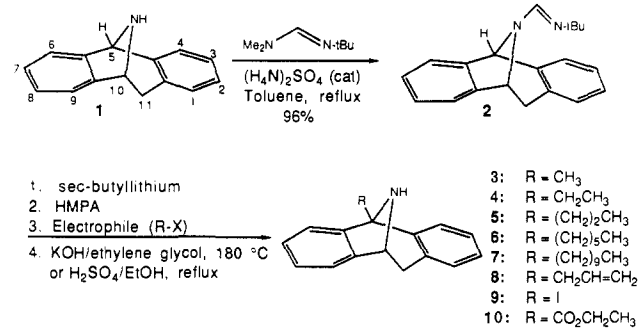
Chart I. NMDA Receptor Ligands



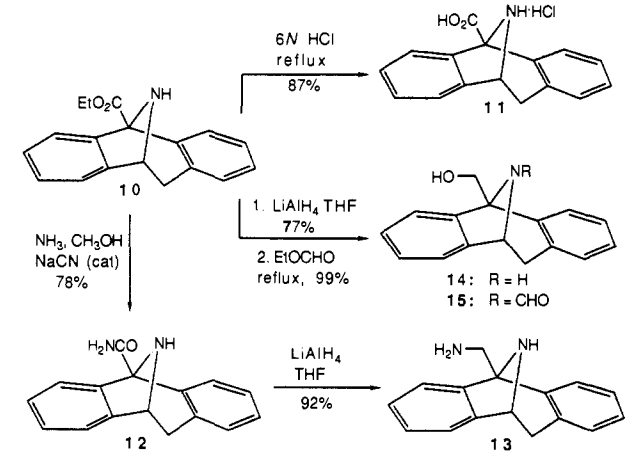
(CNS) functions as memory and learning, epilepsy, and neurodegeneration.

There are a variety of agents which modulate the activity of the NMDA receptor (Chart I), including competitive agonists (L-glutamate, L-aspartate, NMDA),[5] and antagonists [D-5-(aminophosphono)valeric acid (AP5),[6] D-7-(aminophosphono)heptanoic acid (AP7),[7] and 3-[(±)-2-carboxypiperizin-4-yl]propane-1-phosphonic acid (CPP)[8-10]] as well as allosteric modulators (glycine,[11-15] spermine,[15] and spermidine[15]) and noncompetitive antagonists [1-(1-phenylcyclohexyl)piperidine (phencyclidine, PCP),[16-18] (4*S*,6*S*)-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane (dexoxadrol),[19,20] (2*S*)-2-methyl-3,3-diphenylpropanolamine 21 (2-MDP),[21] and (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (MK801, (+)-**3**[22-26])].

Scheme I



Scheme II



Conformationally defined (+)-**3** is a potent and selective noncompetitive antagonist of EAA depolarization mediated by the NMDA receptor. Its biochemical site of action appears to be the high-affinity binding site for the dissociative anesthetic and psychotomimetic agent phencyclidine (PCP);[23,24] furthermore, electrophysiological evidence suggests that this site is the cation channel associated with the NMDA receptor.[25] Noncompetitive NMDA antagonists are thus believed to manifest their effect through the blockade of calcium influx induced by agonists. In agreement with theories postulating a convulsant and neurotoxic effect resulting from excessive stimulation of the NMDA receptor by EAAs, (+)-**3** has been demonstrated to possess anticonvulsant properties (and has been evaluated in humans as such)[27] and has also proved efficacious in preventing neuronal degeneration both in vitro (degeneration of cultured neurons resulting from hypoxic conditions or from administration of NMDA agonists)[28-30]

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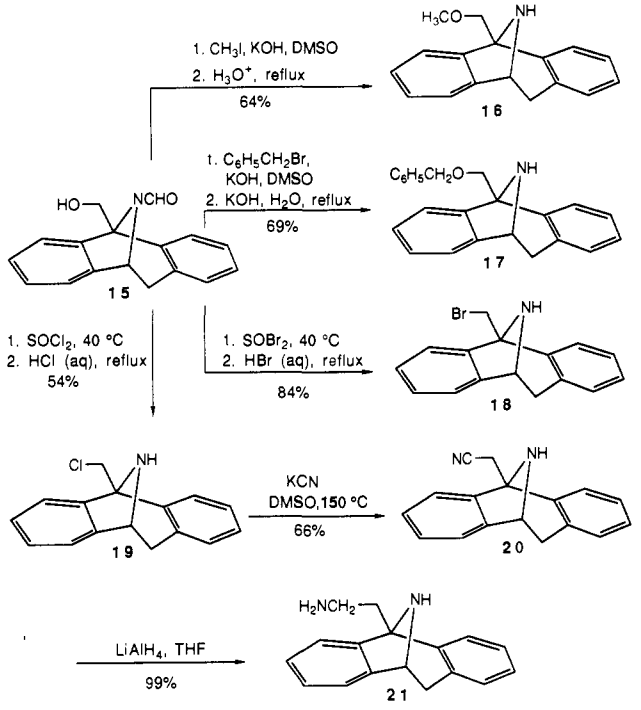
Scheme III



and in vivo (degeneration due to carotid artery occlusion).[31-33]

We have recently reported a method for the preparation of C5-substituted analogues of (±)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (**1**) in which the bond between the doubly benzylic bridgehead position (C5) of **1** and the C5-substituent is formed at a late stage of the synthetic sequence.[34] Furthermore, we have utilized this methodology in the preparation of (±)-[^{11}C]methyl-**3**, a short-lived ($t_{1/2}$ = 20 min), positron-emitting radioisotope of (±)-**3** for real-time imaging of the NMDA receptor complex in the living primate brain.[35] Given the ability to prepare a wide variety of C5-substituted derivatives of **1** and the paucity of structure–activity relationships (SAR) for compounds of this type in the literature, we undertook a program aimed at defining the physicochemical properties of the binding site adjacent to the C5 position of the dibenzo[*a*,*d*]cyclohepten-5,10-imine skeleton. We now report the results of our investigation.

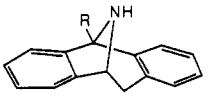
Chemistry

Compound **1** was prepared according to the literature procedure.[36] Conversion of **1** to its *N*-*tert*-butylformamidine derivative (**2**) was accomplished in high yield (96%) by formamidine exchange with *N*′-*tert*-butyl-*N*,*N*-dimethylformamidine in the presence of ammonium sulfate (Scheme I). The directed lithiation–alkylation (and acylation) of **2** followed by formamidine solvolysis has been reported in a preliminary communication.[34] Utilizing this methodology, we have successfully prepared a number of C5-substituted derivatives (**3**–**10**) of **1**.

