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Synthesis and Structure–Activity Relationships of *N,N'*-Di-*o*-tolylguanidine Analogues, High-Affinity Ligands for the Haloperidol-Sensitive σ Receptor

Michael W. Scherz,[†] Michelle Fialeix,[†] James B. Fischer,[‡] N. Laxma Reddy,[‡] Alfred C. Server,[‡] Mark S. Sonders,[§] Barbara C. Tester,[§] Eckard Weber,[§,∥] Scott T. Wong,[†] and John F. W. Keana*[,†]

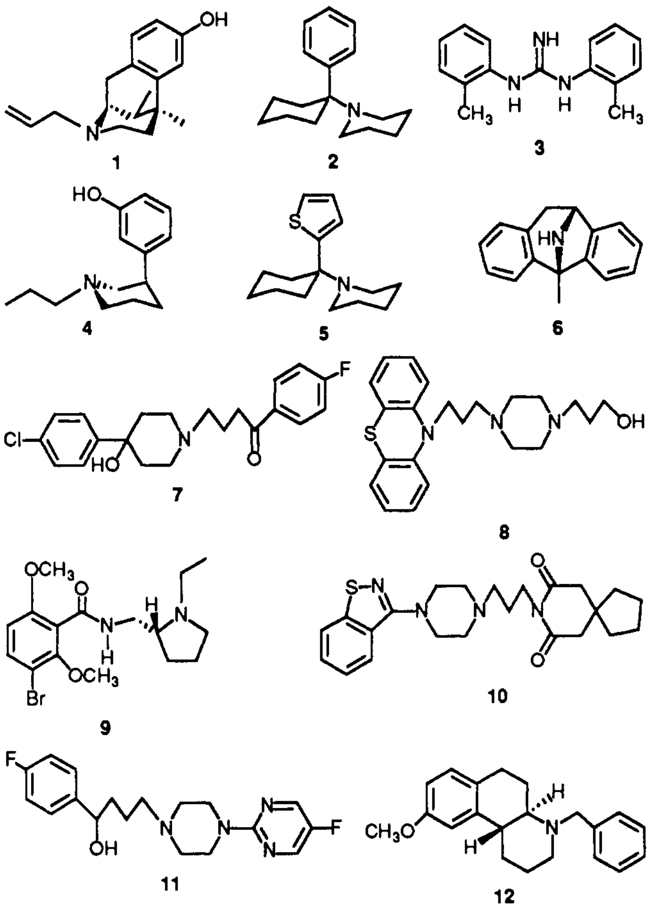
Department of Chemistry, University of Oregon, Eugene, Oregon 97403, and Vollum Institute for Advanced Biomedical Research, Oregon Health Sciences University, Portland, Oregon 97201, and Cambridge NeuroScience Research, Inc., Cambridge, Massachusetts 02139. *Received December 4, 1989*

With an eye toward the development of novel atypical antipsychotic agents, we have studied the structure–affinity relationships of *N,N'*-di-*o*-tolylguanidine (DTG, **3**) and its congeners at the haloperidol-sensitive σ receptor. A number of DTG analogues were synthesized and evaluated in in vitro radioligand displacement experiments with guinea pig brain membrane homogenates, using the highly σ-specific radioligands [^{3}H]-**3** and [^{3}H]-(+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine and the phencyclidine (PCP) receptor specific compounds [^{3}H]-*N*-[1-(2-thienyl)cyclohexyl]piperidine and [^{3}H]-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine. The affinity of *N,N'*-diarylguanidines for the σ receptor decreases with increasing steric bulk of ortho substituents larger than C_2H_5. Hydrophobic substituents are generally preferred over similarly positioned hydrophilic ones. Furthermore, electroneutral substituents are preferred over strongly electron donating or withdrawing groups. Significant binding to the σ receptor is usually retained as long as at least one side of the guanidine bears a preferred group (e.g. 2-$CH_3C_6H_5$). Replacement of one or both aryl rings with certain saturated carbocycles (e.g. cyclohexyl, norbornyl, or adamantyl) leads to a significant increase in affinity. By combining the best aromatic and best saturated carbocyclic substituents in the same molecule, we arrived at some of the most potent σ ligands described to date (e.g. *N*-*exo*-2-norbornyl-*N'*-(2-iodophenyl)guanidine, IC_{50} = 3 nM vs [^{3}H]-**3**). All of the compounds tested were several orders of magnitude more potent at the σ receptor than at the PCP receptor, with a few notable exceptions. This series of disubstituted guanidines may be of value in the development of potential antipsychotics and in the further pharmacological and biochemical characterization of the σ receptor.

Introduction

Certain benzomorphan opioids, represented by (+)-*N*-allylnormetazocine ((+) SKF-10,047, **1**) (Chart I), cause hallucinations and other bizarre behavioral effects in mammals.[1] A similar syndrome is elicited by phencyclidine (PCP, **2**),[2-4] which has been described as the best available drug model for schizophrenia.[5] In vitro radioligand binding and brain distribution experiments have distinguished two receptors which may mediate the psychotomimetic syndrome.[6-19] They have been termed the haloperidol-sensitive σ receptor,[20] characterized by the selective ligands [^{3}H]-*N,N'*-di-*o*-tolylguanidine ([^{3}H]DTG, [^{3}H]-**3**)[21] and [^{3}H]-(+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine ([^{3}H] (+)-3-PPP, [^{3}H]-**4**),[15,22] and the PCP receptor, characterized by its selective ligands [^{3}H]-*N*-[1-(2-thienyl)cyclohexyl]piperidine ([^{3}H]TCP, [^{3}H]-**5**)[23] and [^{3}H]-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine ([^{3}H](+)-MK-801, [^{3}H]-**6**).[24-26] Benzomorphans and PCP (**2**) can bind to both σ and PCP receptors. Although drug-discrimination studies in animals indicate that a significant part of the behavioral effects of PCP (**2**) and benzomorphans are mediated by PCP receptors, it remains to be established which of the two receptors mediates the psychotomimetic syndrome caused by these drugs in humans.[27,28]

Chart I



Antipsychotic neuroleptic drugs, widely used in the treatment of schizophrenia, act as antagonists of the dopamine D_2 receptor. Antagonist actions at this site are thought to mediate the therapeutic effects as well as the serious extrapyramidal side effects of these drugs. Interestingly, some of the most potent and clinically useful neuroleptics, such as haloperidol (**7**) and perphenazine (**8**), have high affinity for the σ receptors.[6-9] Furthermore, several atypical antipsychotic drugs, including remoxipride (**9**) and tiospirone (**10**), have recently been shown to bind tightly to the σ receptor, and may exert their beneficial effects through this site.[29-35] In clinical trials and in animal

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[†] University of Oregon.

[‡] Cambridge NeuroScience Research, Inc.

[§] Oregon Health Sciences University.

[∥] Present address: Department of Pharmacology, University of California, Irvine, CA 92717.

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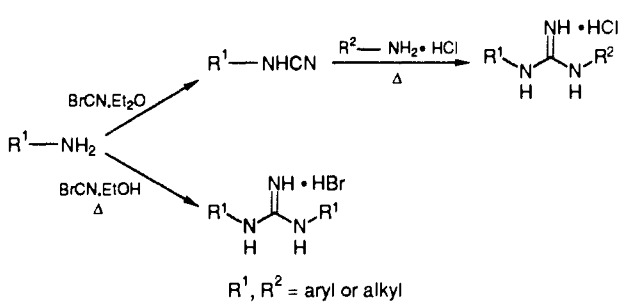
models predictive of antipsychotic efficacy, these and certain other non-dopaminergic antipsychotics (e.g. [α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol, BMY 14802, **11**) are devoid of the severe extrapyramidal side effects typically associated with D_2 receptor antagonism.[30,31] These findings suggest that the σ receptor may provide a novel therapeutic target in the treatment of schizophrenia. The biochemical function of the σ receptor is, however, still unclear.

The σ receptor is evidently not a dopamine receptor,[6,8,9] but it does appear to be involved in catecholamine release. Su et al.[36,37] and Campbell et al.[38] have described biochemically functional σ receptors in rodent vasa deferentia, in which (+)-3-PPP (**4**) enhances the electrically stimulated release of norepinephrine. Steinfels and Tam have reported that microinjected (+)-3-PPP (**4**) dose dependently inhibits the firing of dopaminergic neurons in anesthesized rats, and that **11** dose dependently antagonizes this response.[39] In experiments in a guinea pig ileum longitudinal muscle/myenteric plexus (LMMP) preparation, Campbell et al. have shown that certain σ receptor ligands dose dependently inhibit electrochemically or serotonin induced contractions of the LMMP via an opioid receptor independent mechanism.[40] These results suggest that the σ receptor may mediate its antipsychotic effects by inhibiting neurotransmitter release.

Scheme I. Synthetic Routes to Unsymmetrical (Top) and Symmetrical (Bottom) N,N′-Disubstituted Guanidines



The biological function of the PCP receptor is now well characterized. In in vitro electrophysiological experiments, PCP receptor ligands such as **6**,[41–43] TCP (**5**),[44,45] PCP (**2**),[46] and certain N,N′-disubstituted guanidines[47–49] (vide infra) potently obstruct the *N*-methyl-D-aspartate (NMDA) class of glutamate-gated, nonselective cation channels.[50–54] As a result, PCP receptor ligands are powerful neuroprotective agents against glutamate-induced neuronal cell death.[55–58]

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Such compounds have considerable therapeutic potential in the treatment of stroke, heart attack, brain trauma, or any other acute disorder involving ischemia.[51,59,60] NMDA receptor antagonism may also be responsible for the psychotomimetic effects of PCP receptor ligands.[14,27,61–64] These unwanted side effects may limit the usefulness of NMDA receptor antagonists as neuroprotective agents.

Our eventual goal is the complete biochemical characterization of the σ receptor. The combination of both the physiological and biochemical characterization of the σ receptor may yield new medicinal strategies for the development of novel antipsychotic agents. The design and synthesis of potent, highly specific probes for the σ receptor plays a central role in our efforts. Structurally simple derivatives of DTG (**3**) have already provided powerful tools for the characterization and isolation of the σ receptor.[19,21,65,66]

Herein, we report the preparation of more than 70 DTG congeners (Tables I–V) and their affinities for the σ receptor, as measured by their ability to displace $[^3H]$-**3** and/or $[^3H]$-**4** from guinea pig brain membrane suspensions. Given the tendency of other σ receptor ligands to cross-react with the PCP receptor, and the therapeutic potential of PCP receptor ligands, we also compiled displacement data for all compounds against $[^3H]$-**5** and/or $[^3H]$-**6**.[67] We discuss structure–activity relationships in this series of guanidines and compare our results with recent efforts by Largent et al.[68–70] and Manallack et al.[28,71,72] to define the the topographical requirements for high affinity binding to the σ receptor.

Chemistry

Unsymmetrical N,N′-disubstituted guanidines were prepared by the following known methods (Scheme I): (a) coupling an aryl or alkyl cyanamide with the appropriate amine hydrohalide salt either in refluxing chlorobenzene,[73] or (b) directly in a 1:1 melt without solvent.[74] The requisite cyanamides were synthesized from the corresponding amines by treatment with cyanogen bromide (BrCN) in dry ethereal solution,[73,74] or in the case of deactivated aromatic amines, in aqueous solution.[73] Symmetrical N,N′-disubstituted guanidines were readily obtained by directly reacting 2 equiv of the amine with 1 equiv of BrCN in ethanol (EtOH), without isolating the intermediate cyanamide. The N,N′,N″-trisubstituted guanidines were prepared by reacting dicyclohexylcarbodiimide with an amine in tetrahydrofuran (THF).[75] Cyclization of the appropriate diamine with BrCN in EtOH gave rise to the rigid guanidines **82**,[76] **84**,[77] **85**,[78] **86**,[79] and **87**.[80] Catalytic hydrogenation[19] of nitrophenylguanidines **19**, **26**, **27**, and **41** gave the corresponding aminophenylguanidines smoothly. The recent report of steroid binding at the σ receptor[81] prompted us to prepare several steroidal guanidines (Table V). The preparation of the requisite aminosteroids was achieved by published procedures.[82]

Binding Studies

In vitro radioligand binding assays using guinea pig brain membrane suspensions provided a rank order of potency of all compounds at the σ receptor and the PCP receptor, as determined by their IC_{50} vs $[^3H]$-**3** and $[^3H]$-**4**, or $[^3H]$-**5**, and $[^3H]$-**6**, respectively. The data are compiled in Tables I–V in order of decreasing potency at the σ receptor (i.e. increasing IC_{50} versus $[^3H]$-**3**). In general, all compounds are orders of magnitude more potent at the σ receptor than at the PCP receptor, with several notable exceptions (vide infra).

Results and Discussion

σ Receptor Affinity. The affinity of *N,N′*-diarylguanidines for the σ receptor is a sensitive function of their substitution pattern. Of the metasubstituted guanidines, *N,N′*-bis(3-ethylphenyl)guanidine (**13**) is the most potent (IC_{50} of 8.3 nM vs $[^3H]$-**3**). Modification of the meta substituent, either by decreasing (**21**) or increasing (**24**) steric bulk or by introducing iodine (**29**) or an hydroxyl group (**30**), results in reduced affinity.