Additional compounds were prepared (Scheme II) from C5-ethyl ester **10**. Hydrolysis of **10** in aqueous HCl provided amino acid hydrochloride **11**, while aminolysis of **10** with ammonia in the presence of a catalytic amount of NaCN[37] gave primary carboxamide **12**. Reduction of **12** and **10** with $LiAlH_4$ yielded diamine **13** and amino alcohol **14**, respectively. Conversion of the amino alcohol to its *N*-formyl derivative was readily achieved by heating **14** in ethyl formate at 100 °C, yielding an essentially quantitative yield of **15**.

Protected amino alcohol **15** was then employed as an intermediate leading to additional C5-substituted analogues (Scheme III). Alkylation of the primary alcohol with methyl iodide and benzyl bromide under standard conditions (KOH, DMSO), followed by hydrolysis of the formamide protecting group, afforded methyl ether **16** and benzyl ether **17** in 64% and 69% yield, respectively. Alternatively, the primary alcohol could be replaced by bromide and chloride by treatment of **15** with the appropriate thionyl halide at 40 °C in the presence of DMF. Subsequent hydrolysis of the halomethyl-substituted formamide with the corresponding mineral acid then generated the desired bromomethyl (**18**) and chloromethyl (**19**) derivatives in 54% and 84% yield, respectively. Nucleophilic substitution of **19** with NaCN in DMSO generated carbonitrile **20** (66%), and reduction of this material afforded 2-aminoethyl analogue **21** (99%).

Table I. Apparent Equilibrium Dissociation Constants (K_i Values) for (±)-1 and Its C5-Substituted Derivatives



no.	R	K_i, nM	no.	R	K_i, nM
1	H	120	13	CH_2NH_2	117
3	CH_3	9	14	CH_2OH	40
4	CH_2CH_3	12	16	CH_2OCH_3	300
5	$(CH_2)_2CH_3$	1100	17	$CH_2OCH_2C_6H_5$	10000
6	$(CH_2)_5CH_3$	980	18	CH_2Br	33
7	$(CH_2)_9CH_3$	21600	19	CH_2Cl	12
8	$CH_2CH{=}CH_2$	70	20	CH_2CN	967
9	I	430	21	$CH_2CH_2NH_2$	20
10	$CO_2CH_2CH_3$	7500	(+)-3		8
11	CO_2H	32300	(−)-3		31
12	$CONH_2$	11300			

Biochemistry

Binding studies were performed as previously described by Jacobson et al.,[19] using a tissue homogenate preparation of fresh whole rat brain minus cerebellum. Incubation of the test ligands was carried out a 5 °C with [^{3}H]-1-(1-thienylcyclohexyl)piperidine ([^{3}H]TCP) as the radioligand. Rapid filtration was carried out through filters presoaked in 0.03% polylysine. The inhibition constants (K_i) were calculated from the Cheng–Prusoff equation with our predetermined K_d for TCP (16.5 nM) from Scatchard analysis. Experiments were performed in triplicate, and 10 μM TCP was used for the determination of nonspecific binding.

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Table II. Substituent Constants for QSAR Analysis[a]

no.	log $(1/K_i)^b$	log $(1/K_i)^c$	π^d	σ^{*e}	$\mathcal{F}^f$	$\mathcal{R}^g$	Fr[h]	MR[i]	H-acpt[j]	H-don[k]	L^l	B_1^m	B_2^n
1	6.92	7.41	0.0	0.49	0.00	0.00	0.23	1.03	0	0	2.06	1.00	1.00
3	8.00	8.01	0.56	0.00	−0.04	−0.13	0.77	5.65	0	0	3.00	1.52	1.90
4	7.92	8.36	1.02	−0.10	−0.05	−0.10	1.43	10.30	0	0	4.11	1.52	1.90
5	5.96		1.55	−0.12	−0.06	−0.08	1.97	14.96	0	0	5.05	1.52	1.90
6	6.01		–	–	–	–	–	–	0	0	–	–	–
7	4.67		–	–	–	–	–	–	0	0	–	–	–
8	7.15		1.10	0.23	–	–	–	14.49	0	0	–	–	–
9	6.12	5.80	1.12	2.38	0.40	−0.19	0.59	13.76	0	0	4.23	2.15	2.15
10	5.12		0.51	–	0.33	0.15	−0.18	16.76	1	0	5.96	1.90	1.90
11	4.49	5.28	−0.32	2.94	0.33	0.15	−1.10	6.03	1	1	3.91	1.60	1.60
12	4.95	5.06	−1.49	–	0.24	0.14	−2.18	9.81	1	1	4.06	1.60	1.60
13	6.93		–	–	–	–	–	–	1	1	–	–	–
14	7.40	6.75	−1.03	0.56	0.00	0.00	−1.54	7.19	1	1	3.97	1.52	1.90
16	6.52	6.85	−0.78	0.52	0.01	0.02	−0.23	12.07	1	0	4.91	1.52	1.90
17	5.00		–	–	–	–	–	–	1	0	–	–	–
18	7.37	7.34	0.79	1.00	0.10	0.05	0.74	13.39	0	0	4.09	1.52	1.95
19	7.92	6.94	0.17	1.05	0.10	0.03	0.60	10.49	0	0	3.89	1.52	1.90
20	6.01	5.82	−0.57	1.30	0.21	−0.18	−0.73	10.11	1	0	3.99	1.52	1.90
21	7.70		–	–	–	–	–	–	1	1	–	–	–

[a] All substituent constants were included in QSAR-PC:PAR program (ref 40). [b] Observed values. [c] Calculated from eq 2. [d] Hansch–Fujita hydrophobicity constant derived from aromatic substituents. [e] Taft polar constant. [f] Swain and Lupton electronic field constant. [g] Swain and Lupton electronic resonance constant. [h] Hydrophobic fragmental constant. [i] Molar refraction. [j] Hydrogen bond acceptor group. [k] Hydrogen bond donor group. [l–n] Verloop sterimol constants.

Results and Discussion

Analogues **1**,**3**–**14**, and **16**–**21** were evaluated for their ability to displace [^{3}H]TCP from rat brain homogenates in vitro. The results are given in Table I. All compounds in the present study are racemic, a fact which must be kept in mind when forming hypotheses from the analyzed data; however, as seen in Table I, the difference between (+)-**3** and its (−)-isomer is relatively small (ca. 4-fold), and the racemic mixture ((±)-**3**, K_i = 9 nM) is essentially equipotent with the (+)-isomer (K_i = 8 nM).

It can be seen that the relative potency of the analogues is influenced by a combination of steric and electronic factors. In the alkyl series (compounds **3**–**7**) and alkoxyalkyl series (**16**, **17**) it appears that the binding site will not easily accommodate groups larger than ethyl. Increasing the carbon chain length from ethyl (**4**, K_i = 12 nM) to propyl (**5**, K_i = 1100 nM) amounts to a loss of approximately 2 kcal in apparent binding energy. Thus, it appears that a strict boundary condition exists approximately 4–5 Å remote from the C5 position of dibenzocyclohepten-5,10-imines for large, lipophilic groups. In addition, it appears that the relative chain length rather than the chemical nature of the atoms which make up the chain is the most dominant contributor to the diminishment of activity with chain length. This is indicated by the fact that the bromomethyl (**18**, K_i = 33 nM), chloromethyl (**19**, K_i = 12 nM), and hydroxymethyl (**14**, K_i = 40 nM) compounds retain significant activity while the methoxymethyl (**16**, K_i = 300 nM) and the cyanomethyl (**20**, K_i = 967 nM) derivatives have attenuated activity. Allyl derivative **8** retains some of the activity (K_i = 70 nM) and this may reflect upon a secondary interaction of the olefin with the binding site.