The ortho position appears to be more tolerant to structural modifications. Small alkyl substituents such as CH_3 (DTG, **3**) or C_2H_5 (**14**), or especially iodine (cf. **15** and **16**), bestow high σ affinity. Thus, *N,N′*-bis(2-iodophenyl)guanidine (**15**, IC_{50} 14 nM vs $[^3H]$-**3**) proved to be among the most potent σ ligands of the *N,N′*-diarylguanidines (Table I) series. σ affinity decreases with increasing steric bulk in the ortho position: cf. ethyl (**14**) vs isopropyl (**22**) vs *tert*-butyl (**35**). Larger unsaturated substituents, such as phenyl (**47**) or styryl (**41** and **44**) result in a sharp drop in potency. Strongly electron withdrawing or donating ortho substituents such as nitro (**26**), trifluoromethyl (**31**), amino (**37**), or methoxy (**45**) decrease binding significantly.

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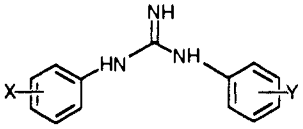
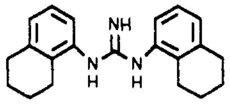
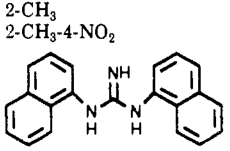
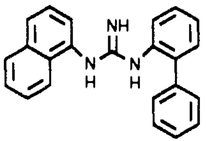
Table I. *N,N'*-Diarylguanidines and Their IC_{50}s against [^{3}H]-3, [^{3}H]-4, [^{3}H]-5, and/or [^{3}H]-6



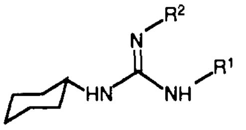
compd	X[b]	Y	mp, °C	proced (yield, %)[c]	formula[d]	IC_{50} (n*M*) against[a] [^{3}H]-3	[^{3}H]-4	[^{3}H]-5	[^{3}H]-6
13	3-C_2H_5	3-C_2H_5	96–98	B (20)	$C_{17}H_{21}N_3$	8.3 ± 0.2	30	82 ± 10	168 ± 38
14	2-C_2H_5	2-C_2H_5	158–161[e]	B (59)	$C_{17}H_{21}N_3$	13.8 ± 0.9	44	358 ± 53	820 ± 66
15	2-I	2-I	161–162	B (39)	$C_{13}H_{11}I_2N_3$	14 ± 1	16 ± 1	210 ± 60	240 ± 60
16	2-CH_3	2-I	163–165	A (57)	$C_{14}H_{14}IN_3$	21 ± 1	23 ± 2	2050 ± 50	nd
3	2-CH_3	2-CH_3	148–150	*f*	$C_{13}H_{17}N_3$	32 ± 1	38 ± 6	7800 ± 400	10700 ± 2100
17	3-$CH_3(CH_2)_2$	3-$CH_3(CH_2)_2$	69–70	B (20)	$C_{19}H_{25}N_3$	36 ± 2	nd	nd	2110 ± 10
18	4-Br-2-CH_3	4-Br-2-CH_3	209–210	A (8)[g]	$C_{15}H_{15}Br_2N_3$	37 ± 3	32 ± 1	>10000	nd
19	2-CH_3	2-CH_3-4-NO_2	177–179	A (91)[h]	$C_{15}H_{16}N_4O_2$	37 ± 5	39 ± 2	5700 ± 495	nd
20			217–218	B (48)	$C_{21}H_{25}N_3$[i]	58.8 ± 3.2	nd	nd	1570 ± 210
21	3-CH_3	3-CH_3	105–107[j]	B (38)	$C_{15}H_{17}N_3$	59 ± 4	84 ± 3	370 ± 30	330 ± 30
22	2-$(CH_3)_2CH$	2-$(CH_3)_2CH$	175–177[k]	B (53)	$C_{19}H_{25}N_3$	65 ± 7	nd	nd	275 ± 69
23	2-CH_3	2,6-CH_3	216–218	A (47)	$C_{16}H_{19}N_3$	70 ± 5	42 ± 7	1900	nd
24	3-$(CH_3)_2CH$	3-$(CH_3)_2CH$	118–119	B (32)[l]	$C_{19}H_{25}N_3$	77 ± 23	nd	nd	498
25	2,6-CH_3	2,6-CH_3	245–246[m]	B (25)	$C_{17}H_{21}N_3$	90 ± 18	66 ± 8	32000	nd
26	2-CH_3	2-NO_2	124–125	A (67)	$C_{14}H_{14}N_4O_2$	113 ± 15	nd	2100 ± 71	nd
27	2-CH_3-4-NO_2	3-OH	222–223	A (58)	$C_{14}H_{14}N_4O_3$	118 ± 5	94 ± 4	37000	nd
28			210–211[n]	B (30)	$C_{21}H_{17}N_3$	133 ± 39	nd	nd	134 ± 39
29	3-I	3-I	172–173	B (15)	$C_{13}H_{11}I_2N_3$[o]	173 ± 42	nd	1100 ± 88	nd
30	2-CH_3	3-OH	157–159	A (85)	$C_{14}H_{15}N_3O \cdot HCl \cdot 0.25H_2O$	207 ± 19	155 ± 25	2500 ± 212	nd
31	2-CF_3	2-CF_3	149–150	B (3)	$C_{15}H_{11}F_6N_3$	215 ± 7	766 ± 119	4150 ± 350	nd
32	4-C_2H_5	4-C_2H_5	136–138[p]	B (38)	$C_{17}H_{21}N_3$	245 ± 38	nd	nd	10300 ± 600
33	4-$(CH_3)_2CH$	4-$(CH_3)_2CH$	137–139	B (27)	$C_{19}H_{25}N_3$	270 ± 26	nd	nd	26800 ± 15100
34	2-CH_3	2-CH_3-4-NH_2	232.5–234.5	(78)[h]	$C_{15}H_{18}N_4 \cdot HCl$	280 ± 14	220 ± 14	4350 ± 389	nd
35	2-$(CH_3)_3C$	2-$(CH_3)_3C$	204–205	B (33)	$C_{21}H_{29}N_3$	356 ± 63	nd	nd	38300 ± 14900
36	H	H	176–178	*f*	$C_{15}H_{17}N_3$	397 ± 21	400	3450 ± 318	nd
37	2-CH_3	2-NH_2	161–162	(91)[q]	$C_{14}H_{16}N_4$	463 ± 15	440 ± 35	12000	nd
38	4-CH_3	4-CH_3	168–170[r]	B (20)	$C_{15}H_{17}N_3$[s]	535 ± 62	nd	31000	13300 ± 3300
39	4-Br	4-Br	166–168	B (27)	$C_{15}H_{11}Br_2N_3$	540 ± 25	350 ± 35	34000	nd
40	2-CH_3-4-NO_2	2-CH_3-4-NO_2	248–249	A (63)	$C_{15}H_{15}N_5O_4 \cdot HCl$	760 ± 169	850	4300	nd
41	2-CH_3	2-(*E*-$CHCHC_6H_5$)	168–169	A (41)[t]	$C_{22}H_{21}N_3 \cdot 0.25H_2O$	920 ± 201	nd	nd	>10000
42			190–191	A (36)	$C_{23}H_{19}N_3$	935 ± 44	nd	nd	>10000
43	2-CH_3-4-NH_2	3-OH	242–248	(100)[u]	$C_{14}H_{16}N_4O \cdot 2HCl$	962 ± 89	nd	nd	>10000
44	2-I	2-(*E*-$CHCHC_6H_5$)	159–161	A (45)	$C_{21}H_{18}IN_3$	1200 ± 200	nd	nd	>10000
45	2-CH_3O	2-CH_3O	117–119[v]	B (35)	$C_{15}H_{17}N_3O_2$	2200	3800	nd	1600
46	2-CH_3-4-NH_2	2-CH_3-4-NH_2	>350, dec	(100)[w]	$C_{15}H_{19}N_5 \cdot 3HCl$	7150 ± 106	5100 ± 353	>100000	nd
47	C_6H_5	C_6H_5	181–182	B (62)	$C_{25}H_{21}N_3$	8113 ± 43	nd	nd	>10000

[a] [^{3}H]-3, [^{3}H]*N,N'*-Di-*o*-tolylguanidine; [^{3}H]-4, [^{3}H]-(+)-3-(3-hydroxyphenyl)-*N*-(1-propyl)piperidine; [^{3}H]-5, [^{3}H]-*N*-[1-(2-thienyl)cyclohexyl]piperidine; [^{3}H]-6, [^{3}H]-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine; nd, not determined. IC_{50} values are mean ± SEM and, with a few exceptions, are the result of three to seven determinations. Values without error limits were obtained from single determinations. [b] For those compounds, in which X ≠ Y, the guanidine was prepared by coupling the cyanamid derived from the X entry with the amine hydrohalide salt of the Y entry. For compounds **20**, **28**, and **42** the entire structure is shown. See the Experimental Section for details. [c] Yields refer to analytically pure products. [d] Elemental analyses for all new compounds were obtained for C, H, and N, and were within 0.4% of the theoretical values for the indicated molecular formula. [e] Lit. mp 161–162 °C. Beaver, D. J. U.S. Patent 2 633 474, 1953; *Chem. Abstr.* **1953**, *47*, 6171f. [f] Purchased from Aldrich Chemical Co. [g] Reference 21. [h] Reference 19. [i] C: calcd, 78.96; found, 78.40. [j] Lit. mp 110 °C. Ali, M. U.; Paranjpe, M. G. *J. Indian Chem. Soc.* **1986**, *63*, 253. [k] Ikeda, T.; Imai, E.; Fukumoto, H.; Tanaka, K.; Suematsu, K.; Urawa, M.; Takenouchi, M. Eur. Patent 179 642, 1986; *Chem. Abstr.* **1986**, *105*, 181470h. [l] 3-Isopropylaniline was prepared according to the literature procedure: Saxena, A. K.; Arunamurthy, V.; Patnaik, G. K.; Jain, P. C.; Anand, N. *Indian J. Chem.* **1980**, *19B*, 873. [m] Lit. mp 252–253 °C. Lempert, K.; Puskas, J.; Bekassy, S. Period. *Polytech., Chem. Eng. (Budapest)* **1968**, *12*, 123; *Chem. Abstr.* **1969**, *70*, 11239f. [n] Lit. mp 197.5–198 °C. Naunton, W. J. S. *J. Soc. Chem. Ind.* **1926**, *45*, 376; *Chem. Abstr.* **1927**, *21*, 672.[3,4] [o] N: calcd, 9.07; found, 8.54. [p] Lit. mp 137–138 °C. Pauksch, H. *Chem. Ber.* **1884**, *17*, 2804; *Beilstein* **12**, 1091c. [q] Prepared by catalytic hygrogenation of **26**, as described in ref 19. [r] Lit. mp 166.5–167.5 °C. Nauton, W. J. S. *J. Soc. Chem. Ind.* **1926**, *45*, 376; *Chem. Abstr.* **1927**, *21*, 672. [s] C: calcd, 75.28; found, 74.79. [t] 2-Aminostilbene was prepared according to the literature procedure: Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941. [u] Prepared by catalytic hygrogenation of **27**, as described in ref 19. [v] Lit. mp 116–117 °C. Schotte, G. Ger. Patent 509 264, 1927; *Chem. Abstr.* **1931**, *25*, 712.[5] [w] Prepared by catalytic hydrogenation of **40**, as described in ref 19.

Para substituents of increasing steric bulk lead to a rise in binding affinity: cf. methyl (**38**) vs ethyl (**32**) and isopropyl (**33**). High affinity for the σ receptor is usually but not always (e.g. **37**, **41**, and **44**) retained as long as one of the two aryl rings bears a preferred group such as 2-CH_3 or 2-I. Thus, a para-situated electron withdrawing group is well tolerated in *N*-(2-methylphenyl)-*N'*-(2-methyl-4-nitrophenyl)guanidine (**19**), but not in the symmetrical *N,N'*-bis(2-methyl-4-nitrophenyl)guanidine (**40**). A similar trend is illustrated by the decreasing potency of **3** vs **34** vs **46**.

Replacement of one or both of the aryl rings with certain saturated carbocycles such as cyclohexyl (Table II), norbornyl (Table III), or adamantyl (Table IV) leads to a

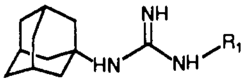
Table II. Cyclohexyl-Substituted Guanidines and Their IC_{50}s against [^{3}H]-3, [^{3}H]-4, [^{3}H]-5, and/or [^{3}H]-6



compd	R_1	R_2	mp °C	proced (yield, %)[b]	formula[c]	IC_{50} (nM) against[a] [^{3}H]-3	[^{3}H]-4	[^{3}H]-5	[^{3}H]-6
48	2-CH_3-C_6H_4	H	145–146	A (22)	$C_{14}H_{21}N_3$	12 ± 3	15 ± 1	>10 000	10 000
49	adamant-1-yl	H	269–271[d]	(44)[e]	$C_{17}H_{29}N_3 \cdot HCl$	13 ± 2	8	>10 000	nd
50	C_6H_{11}	H	181–182[f]	B (30)	$C_{13}H_{25}N_3$	71 ± 7	48 ± 5	>10 000	nd
51	C_6H_{11}	OH	123–124[g]	C	$C_{13}H_{25}N_3O$	217 ± 36	140 ± 17	>10 000	nd
52	C_6H_{11}	CH_3	278–279[h]	C (18)	$C_{14}H_{27}N_3 \cdot HCl$[i]	237 ± 56	145 ± 24	>10 000	>10 000
53	C_6H_{11}	*n*-C_8H_{17}	174–178	C (37)	$C_{21}H_{41}N_3 \cdot HCl$	238 ± 76	237 ± 16	nd	>10 000
54	C_6H_{11}	CH_2CHCH_2	238–241	C (15)	$C_{16}H_{29}N_3$	513 ± 57	163 ± 15	>10 000	>10 000