Carbonyl substitution at C5 leads to compounds which are essentially inactive. The fact that the larger ethyl ester derivative **10** (K_i = 7500 nM) shows some improvement in binding efficacy over the shorter carboxylic acid **11** (K_i = 32300 nM) suggests that the acidic nature of the latter contributes to its reduced potency through direct repulsive interactions with the binding site or, alternatively, that desolvation of zwitterionic **11** (an assumed process prior to binding of the ligand) is rate-limiting.

An unusual facet of the C5 SAR is brought into play by the observation that 2-aminoethyl derivative **21** (K_i = 20 nM) retains high receptor affinity. Although **21** possesses chain length at C5 equivalent to the propyl compound **5** (K_i = 1100 nM), it has a receptor affinity approximately 50 times that of the alkyl. This represents a recovery of 1.75 kcal of the 2 kcal apparent binding energy lost on extending the side chain from ethyl to propyl (see above). The fact that C5 derivatives of two-atom chain length lose activity when the terminal atom is a hydrophilic hetroatom (**13**, K_i = 117 nM; **14**, K_i = 40 nM) rather than a proton (**3**, K_i = 9 nM), methyl (**4**, K_i = 12 nM), or chloro (**19**, K_i = 12 nM) and the reverse is apparently true for C5 derivatives of three-atom chain length (**21**, K_i = 20 nM vs **5**, K_i = 1100 nM) suggests that a short lipophilic pocket is present in the binding site directly adjacent to the C5-position of dibenzocyclohepten-5,10-imines, and a more hydrophilic site is present at a distance of approximately 4–5 Å (three bond lengths) remote from the C5-position. The postulate that a hydrogen-bonding interaction at a three-atom distance from C5 contributes to the binding affinity of analogues of **1** is supported by the fact that the allyl derivative retains some efficacy in receptor binding. Olefins have previously been shown the ability to act as hydrogen acceptors in hydrogen-bonding interactions.[39]

Quantitative Structure–Activity Relationships

Multivariate linear free energy regression analyses between the negative log of the reciprocal of the observed inhibitory constant [−log $(1/K_i)$] and various published substituent constants (π, σ^*, MR, E_s, $\mathcal{F}$, $\mathcal{R}$, Fr, L, B_1, B_2, H-acpt, H-don) were performed with the QSAR-PC:PAR program (Biosoft, Cambridge, U.K.).[40] Initially, the ALLREGR routine was employed in order to rapidly identify individual substituent constants (and combinations of substituent constants) of greatest interest. Detailed regression analyses for the substituent parameters of most interest were then performed by employing the REGRES routine.

Substituent constants (Table II)[40] were not available for several members of the data set (**6**–**8**, **13**, **17**, and **21**). However, most of these analogues (all except **13**) possess a relatively large C5-substituent (MR ≥ 14). Given this

(39) West, R. *J. Am. Chem. Soc.* **1959**, *81*, 1614.
(40) Coburn, R. A. *Quantitative Structure–Activity Relationship Studies, Physiochemical-Activity Relationship Methods: Medicinal Chemistry Regression Machine*; Biosoft: Cambridge, U.K., 1987.

Table III. Intervariable Correlation Matrix for QSAR Analysis

	log $(1/K_i)$	π	$\mathcal{F}$	$\mathcal{R}$	MR	H-acpt	H-don	L	B_1	B_2	σ^*	Fr
log $(1/K_i)$	1.000											
π	0.496	1.000										
$\mathcal{F}$	−0.773	−0.043	1.000									
$\mathcal{R}$	−0.403	−0.513	0.069	1.000								
MR	−0.045	0.217	0.374	−0.152	1.000							
H-acpt	−0.652	−0.870	0.245	0.368	0.012	1.000						
H-don	−0.577	−0.664	0.297	0.635	−0.205	0.671	1.000					
L	−0.215	−0.150	0.286	0.067	0.859	0.430	0.124	1.000				
B_1	−0.255	0.254	0.659	−0.300	0.730	0.028	0.071	0.627	1.000			
B_2	0.238	0.305	0.161	−0.435	0.808	−0.034	−0.192	0.726	0.769	1.000		
σ^*	−0.549	0.159	0.797	0.044	0.214	0.139	0.161	0.192	0.484	0.144	1.000	
Fr	0.683	0.886	−0.351	−0.559	0.094	−0.849	−0.835	−0.187	0.014	0.213	−0.110	1.000

constraint and the qualitative assessment (see above) that a boundary condition exists some 4–5 Å remote from the C5 position of the parent ring system, our QSAR analysis was performed only on those derivatives bearing a small (MR < 14) C5 substituent (compounds **1**, **3**, **4**, **9**, **11**, **12**, **14**, **16**, and **18–20**). For these 11 analogues, activity in displacement of [^{3}H]TCP in vitro varies widely, from 9 nM for compound **3** to 32 300 nM for compound **12**. This, in fact, represents the full range in activity observed for the whole data set. In addition, the substituents in this data subset represent a wide variation in each of the individual substituent constants.

The best single parameter equation (eq 1, r = 0.773) which could be derived from these data involves the Swain and Lupton electronic field inductive term $\mathcal{F}$.[41] An in-

$$\log (1/K_i) = -5.98\ (\pm 3.70)\mathcal{F} + 7.39\ (\pm 0.70) \quad (1)$$

$$n = 11,\ r = 0.773,\ s = 0.804,\ F_{1,9} = 13.35$$

tervariable correlation analysis is depicted in Table III. Correlation coefficients for all other single-parameter equations can be discerned by examination of the values in Table III.

Addition of a lipophilicity term (π) to the linear regression (eq 2) improved the correlation dramatically (r = 0.901). If more than one variable is employed in a single

$$\log (1/K_i) = -5.83\ (\pm 2.74)\mathcal{F} + 0.64\ (\pm 0.49)\pi + 7.41\ (\pm 0.52) \quad (2)$$

$$n = 11,\ r = 0.901,\ s = 0.582,\ F_{2,8} = 17.32$$

regression equation (e.g. eq 2), the correlation between individual variables should ideally be less than 0.30.[42] Inspection of Table III demonstrates the lack of correlation between $\mathcal{F}$ and π (r = −0.043).

An examination of other intervariable correlations involving $\mathcal{F}$ and π demonstrates relatively large correlations between $\mathcal{F}$ and B_1 (0.659), $\mathcal{F}$ and σ^* (0.797), and π and Fr (0.886). Substitution of the fragmental hydrophobic constant Fr in the place of π results (eq 3) in a correlation (r

$$\log (1/K_i) = -4.71\ (\pm 1.34)\mathcal{F} + 0.52\ (\pm 0.19)\mathrm{Fr} + 7.35(\pm 0.24) \quad (3)$$

$$n = 11,\ r = 0.889,\ s = 0.616,\ F_{2,8} = 15.06$$

= 0.889) which is not statistically different from that observed in eq 2, although the two substituent constants Fr and $\mathcal{F}$ are marginally correlated (r = −0.351). All other possible combinations of $\mathcal{F}$, B_1, or σ^* with π or Fr resulted, in each case, in unremarkable correlations ($r \leq 0.83$).

In eq 1–3 the values in parentheses are the 95% confidence intervals, n represents the number of data points (analogues) employed, r is the correlation coefficient, s is the standard error of the regression, and $F_{n,x}$ is the stepwise F statistic ($F_{1,9;\alpha=0.01}$ = 10.56; $F_{2,8;\alpha=0.01}$ = 8.65). Thus, eq 1–3 are significant at the 99% confidence level. Calculated values of log (1/Ki) (from eq 2) for n = 11 are given in Table II.

Use of more than two independent variables for this data set (n = 11) is not justified due to a significantly increased probability of obtaining chance correlations.[43] Together, eq 1–3 strongly suggest that the interaction of small (MR < 14) C5-substituents with the PCP binding site is influenced most strongly (ρ = −5.98, −5.83, and −4.71) by inductive electronic and, to a lesser degree (ρ = 0.64 and 0.52), by hydrophobic effects.

In summary, all modifications at C5 showed some diminishment in the ability of the resulting analogues to displace [^{3}H]TCP from its high affinity binding site in rat brain homogenates compared to (±)-**3**. Alkyl and substituted-alkyl derivatives had strict steric requirements, with nonpolar groups larger than ethyl showing greatly attenuated receptor affinities. QSAR analysis of 11 analogues possessing small (MR < 14) C5 substituents suggests that the binding to the PCP site by these derivatives is influenced by both inductive electronic field effects and hydrophobic effects, with those substituents which are both lipophilic and inductively electron donating being preferred.

The poor receptor affinities of larger lipophilic alkyl substituents (MR > 14) and the good receptor affinities of analogues having groups capable of hydrogen bonding at a three-atom distance from the C5-position of the dibenzocyclohepten-5,10-imine ring system strongly suggest that a secondary ionic binding site is present in this region of space within the receptor. It is intriguing to speculate that this site may in fact be that which interacts with the amino functionality of two other classes of noncompetitive NMDA receptor antagonists—those related to 2-MDP and to dexoxadrol (Chart I), in which the basic amine functionality is some 4–5 Å remote from the benzhydryl position of these structures. Further investigation of this hypothesis is underway.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Capillary gas chromatographic (GC) analyses were performed on a Hewlett-Packard 5880 or 5890 instrument using an OV-1 capillary column (0.32 mm i.d.) and flame ionization detector. Proton (^{1}H) NMR spectra were recorded on either a Varian XL-300 or HR-220 spectrometer using deuteriated chloroform ($CDCl_3$) as the solvent. Chemical shift values (δ) are reported in parts per million (ppm)

(41) Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328.

(42) Hansch, C.; Leo, A. *Substituent Constants For Correlation Analysis in Chemistry and Biology*; Wiley-Interscience: New York, 1979.

(43) Topliss, C.; Costello, R. J. *J. Med. Chem.* **1972**, *15*, 1066.

relative to tetramethylsilane (Me_4Si; 0.0 ppm). Coupling constants (J) are reported in hertz (Hz) and s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Carbon (^{13}C) NMR spectra were recorded on a Varian XL-300 spectrometer using deuteriated chloroform ($CDCl_3$) as the solvent. Chemical shift values (δ) are reported in parts per million (ppm) relative to deuteriated chloroform ($CDCl_3$; 77.0 ppm). Electron-impact mass spectra (EIMS) and high-resolution (electron impact) mass spectra (HRMS) were obtained with a VG mass spectrometer, and chemical-ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Infrared spectra were recorded with a Beckman IR 4230 instrument and are calibrated relative to polystyrene (1601 cm^{-1}). Combustion analyses were performed by Atlanta Microlabs (Atlanta, GA) and are within 0.4% of the calculated values. Measurement of pH was made with moist colorpHast pH indicator strips (EM Science). KOH equivalents are based on 100% KOH. Preparative centrifugal thin-layer chromatography (PC-TLC) was performed on a Harrison Model 7924 chromatotron using Merck silica gel 60 PF254 containing $CaSO_4 \cdot 0.5H_2O$ binder. Plate thickness and eluent systems employed are reported in parentheses.

(±)-*N*-[(*tert*-Butylimino)methyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (2). A mixture of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (1,[36] 5.18 g, 25.0 mmol), *N'-tert*-butyl-*N*,*N*-dimethylformamidine (12.84 g, 100.0 mmol) and a few crystals of ammonium sulfate in anhydrous toluene was heated under reflux for 6 days. Evaporation of the solvent and purification of the crude product by column chromatography (silical gel 60, 230–400 mesh) employing 7% triethylamine in hexanes as the eluent afforded the desired *N-tert*-butylformamidine derivative **2** (6.98 g, 24.1 mmol, 96%): mp 63–64 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9 H; *tert*-butyl), 2.55 (d, 1 H, J = 17 Hz; H_{11ax}), 3.66 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 5.34 (d, 1 H, J = 5 Hz; H_{10}), 5.42 (s, 1 H, H_5), 6.89–7.52 (m, 8 H; H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.22, 30.70, 53.62, 58.59, 63.77, 119.85, 121.72, 123.89, 125.56, 126.83, 126.96, 127.31, 130.26, 132.55, 140.54, 141.85, 146.88, 147.35; CIMS, m/z (NH_3) 291 (M^+). Anal. ($C_{20}H_{22}N_2$) C, H, N.