[a] See footnote *a* in Table I. [b] See footnote *c* in Table I. [c] See footnote *d* in Table I. [d] Lit.[74] mp 267–268 °C. [e] Prepared according to the literature procedure (ref 74). [f] Lit. mp 181–182 °C. Chambers, R. W.; Moffatt, J. G.; Khorana, H. G. *J. Am. Chem. Soc.* **1957**, *79*, 4240. [g] Lit.[75] mp 123–124 °C. [h] Ouchi, S.; Hayashi, E. Jap. Patent 46/27781, 1971; *Chem. Abstr.* **1971**, *77*, 36249s. [i] N: calcd, 15.34; found, 14.81.

Table III. Variously Substituted Adamantylguanidines and Their IC_{50}s against [^{3}H]-3, [^{3}H]-4, [^{3}H]-5, and/or [^{3}H]-6



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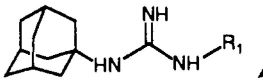

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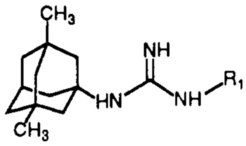
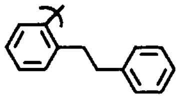
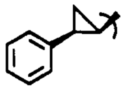
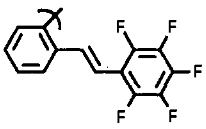
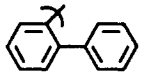
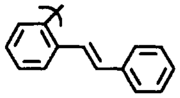
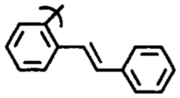
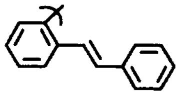
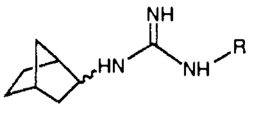


III

compd	structure	R_1	mp, °C	proced (yield, %)[b]	formula[c]	IC_{50} (nM) against[a] [^{3}H]-3	[^{3}H]-4	[^{3}H]-5	[^{3}H]-6
55	II	2-I-C_6H_4	248–250	A (43)	$C_{17}H_{22}IN_3 \cdot HCl$	5.2 ± 0.4	nd	nd	>10 000
56	II	2-CH_3-C_6H_4	166–167	A (64)	$C_{18}H_{25}N_3$[d]	6 ± 2	nd	nd	>10 000
57	I	2-I-C_6H_4	264–265	A (66)	$C_{17}H_{22}IN_3 \cdot HCl$	6 ± 5	5	nd	>10 000
58	I	2-CH_3-C_6H_4	160–161	A (71)	$C_{18}H_{25}N_3$	8 ± 0.3	8 ± 0.3	32 000	nd
49	I	C_6H_{11}	269–271	(44)[e]	$C_{17}H_{29}N_3 \cdot HCl$	13 ± 2	8	>10 000	nd
59	III	2-CH_3-C_6H_4	248–250	A (59)[f]	$C_{20}H_{29}N_3 \cdot HCl$	15 ± 7	nd	nd	2000
60	I	adamant-1-yl	289–291[g]	(15)[e]	$C_{21}H_{33}N_3 \cdot HCl$	16 ± 1	11	>10 000	nd
61	III	2-I-C_6H_4	264–266	A (46)	$C_{19}H_{26}IN_3 \cdot HCl$	16 ± 6	nd	nd	4000
62	I	2-NO_2-C_6H_4	135–136	A (48)	$C_{17}H_{22}N_4O_2$	30	20	nd	>10 000
63	I		235–236	(80)[h]	$C_{25}H_{31}N_3 \cdot HCl$[i]	112 ± 40	nd	nd	>10 000
64	I		254–255	A (49)	$C_{20}H_{27}N_3 \cdot HCl$	120 ± 8	nd	nd	>10 000
65	II	adamant-2-yl	336–338	(48)[j]	$C_{21}H_{33}N_3 \cdot HCl$	203 ± 80	nd	>10 000	nd
66	I		257–258	A (45)	$C_{25}H_{24}F_5N_3 \cdot HCl \cdot 0.8H_2O$	245 ± 35	nd	nd	>10 000
67	I		173–174	A (76)	$C_{23}H_{27}N_3$	300 ± 101	nd	nd	>10 000
68	I		234–235	A (60)	$C_{25}H_{29}N_3 \cdot HCl$	345 ± 136	nd	nd	3500 ± 1314
69	II		205–207	A (58)	$C_{25}H_{29}N_3 \cdot HCl \cdot 0.5H_2O$	370 ± 2	nd	nd	>10 000
70	III		240–241	A (47)	$C_{27}H_{33}N_3 \cdot HCl$[k]	970 ± 47	nd	nd	>10 000

[a] See footnote *a* in Table I. [b] See footnote *c* in Table I. The guanidines were prepared from the corresponding adamantyl cyanamides. [c] See footnote *d* in Table I. [d] C: calcd, 76.32; found, 75.85. [e] See footnote *e* in Table II. [f] 1-Amino-3,5-dimethyladamantane was prepared according to the literature procedure: Stetter, H.; Mayer, J.; Schwarz, M.; Wulff, K. *Chem. Ber.* **1960**, *93*, 226. [g] Lit.[74] mp 288–290 °C. [h] Prepared by catalytic hydrogenation of **68**, following the procedure in ref 19. [i] C: calcd, 73.28; found, 72.82. [j] Prepared following the literature[74] procedure for the preparation of **60**. [k] C: calcd, 74.39; found, 73.92.