General Procedure for Lithiation–Alkylation–Hydrolysis of 2: (±)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine [(±)-MK801, 3]. A solution of **2** (1.0 g, 3.4 mmol) in anhydrous ethyl ether (34 mL) under an atmosphere of nitrogen was treated at room temperature with a 1.1 M solution of *sec*-butyllithium in cyclohexane (3.5 mL, 3.8 mmol). The deep red solution of the anion was allowed to stir at room temperature for 30 minutes and then was cooled to −78 °C and treated with hexamethylphosphoric triamide (HMPA, 1.2 mL, 6.8 mmol) followed by methyl iodide (0.25 mL, 4.1 mmol). The reaction mixture was allowed to warm to room temperature, and GC analysis of the reaction mixture demonstrated the absence of **2**. The reaction mixture was treated with H_2O (50 mL), the layers were separated, and the aqueous solution was extracted with ethyl ether (3 × 50 mL). The combined organic phase was washed once with H_2O (100 mL), dried over K_2CO_3, and concentrated to dryness (1.06 g). The crude product was purified by radial chromatography (4 mm plate thickness, chloroform/methanol/ammonia 95:5:1 eluent), affording a white solid (0.90 g, 2.96 mmol, 87%). A solution of potassium hydroxide (0.30 g, 5.3 mmol) and this intermediate was warmed to 180 °C in ethylene glycol (5 mL) for 15 min. The reaction mixture was allowed to cool to room temperature and was subsequently diluted with ethyl ether (50 mL) and H_2O (50 mL). The layers were separated, and the aqueous solution was saturated with NaCl and extracted with ethyl ether (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 100 mL) and dried over K_2CO_3. Evaporation of the solvent under reduced pressure afforded **3** as a pale yellow oil (0.54 g, 2.45 mmol, 72% from **2**). Compound **3** is chromatographically and spectroscopically identical with material prepared independently by the literature method.[36]

(±)-5-Ethyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (4).[44] Compound **4** (0.13 g, 0.55 mmol) was prepared from **2** (0.29 g, 1.0 mmol) according to the general procedure (56% yield) employing ethyl iodide as the electrophile: IR (film) 3220 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz; CH_2CH_3), 2.07–2.50 (m, 3 H; N*H*, CH_2CH_3), 2.58 (d, 1 H, J = 17 Hz; H_{11ax}), 3.30 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.56 (d, 1 H, J = 5 Hz; H_{10}), 6.77–7.20 (m, 8 H; H_{ar}); EIMS m/z 235 (M^+) 220, 206. The hydrogen oxalate salt was prepared by treating **4** with an excess of oxalic acid in 2-propanol, mp 234–235 °C. Anal. ($C_{19}H_{19}NO_4$) C, H, N.

(±)-5-*n*-Propyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (5).[44] Compound **5** (0.15 g, 0.60 mmol) was prepared from **2** (0.29 g, 1.0 mmol) according to the general procedure (60%) employing 1-iodopropane as the electrophile: IR (film) 3250 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz; $CH_2CH_2CH_3$), 1.25–1.55 (m, 3 H; N*H*, $CH_2CH_2CH_3$), 2.00–2.50 (m, 2 H; $CH_2CH_2CH_3$), 2.59 (d, 1 H, J = 17 Hz; H_{11ax}), 3.30 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.59 (d, 1 H, J = 5 Hz; H_{10}), 6.78–7.25 (m, 8 H; H_{ar}); EIMS m/z 249 (M^+), 220, 206. The hydrogen oxalate salt was prepared by treating **5** with an excess of oxalic acid in 2-propanol and was recrystallized from 2-propanol/ether, mp 207–209 °C. Anal. ($C_{20}H_{21}NO_4$) C, H, N.

(±)-5-*n*-Hexyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (6). Compound **6** (0.17 g, 0.58 mmol) was prepared from **2** (0.29 g, 1.0 mmol) according to the general procedure (58%) employing 1-iodohexane as the electrophile: IR (film) 3240 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 7 Hz; $C_5H_{10}CH_3$), 1.25–1.55 (m, 7 H), 2.18–2.60 (m, 4 H), 2.68 (d, 1 H, J = 17 Hz; H_{11ax}), 3.40 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.65 (d, 1 H, J = 5 Hz; H_{10}), 6.78–7.30 (m, 8 H, H_{ar}); EIMS m/z 291 (M^+), 249, 234, 220, 206. The hydrogen oxalate salt was prepared by treating **6** with an excess of oxalic acid in 2-propanol and was recrystallized from 2-propanol/ether: mp 134–135 °C; HRMS calcd for $C_{21}H_{25}N$ 291.1987, found 291.1989. Anal. ($C_{23}H_{27}NO_4 \cdot {}^3/_2H_2O$) C, N; H: calcd, 7.40; found, 6.81.

(±)-5-*n*-Decyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (7). Compound **7** (0.22 g, 0.63 mmol) was prepared from **2** (0.29 g, 1.0 mmol) according to the general procedure (63%) employing 1-iododecane as the electrophile: IR (film) 3230 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6 Hz; $C_9H_{18}CH_3$), 1.20–1.55 (m, 17 H), 2.05–2.55 (m, 2 H), 2.65 (d, 1 H, J = 17 Hz; H_{11ax}), 3.40 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.70 (d, 1 H, J = 5 Hz; H_{10}), 6.80–7.25 (m, 8 H; H_{ar}); EIMS m/z 347 (M^+), 319, 305, 270, 256, 234, 220, 206. The hydrogen oxalate salt was prepared by treating **7** with an excess of oxalic acid in 2-propanol and was recrystallized from 2-propanol/ether: mp 118–119 °C; HRMS calcd for $C_{25}H_{33}N$ 347.2613, found 347.2600. Anal. ($C_{27}H_{35}NO_4 \cdot {}^3/_2H_2O$) C, H, N.

(±)-5-Allyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (8). Compound **8** (0.05 g, 0.2 mmol) was prepared from **2** (0.14 g, 0.47 mmol) according to the general procedure (43%) employing allyl bromide as the electrophile: IR (film) 3240 (NH), 3080, 3020, 1647, 990, 910 cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 2.15–2.50 (m, 1 H; N*H*), 2.65 (d, 1 H, J = 17 Hz; H_{11ax}), 3.20 (t, 2 H, J = 6 Hz; $CH_2C_2H_3$); 3.45 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.70 (d, 1 H, J = 5 Hz; H_{10}); 5.20 (dd, 1 H, J_{AB} = 2 Hz, J_{BX} = 9 Hz; $CH_x{=}CH_AH_B$), 5.30 (dd, 1 H, J_{AB} = 2 Hz, J_{AX} = 18 Hz; $CH_x{=}CH_ACH_B$), 5.20–5.90 (m, 1 H; $CH_xCH_ACH_B$), 6.80–7.30 (m, 8 H; H_{ar}); EIMS m/z 247 (M^+), 232, 220, 219, 218, 206, 178, 44. The hydrogen oxalate salt was prepared by treating **8** with an excess of oxalic acid in 2-propanol and was recrystallized from 2-propanol/ether: mp 201–204 °C. Anal. ($C_{20}H_{19}NO_4$) C, H, N.

(±)-5-Iodo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (9). Compound **9** (0.35 g, 1.1 mmol) was prepared from **2** (0.58 g, 2.0 mmol) according to the general procedure employing 2,2,2-trifluoroethyliodide as the electrophile. In this example, the intermediate formamidine was solvolyzed under acidic conditions (1 N H_2SO_4/EtOH 1:1; reflux, 12 h; 53%): IR 3300 cm^{-1} (NH). The hydrogen oxalate salt was prepared by treatment of **9** with an excess of oxalic acid in CH_2Cl_2, precipitation with Et_2O, and recrystallization from acetone: mp 207–209 °C; ^1H NMR (300 MHz, acetone-d_6) δ 2.63 (d, 1 H, J = 17 Hz; H_{11ax}), 3.56 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.82 (d, 1 H, J = 5 Hz; H_{10}), 6.00 (br s, 3 H; N*H*·oxalate), 6.85–7.60 (m, 8 H; H_{ar}); EIMS m/z 333 (M^+), 206, 179, 178; HRMS calcd for $C_{15}H_{12}NI$ 333.0014, found 333.0013. Anal. ($C_{17}H_{14}INO_4$) C, H, N.