Table IV. Norbornyl-Substituted (I) and Isobornyl-Substituted (II) Guanidines and Their IC_{50}s against [^{3}H]-3, [^{3}H]-4, [^{3}H]-5, and/or [^{3}H]-6



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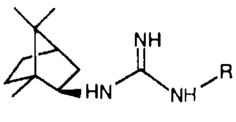

II

compd	structure (endo/exo)	R	mp, °C	proced (yield, %)[b]	formula[c]	IC_{50} (nM) against[a]			
						[^{3}H]-3	[^{3}H]-4	[^{3}H]-5	[^{3}H]-6
71	I (exo)	2-I-C_6H_4	170–171	A (24)	$C_{14}H_{18}IN_3$	4 ± 1	nd	nd	>10 000
72	I (endo)	2-I-C_6H_4	158–159	A (77)	$C_{14}H_{18}IN_3$	5 ± 2	nd	nd	>10 000
73	I (endo)	2-CH_3-C_6H_4	156–158	A (68)	$C_{15}H_{21}N_3$	6 ± 1	nd	nd	>10 000
74	I (exo)	2-CH_3-C_6H_4	169–170	A (86)	$C_{15}H_{21}N_3 \cdot 0.15H_2O$	7.7 ± 0.2	nd	nd	>10 000
75	I (endo)	*endo*-norborn-2-yl	248–250	A (68)	$C_{15}H_{25}N_3 \cdot HCl$	16 ± 1	nd	nd	>10 000
76	II	2-I-C_6H_4	248–250	A (25)	$C_{18}H_{27}N_3 \cdot HCl$	18 ± 6	nd	nd	>10 000
77	I (exo)	*exo*-norborn-2-yl	293–295	A (80)	$C_{15}H_{21}N_3 \cdot HBr$	22	nd	nd	5 000
78	II	2-CH_3-C_6H_4	156–157	A (68)	$C_{15}H_{25}N_3$	25 ± 4	nd	nd	5 000

[a] See footnote *a* in Table I. [b] See footnote *c* in Table I. The guanidines were prepared from the corresponding (±)-norbornyl or (*R*)-(−)-isobornyl amines. [c] See footnote *d* in Table I.

significant increase in affinity for the σ receptor. For example *N*-cyclohexyl-*N*′-(2-methylphenyl)guanidine (**48**) exhibits an IC_{50} of 12 nM vs [^{3}H]-**3**, compared to 32 nM for DTG (**3**). Symmetrical *N*,*N*′-diadamantyl-(**60**) and *N*,*N*′-dinorbornylguanidines (**75** and **77**) are potent σ receptor ligands, with affinities in the low nanomolar range. The structure–activity relationships described above in the N,N′-diarylsubstituted guanidines series are also born out in the *N*-aryl-*N*′-norbornyl (Table IV), and *N*-aryl-*N*′-adamantyl (Table III) guanidines. Thus, large aromatic ortho substituents greatly reduce affinity (**63**, **64**, **66–70**). We were gratified to find that ortho substitution with preferred groups (**55–58** and **71–74**) provides some of the most potent σ receptor ligands reported to date (e.g. *N*-(*exo*-norborn-2-yl)-*N*′-(2-iodophenyl)guanidine (**71**), IC_{50} 4 nM vs [^{3}H]-**3**). The sheer steric bulk of the saturated carbocycles does not appear to be solely responsible for the high affinity of these ligands, since increasing the steric bulk further does not result in increased σ receptor affinity. Thus, the 1- or 2-adamantylguanidines (**57** and **58**, **55** and **56**, respectively) are by a factor of approximately 3 more potent than their 3,5-dimethyladamant-1-yl analogues (**59** and **61**). Similarly, the *exo*- or *endo*-2-norbornylguanidines (**71** and **74**, **72** and **73**, respectively) are approximately 4 times more potent than their *exo*-2-isobornyl-substituted analogues (**76** and **78**). In summary, this series of cycloalkyl-substituted guanidines includes excellent σ receptor ligands, with several compounds approaching subnanomolar IC_{50}s against [^{3}H]-**3**.

Several *N*,*N*′-dicyclohexyl-*N*″-substituted-guanidines (**51–54**) were prepared (Table II). Although they are all less potent than the parent *N*,*N*′-dicyclohexylguanidine (**50**), they retain significant binding to the σ receptor.

Recently, Su et al. have reported the binding of several steroids, notably progesterone, to the σ receptor.[81] This prompted us to prepare the steroidal guanidines **81** and **88** (Table V). We chose these particular steroids for their structural similarity to progesterone and their availability. The pregnen-20-one derivative **81** proved to have moderate affinity for the σ receptor. The structural requirements for steroid binding at the σ receptor are not known. It is interesting to note that the octahydrobenzo[*f*]quinoline (OHBQ) series of σ receptor ligands[68–70] (e.g. (±)-*trans*-9-methoxy-*N*-benzyl-OHBQ, **12**) share the same ring system with the A, B, and C rings of the steroid nucleus. Unlike the OHBQ series however, the steroids reported to bind at the σ receptor lack of nitrogen atom.

Rigid Analogues. We have prepared (Table V) several rigid guanidines as an approach toward defining the conformation in which N,N′-disubstituted guanidines bind at the σ receptor. Space-filling molecular models clearly indicate that steric crowding precludes those rotational isomers around the guanidine carbon–nitrogen bond in which both guanidine substituents simultaneously occupy the positions anti to the unsubstituted nitrogen (i.e. conformation A in Figure 1). Therefore, two possible rotomers around a symmetrically N,N′-disubstituted guanidine function remain (Figure 1): either a syn,anti conformation (B), or a syn,syn conformation (C). In the single-crystal X-ray crystallographic analysis of both the free base and the hydrochloride salt of *N*-adamant-1-yl-*N*′-(2-iodophenyl)guanidine (**57**), we found that the former crystallized in the syn,anti, and the latter in the syn,syn conformation.[83] In both cases the phenyl ring was essentially perpendicular to the plane of the guanidine function. This solid state analysis suggests that both syn,syn and syn,anti conformations are energetically accessible to the N,N′-disubstituted guanidines.

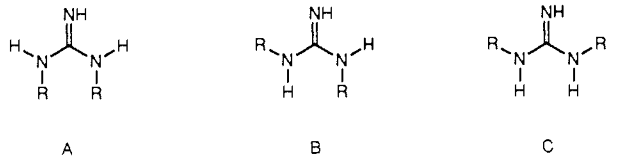

Figure 1. The three possible conformations of symmetrical N,N′-disubstituted guanidines. Conformation A is designated as anti,anti; B as syn,anti; C as syn,syn.

We prepared rigid guanidines which were designed to test all three of these conformations. Amino diazepine **86** and amino perimidine **87** are analogues of the anti,anti conformation, and proved to be, as expected, completely devoid of affinity for the σ receptor. The amino quinazoline **85** simulates the syn,anti conformation, and shows poor σ binding (IC_{50} 4100 nM vs [^{3}H]-**3**); imino imidazolidine **82** mimics the syn,syn conformation and has an IC_{50} of 340 nM vs [^{3}H]-**3**, slightly better than its nonrigid analogue, *N*,*N*′-diphenylguanidine (**36**). Removal of one of the phenyl rings (**84**) results in a large drop of binding affinity. These results suggest that the *N*,*N*′-diarylguanidines may prefer to bind in a syn,syn conformation at the σ receptor, and that the ethylene bridge in **82** does not interfere with high-affinity binding.