(44) Christy, M. E.; Anderson, P. S.; Britcher, S. F.; Colton, C. D.; Evans, B. E.; Remy, D. C.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3117.

(±)-5-(Ethoxycarbonyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (10). Compound **10** (2.10 g, 7.53 mmol) was prepared from **2** (2.90 g, 10.0 mmol) according to the general procedure employing ethyl chloroformate as the electrophile. In this example, the intermediate formamidine was solvolyzed under acidic conditions[46] (0.5 equiv of H_2SO_4 in EtOH, reflux, 12 h; 75%): IR (film) 3260 (NH), 1745 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3 H, J = 7 Hz; OCH_2CH_3), 2.60 (br s, 1 H; N*H*), 2.71 (d, 1 H, J = 17 Hz; H_{11ax}), 3.44 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.42 (q, 2 H, J = 7 Hz; OCH_2CH_3), 4.77 (d, 1 H, J = 5 Hz; H_{10}), 6.90–7.66 (m, 8 H; H_{ar}). The hydrochloride salt was prepared by acidification of an ethereal solution of **10** with anhydrous HCl gas. The salt was recrystallized from EtOH/Et_2O: mp 229–230 °C; EIMS m/z 279 (M^+), 250, 233, 206, 205, 178. Anal. ($C_{18}H_{18}ClN$) C, H, N.

(±)-5-Carboxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine Hydrochloride (11). A solution of **10** (0.5 g, 1.8 mmol) in 6 N HCl (10 mL) was warmed under reflux for 14 h. The water was removed under reduced pressure, affording **11** as a white crystalline solid (0.45 g, 1.6 mmol, 87%): mp 275–280 °C; IR (KBr) 3500–2300 (NH·HCl, CO_2H), 1750 (C=O) cm^{-1}; ^1H NMR (220 MHz, D_2O) δ 2.75 (d, 1 H, J = 17 Hz; H_{11ax}), 3.48 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 5.20 (d, 1 H, J = 5 Hz; H_{10}), 6.75–7.40 (m, 8 H, H_{ar}); EIMS m/z 251 (M^+), 233, 206, 205, 178. Anal. ($C_{16}H_{14}ClNO_2 \cdot 0.25H_2O$) C, H, N.

(±)-5-(Aminocarbonyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (12). A solution of **10** (0.53 g, 1.90 mmol) and sodium cyanide (10 mg) in anhydrous methanol (40 mL) which had been previously saturated at 5 °C with NH_3(g) was warmed to 60 °C in a sealed tube for 40 h.[37] After cooling to 5 °C, the solid which had formed was filtered, washed with H_2O, and air-dried, affording **12** (0.25 g, 1.0 mmol). The filtrate was extracted with CH_2Cl_2 (3 × 50), the organic phase was dried (K_2CO_3) and evaporated under reduced pressure, affording an additional quantity of **12** (0.19 g, 0.76 mmol). Recrystallization of the combined samples from ethanol gave analytically pure material (0.37 g, 1.5 mmol, 78%): mp 235–236 °C; IR (KBr) 3320–3000 ($CONH_2$, NH), 1680, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 2 H; $CONH_2$), 2.74 (d, 1 H, J = 17 Hz; H_{11ax}), 3.42 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.78 (d, 1 H, J = 5 Hz; H_{10}), 5.47 (br s, 1 H; N*H*), 6.95–7.93 (m, 8 H; H_{ar}); EIMS m/z 250 (M^+), 233, 206, 205, 179, 178. Anal. $C_{16}H_{14}N_2O \cdot 0.25H_2O$) C, H, N.

(±)-5-(Aminomethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (13). A suspension of **12** (0.23 g, 0.92 mmol) in THF (10 mL) was treated with a solution of $LiAlH_4$ in THF (2.0 mL of a 1.0 M solution, 2.0 mmol), and the resulting solution was allowed to stir at reflux under N_2 overnight. Excess $LiAlH_4$ was destroyed by addition of 1 N NaOH (2 mL) followed by H_2O (2 mL). The reaction mixture was subsequently partitioned between 1 N HCl (50 mL) and Et_2O (50 mL), and the organic phase was extracted with 1 N HCl (3 × 50 mL). The combined aqueous solution was treated with KOH pellets to pH = 14 and then extracted with Et_2O (4 × 50 mL). The organic fractions were combined, dried (K_2CO_3), and concentrated under reduced pressure, affording **13** as a pale yellow oil (0.20 g, 0.85 mmol, 92%). IR (film) 3290 (NH), 3240 and 3210 (NH_2) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 1.60–1.90 (m, 3 H; N*H*, NH_2), 2.65 (d, 1 H, J = 17 Hz; H_{11ax}), 3.33 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 3.48 (d, 1 H, J = 12 Hz; $CH_AH_BNH_2$), 3.65 (d, 1 H, J = 12 Hz; $CH_AH_BNH_2$), 4.65 (d, 1 H, J = 5 Hz; H_{10}), 6.75–7.25 (m, 8 H; H_{ar}). The dihydrochloride salt was generated by dissolving **13** in CH_3OH saturated with HCl(g) and crystallized by addition of Et_2O: mp broad dec >200 °C; EIMS m/z 236 (M^+), 219, 218, 207, 206, 179, 178. Anal. ($C_{16}H_{18}Cl_2N_2 \cdot 0.5H_2O$) C, H, N.

(±)-5-(Hydroxymethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (14). A suspension of **10**-HCl (0.41 g, 1.3 mmol) in THF (20 mL) at room temperature was treated with a solution of $LiAlH_4$ in THF (1.3 mL of a 1.0 M solution, 1.3 mmol), and the resulting solution was allowed to stir under N_2 overnight. Excess $LiAlH_4$ was destroyed by addition of 1 N NaOH (2 mL) followed by 2 mL of H_2O. The reaction mixture was subsequently partitioned between 1 N HCl (50 mL) and Et_2O (50 mL), and the organic phase was extracted with 1 N HCl (3 × 50 mL). The combined aqueous phase was treated with KOH pellets to pH = 14 and then extracted with Et_2O (4 × 50 mL). The organic fractions were combined, dried (K_2CO_3), and concentrated under reduced pressure, affording **14** as a white solid (0.28 g, 1.2 mmol, 91%) which crystallized from CH_3OH (0.24 g, 1.0 mmol, 77%): mp 229–231 °C; IR (KBr) 3350–2900 cm^{-1} (NH, OH); ^1H NMR (300 MHz, DMSO) δ 2.74 (d, 1 H, J = 17 Hz; H_{11ax}), 3.44 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 3.50–4.20 (br s, 2 H; N*H*, O*H*), 4.32 (d, 1 H, J = 12 Hz, CH_AH_BOH), 4.53 (d, 1 H, J = 12 Hz; CH_AH_BOH), 5.11 (d, 1 H, J = 5 Hz; H_{10}), 6.81–7.37 (m, 8 H; H_{ar}); EIMS m/z 237 (M^+), 220, 206, 179, 178. Anal. ($C_{16}H_{15}NO$) C, H, N.

(±)-*N*-Formyl-5-(hydroxymethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (15). A solution of **14** (0.80 g, 3.38 mmol) in ethyl formate (10 mL) in a sealed tube was warmed to 100 °C for 15 h. The contents were allowed to cool to room temperature and then partitioned between EtOAc (50 mL) and 1 N HCl (50 mL). The layers were separated, and the organic phase was washed with 1 N HCl (2 × 50 mL). The organic phase was dried (K_2CO_3), filtered, and concentrated under reduced pressure, affording **15** as an off-white foam. IR (KBr) 3600–3200 (OH), 1660 (NC=O) cm^{-1}; EIMS m/z 265 (M^+), 247, 236, 220, 206; HRMS calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1095.

(±)-5-(Methoxymethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (16). A solution of **15** (0.13 g, 0.50 mmol), KOH (0.05 g, 1.0 mmol), and CH_3I (0.5 mL, 8.0 mmol) in DMSO (5 mL) at 5 °C was allowed to warm slowly to room temperature and stand for 15 h. The reaction mixture was partitioned between EtOAc (20 mL) and H_2O (20 mL). The layers were separated, and the organic phase was washed with H_2O (20 mL), dried (K_2CO_3), filtered, and concentrated under reduced pressure, affording the crude methylated derivative (0.15 g). A mixture of this formamide (0.15 g) and 6 N HCl (10 mL) was warmed under reflux for 6 h. The resulting aqueous solution was washed with EtOAc (3 × 10 mL) and subsequently made strongly alkaline (pH = 14) by addition of KOH pellets. The alkaline products were extracted into EtOAc (3 × 20 mL), the organic phase was dried (K_2CO_3), filtered, and concentrated under reduced pressure, affording crude **16** (0.10 g). Purification by PC-TLC (1 mm plate thickness, chloroform/methanol/ammonia 95:5:1 eluent) yielded pure **16** as a pale yellow oil (0.08 g, 0.32 mmol, 64% from **15**): IR (film) 3300 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 1.25 (br s, 1 H; N*H*), 2.70 (d, 1 H, J = 17 Hz; H_{11ax}), 3.40 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 3.45 (s, 3 H; OCH_3), 4.20 (d, 1 H, J = 10 Hz; $CH_AH_BOCH_3$), 4.30 (d, 1 H, J = 10 Hz; $CH_AH_BOCH_3$), 4.38 (d, 1 H, J = 5 Hz; H_{10}), 6.80–7.30 (m, 8 H; H_{ar}). The hydrochloride salt of **16** was generated by HCl(g) in CH_3OH: mp broad dec >100 °C; EIMS m/z 251 (M^+), 220, 206, 179, 178. Anal. ($C_{17}H_{18}ClNO \cdot H_2O$) C, H, N.

(±)-5-[(Benzyloxy)methyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (17). A solution of **15** (0.27 g, 1.02 mmol), KOH (0.11 g, 2.04 mmol), and benzyl bromide (0.18 g, 1.02 mmol) in DMSO (10 mL) was allowed to stir at room temperature for 14 h. KOH (2 mL of a 5 M aqueous solution) was added, and the contents were warmed under reflux for 2 h. The mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL), and the layers were separated. The organic phase was washed with H_2O (50 mL), dried (K_2CO_3), filtered, and concentrated under reduced pressure, affording crude **17** as a yellow oil (0.35 g). Purification by PC-TLC (4 mm plate thickness, hexanes/ethyl acetate 1:1 eluent) gave pure **17** as a colorless oil (0.23 g, 0.70 mmol, 69%): IR (film) 3280 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 2.65 (d, 1 H, J = 17 Hz; H_{11ax}), 3.35 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 3.48 (br s, 1 H; N*H*), 4.20 (d, 1 H, J = 10 Hz; CH_AH_BOBz), 4.30 (d, 1 H, J = 10 Hz; CH_AH_BOBz), 4.37 (d, 1 H, J = 5 Hz; H_{10}), 4.65 (s, 2 H; $OCH_2C_6H_5$), 6.80–7.40 (m, 13 H; H_{ar}). The hydrochloride salt of **17** was generated by treating an ethereal solution of the free base with HCl(g) in CH_3OH to pH = 1. The crystals were collected by filtration and air-dried: mp 264–265 °C; EIMS m/z 327 (M^+), 236, 221, 220, 206, 179, 178, 91. Anal. ($C_{23}H_{22}ClNO$) C, H, N.

(±)-5-(Bromomethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (18). A solution of **15** (0.50 g, 1.9 mmol) in DMF (1 mL) was treated with thionyl bromide (0.22 mL, 2.8

(45) The stoichiometric ratio of acid to formamidine is crucial. Use of excess H_2SO_4 results in less than 5% conversion to **10** after 4 days in refluxing EtOH.

mmol) and the resulting solution was warmed to 40 °C over 16 h. Excess thionyl bromide and DMF were evaporated under a stream of N_2(g), and a solution of 48% HBr (5 mL) in CH_3OH (5 mL) was added. The reaction mixture was subsequently warmed under reflux for 65 h. After cooling to room temperature, the resulting solution was diluted with H_2O (50 mL), washed with EtOAc (3 × 50 mL), and then made strongly alkaline (pH = 14) by addition of KOH pellets. The alkaline products were extracted into EtOAc (3 × 50 mL), the organic phase was dried (K_2CO_3), filtered, and concentrated under reduced pressure, affording crude **18** (0.61 g). Purification by PC-TLC (2 mm plate thickness, hexane/ethyl acetate 5:1 eluent) yielded pure **18** as a colorless oil (0.49 g, 1.6 mmol, 84%). IR (film) 3280 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 2.65 (d, 1 H, J = 17 Hz; H_{11ax}), 2.90 (br s, 1 H; N*H*), 3.45 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.20 (d, 1 H, J = 12 Hz; CH_AH_BBr), 4.35 (d, 1 H, J = 12 Hz; CH_AH_BBr), 4.70 (d, 1 H, J = 5 Hz; H_{10}), 6.80–7.30 (m, 8 H; H_{ar}). An ethereal solution of **18** (0.49 g) was added to a solution of oxalic acid (0.20 g) in EtOH (5 mL). The resulting hydrogen oxalate salt crystals were collected by filtration and recrystallized from CH_3OH/Et_2O: mp 227–228 °C; EIMS m/z 301 and 299 (M^+), 221, 220, 179, 178; HRMS calcd for $C_{16}H_{14}{}^{79}BrN$ 299.0310, found 299.0305. Anal. ($C_{18}H_{16}BrNO_4$) C, H, N.