σ **Receptor Site Model.** The structural requirements for high affinity binding to the σ receptor have been dis-

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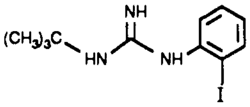
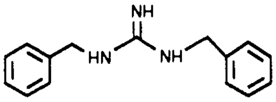
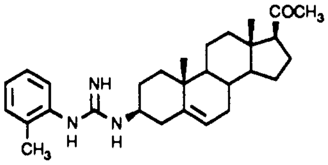
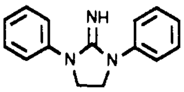
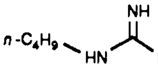
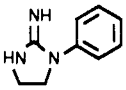
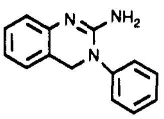
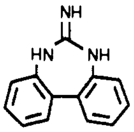
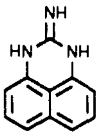
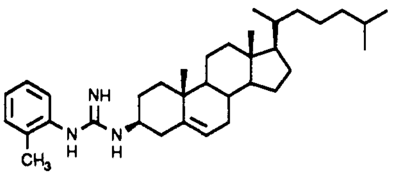
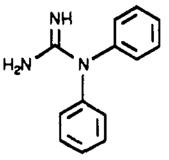
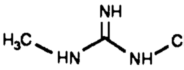
(83) Weakley, T. J. R.; Scherz, M. W.; Keana, J. F. W. *Acta Crystallogr.* **1990**, in press.

Table V. Miscellaneous and Rigid Guanidines and Their IC_{50}s against [^{3}H]-3, [^{3}H]-4, [^{3}H]-5, and/or [^{3}H]-6

compd	structure	mp, °C	proced (yield, %)[b]	formula[c]	IC_{50} (nM) against[a] [^{3}H]-3	[^{3}H]-4	[^{3}H]-5	[^{3}H]-6
79		184–186	A (49)[d]	$C_{11}H_{16}IN_3$·HCl	21.1 ± 1.5	nd	nd	>9600
80		143–145[e]	B (20)	$C_{15}H_{17}N_3$·HBr	90	33 ± 1	6800 ± 300	nd
81		274–276	A (10)[f]	$C_{29}H_{41}N_3O$·HCl	250 ± 100	nd	nd	>10 000
82		159–161[g]	B (43)	$C_{15}H_{15}N_3$	340 ± 43	nd	nd	>10 000
83		121–122	(37)[h]	$C_9H_{21}N_3 \cdot C_6H_3N_3O_7$	750 ± 33	800	49 000 ± 700	nd
84		172–174	B (25)	$C_9H_{11}N_3$·HBr	3,500	nd	>10 000	nd
85		174–180	*i*	$C_{14}H_{13}N_3$	4100	nd	>10 000	nd
86		238–240[j]	B (20)	$C_{13}H_{11}N_3$	>10 000	nd	nd	>10 000
87		297–299	*k*	$C_{11}H_9N_3$	>10 000	nd	nd	>10 000
88		228–230	A (41)[f]	$C_{35}H_{55}N_3$·HCl	>10 000	nd	nd	>10 000
89		140–141	(21)[l]	$C_{13}H_{13}N_3$	>100 000	>100 000	nd	nd
90		142–144[m]	B (20)	$C_3H_9N_3$·HBr	>100 000	>10 000	>10 000	nd

[a] See footnote *a* in Table I. [b] See footnote *c* in Table I. [c] See footnote *d* in Table I. [d] Prepared by reaction of 2-iodophenylcyanamide and *tert*-butylamine. [e] Lit. mp 186 °C (HCl salt). Braun, C. E.; Randall, W. M. *J. Am. Chem. Soc.* **1934**, *56*, 2134. [f] Purified by preparative TLC ($CHCl_3$/EtOH, 95:5). 3α-Amino-5-cholestene and 3α-amino-5-pregnen-20-one were prepared according to the literature[79] procedure. [g] Lit.[76] mp 162 °C. [h] Prepared and characterized as the picrate salt (lit. mp 122 °C) according to the literature procedure: Mold, J. D.; Ladino, J. M.; Scantz, E. J. *J. Am. Chem. Soc.* **1953**, *75*, 6321. [i] Prepared according to the literature[78] procedure (lit. mp 175–178 °C). [j] Lit.[79] mp 208–209 °C. [k] Purchased from Aldrich Chemical Co. [l] Prepared according to the literature procedure: Arndt, F. *Chem. Ber.* 1917, *50*, 1261. [m] Lit. mp 144 °C. Mold, J.; Ladino, J.; Schantz, E. *J. Am. Chem. Soc.* **1953**, *75*, 6321.

cussed by Wikström and Largent et al.[68-70] They find that a 3- or 4-phenylpiperidine ring system and a lipophilic N-substituent are key features in most (but not all) classes of potent σ receptor ligands. We suggest that the diarylguanidines mimic this feature (Figure 2) when binding to the σ receptor. Our data are also in line with the finding of Largent et al. that σ affinity increases with increasing lipophilicity of the N-substituent.[68-70] The σ receptor is not very structure sensitive, since aryl-, cyclohexyl-, norbornyl-, and adamantyl-substituted guanidines all can exhibit high affinity. The σ receptor site model proposed by Manallack et al.[28,71,72] is consistent with our finding that

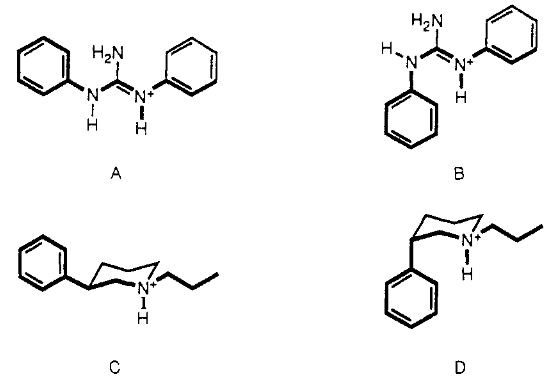


Figure 2. Structural similarities between different conformations of the ring systems of the protonated forms of the σ receptor ligands DTG (A and B) and 3-PPP (C and D). The heavy bonds indicate shared connectivities between A and C, and between B and D. They are not meant to imply that the phenyl rings lie in the plane of the guanidine.