(±)-5-(Chloromethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (19). A solution of **15** (0.27 g, 1.02 mmol) in thionyl chloride (1.0 mL) containing DMF (0.2 mL) was warmed to 40 °C. After 6 h, the reaction mixture was diluted with CH_3OH (5 mL) and 6 N HCl (2 mL), and the contents were warmed under reflux for 46 h. The resulting solution was diluted with H_2O (50 mL), washed with EtOAc (3 × 50 mL), and then made strongly alkaline (pH = 14) by addition of KOH pellets. The alkaline products were extracted into EtOAc (3 × 50 mL), and the organic phase was dried (K_2CO_3), filtered, and concentrated under reduced pressure, affording crude **19** (0.24 g). Purification by PC-TLC (2 mm plate thickness, hexane/ethyl acetate 2:1 eluent) yielded pure **19** as a white solid (0.14 g, 0.55 mmol, 54%). IR (film) 3300 cm^{-1} (NH); ^1H NMR (220 MHz, $CDCl_3$) δ 2.68 (d, 1 H, J = 17 Hz; H_{11ax}), 3.05 (br s, 1 H; NH), 3.45 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.40 (d, 1 H, J = 12 Hz; CH_AH_BCl), 4.50 (d, 1 H, J = 12 Hz; CH_AH_BCl), 4.72 (d, 1 H, J = 5 Hz; H_{10}), 6.80–7.30 (m, 8 H; H_{ar}); EIMS m/z 257 and 255 (M^+), 221, 220, 206, 179, 178. An ethereal solution of **19** was treated with CH_3OH saturated with HCl(g) to pH = 1. The crystals were collected by filtration and recrystallized from CH_3OH/Et_2O: mp broad dec >230 °C. Anal. ($C_{16}H_{15}Cl_2N{\cdot}0.25H_2O$) C, H, N.

(±)-5-(Cyanomethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (20). A stirred slurry of **19** (0.76 g, 3.0 mmol) and NaCN (1.5 g, 30 mmol) in DMSO (10 mL) was warmed under reflux for 4 h. The reaction mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL), the layers were separated, and the organic phase was washed with H_2O (2 × 50 mL). The organic phase was dried (K_2CO_3), filtered, and concentrated under reduced pressure, affording crude **20** as an orange oil (0.82 g). Purification of **20** by PC-TLC (2 mm plate thickness, hexane/ethyl acetate 2:1 eluent) gave the pure sample (0.49 g, 2.0 mmol, 66%). IR (film) 3290 (NH), 2245 (CN) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 2.40 (br s, 1 H; N*H*) 2.45 (d, 1 H, J = 17 Hz; H_{11ax}), 3.25–3.50 (m, 3 H; H_{11eq} and CH_2CN), 4.75 (d, 1 H, J = 5 Hz; H_{10}), 6.80–7.35 (m, 8 H; H_{ar}). An ethereal solution of **20** (0.49 g) was treated with CH_3OH saturated with HCl(g) to pH = 1. The crystals were collected by filtration and recrystallized from CH_3OH/Et_2O: mp broad dec >250 °C; EIMS m/z 246 (M^+), 245, 220, 206, 205, 204, 179, 178. Anal. ($C_{17}H_{15}ClN_2{\cdot}0.25H_2O$) C, H, N.

(±)-5-(2-Aminoethyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (21). A solution of $LiAlH_4$ in THF (2.7 mL of 1.0 M solution, 2.7 mmol) was diluted in an additional 5 mL of THF and subsequently treated with **20**·HCl (0.25 g, 0.89 mmol). After 1 h at room temperature, the reaction was terminated by addition of 1 N NaOH (1 mL) and H_2O (1 mL). The reaction mixture was partitioned between 1 N HCl (25 mL) and Et_2O (50 mL), the layers were separated, and the organic phase was extracted with 1 N HCl (3 × 25 mL). The combined aqueous phase was treated with KOH pellets to pH = 14, and then extracted with Et_2O (4 × 50 mL). The organic fractions were combined, dried (K_2CO_3), and concentrated under reduced pressure, affording **21** as a pale yellow oil (0.22 g, 0.88 mmol, 99%). IR (film) 3380 and 3270 (NH, NH_2), cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 2.15–2.30 (m, 3 H; N*H*, NH_2), 2.35–2.50 (m, 1 H; $CH_2CH_2NH_2$), 2.55–2.70 (m, 1 H; $CH_2CH_2NH_2$); 2.65 (d, 1 H, J = 17 Hz; H_{11ax}), 2.85–3.00 (m, 2 H; CH_2NH_2), 3.35 (dd, 1 H, J = 17 and 5 Hz; H_{11eq}), 4.65 (d, 1 H, J = 5 Hz; H_{10}), 6.85–7.30 (m, 8 H; H_{ar}). The dihydrochloride salt was generated by dissolving **21** in CH_3OH saturated with HCl(g) and crystallized by addition of Et_2O: mp broad dec >260 °C; EIMS m/z 250 (M^+), 233, 220, 206, 179, 178. Anal. ($C_{17}H_{20}Cl_2N_2{\cdot}0.33H_2O$) C, H, N.

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Registry No. 1, 50537-17-2; **2**, 124070-07-1; **3**, 77086-18-1; 4, 87747-33-9; 4·oxalate, 87747-92-0; **5**, 124070-08-2; **5**·oxalate, 124070-26-4; **6**, 124070-09-3; **6**·oxalate, 124070-27-5; **7**, 124070-10-6; **7**·oxalate, 124070-28-6; **8**, 124070-11-7; **8**·oxalate, 124070-29-7; **9**, 124070-12-8; **9**·oxalate, 124098-43-7; **10**, 124070-13-9; **10**·HCl, 124070-31-1; 11, 124070-14-0; **12**, 124070-15-1; **13**, 124070-16-2; **13**·2HCl, 124070-30-0; 14, 124070-17-3; **15**, 124070-18-4; **16**, 124070-19-5; **16**·HCl, 124070-32-2; **17**, 124070-20-8; **17**·HCl, 124070-33-3; **18**, 124070-21-9; **18**·oxalate, 124070-34-4; **19**, 124070-22-0; **19**·HCl, 124070-37-7; **20**, 124070-23-1; **20**·HCl, 124070-35-5; **21**, 124070-24-2; **21**·2HCl, 124070-36-6; $Me_2NCH{=}NBu$-*t*, 23314-06-9; $H_3C(CH_2)_5I$, 638-45-9; $H_3C(CH_2)_9I$, 2050-77-3; (±)-5-methyl-N-[(*tert*-butylimino)methyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine, 124070-25-3.