good σ affinity is usually retained as long as one side of the guanidine bears a preferred group. Thus, the 2-methylphenylguanidine substituent presents to the receptor the "primary pharmacophor", and the proposed "lipophilic cleft" accepts the variously modified guanidine substituents, e.g. cyclohexyl, norbornyl, or adamantyl. However, the model of Manallack et al. must be revised to accommodate the *N*,*N*′-dinorbornyl- and *N*,*N*′-diadamantylguanidines (**75** and **77** and **60**, respectively), which bind tightly to the σ receptor but are too bulky to be accommodated within the hypothesized narrow hydrophobic pocket of the primary pharmacophor. Furthermore, within our series of compounds, we find no evidence for the proposed secondary binding site for phenolic substituents (cf. **30** vs **3**) within the primary pharmacophor.[72]

PCP Receptor Affinity. In general, all of the guanidines we report here are poor ligands for the PCP receptor (IC_{50} vs [^{3}H]-**5** or [^{3}H]-**6** > 5000 nM), with several notable exceptions. The ortho- or meta-substituted *N*,*N*′-diarylguanidines **13**–**15**, **21**, **22**, **24**, and **28** have submicromolar IC_{50}s at the PCP receptor, as well as at the σ receptor. The structural requirements for high-affinity binding of N,N′-disubstituted guanidines to the PCP receptor are more restrictive than for the σ receptor. Only small, nonpolar ortho- and meta-substituents are well tolerated. The most potent PCP receptor ligand in this series is *N*,*N*′-bis(1-naphthyl)guanidine (**28**) (IC_{50} 134 nM vs [^{3}H]-**6**), which also binds with equal affinity at the σ receptor (IC_{50} vs [^{3}H]-**3** 133 nM). Cycloalkyl-substituted guanidines (Tables II–IV) are devoid of significant affinity for the PCP receptor.

In separate studies, we have found that *N*,*N*′-diarylguanidines which bind to the PCP receptor have powerful neuroprotective properties against glutamate-induced neuronal cell death.[48,49] Whether or not they possess psychotomimetic properties similar to other PCP receptor ligands is currently under active investigation. These compounds constitute a novel structural class of noncompetitive *N*-methyl-D-aspartate antagonists, which are of considerable interest as potential therapeutic neuroprotective agents.[55–58]

Conclusions

We have described a new series of substituted guanidines, which includes some of the most potent ligands for the haloperidol-sensitive σ receptor described to date. Their structure and synthesis are uncomplicated, and a wide array of structural variations result in high σ receptor affinity. These compounds are candidates for the development of novel antipsychotics and for the further characterization of the σ receptor through affinity labeling approaches. We have also shown that certain *N*,*N*′-diarylguanidines cross-react with the PCP receptor. Separate studies have demonstrated that these compounds make up a new class of noncompetitive NMDA antagonists, which are of interest as potential therapeutic agents against glutamate-induced neuronal cell death.

Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} (0.2 mm) plastic-coated sheets. Guanidines were visualized on TLC sheets with 254-nM UV light or as a blue spot with bromcresol spray reagent (Aldrich Chemical Co.) Preparative TLC was performed on Analtech GF precoated silica gel (1000 μm) glass-backed plates (20 × 20 cm). The IR and ^{1}H and ^{13}C NMR spectra of all compounds were consistent with their assigned structure. NMR spectra were recorded on a General Electric QE-300, and chemical shifts are reported in ppm (δ) relative to the residual signal of the deuterated solvent ($CHCl_3$, δ 7.26; CHD_2OD, δ 3.30). Infrared spectra were recorded in KBr (unless otherwise noted) on a Nicolet 5DXB FT-IR. C, H, and N elemental analyses for all new compounds were performed by Desert Analytics (Tucson, AZ) or Galbraith Laboratories (Knoxville, TN). Dicyclohexylcarbodiimide, BrCN, *N*,*N*′-di-*o*-tolylguanidine (**3**), *N*,*N*′-diphenylguanidine (**36**), and perimidine (**87**) were obtained from Aldrich Chemical Co. and were recrystallized from aqueous EtOH before use, except dicyclohexylcarbodiimide and BrCN, which were used as received. All starting amines were obtained from commercial sources and were purified by standard procedures before use or, where noted, were prepared by published procedures. (±)-*Endo*-2- and (±)*exo*-2-aminonorbornane and *R*-(−)-isobornylamine hydrochloride served as precursors for the respective norbornyl- and isobornyl-substituted guanidines. Chlorobenzene was freshly distilled from CaH_2. Ether (Et_2O) and THF were refluxed over sodium/benzophenone ketyl radical and freshly distilled under N_2. All other solvents were reagent grade. Alkyl- and arylcyanamides were prepared according to published procedures by reaction of the amines with BrCN in Et_2O,[73,74] or, in the case of (2-methyl-4-nitrophenyl)cyanamide, in H_2O,[73] and were used without further purification.

General Procedure for the Synthesis of Unsymmetrical N,N′-Disubstituted Guanidines. Method A. A stirred mixture of the appropriate cyanamide[84] (10 mmol) and amine hydrohalide salt (10 mmol) in chlorobenzene (30 mL) was heated at 90–130 °C under N_2 for 2–10 h. The reaction was monitored by TLC ($CHCl_3$/EtOH/Et_3N, 75:20:5). On cooling to 25 °C, the title compounds precipitated from solution as their hydrohalide salts, were filtered off, and washed with dichloromethane (CH_2Cl_2) (3 × 5 mL) to remove residual chlorobenzene. When the guanidine hydrohalide did not precipitate from the cooled reaction mixture, the solvent was evaporated, and the residue was taken up in aqueous 1 N HCl (15 mL). The solution was basified with 1 N NaOH, and the precipitated guanidine free base was filtered off. The guanidine free base was crystallized by dissolution in EtOH (20–30 mg/mL), followed by slow addition of H_2O (30–50% volume). The analytical sample was obtained after two further recrystallizations. Typically, the guanidine hydrohalide salts were crystallized inside a closed Et_2O-containing chamber, by the slow diffusion of Et_2O into a loosely covered flask containing a solution of the guanidine salt in absolute EtOH (20–40 mg/mL). Two such recrystallizations provided the analytical material.

***N*-(Adamant-1-yl)-*N*′-(2-iodophenyl)guanidine Hydrochloride (57). Method A.** A suspension of adamant-1-ylcyanamide (4.09 g, 16.0 mmol), 2-iodoaniline hydrochloride (2.82 g, 16.0 mmol), and 2-iodoaniline (50 mg, 0.288 mmol) in chlorobenzene (50 mL) was heated at reflux for 2 days. The resulting white precipitate was filtered off, washed with CH_2Cl_2 (3 × 30 mL), and dried to give **57** (6.45 g, 93%) as a white powder, mp

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[84] See footnote *b* in Table I.

255–257 °C. After crystallization from EtOH/Et_2O, the analytical sample was obtained as white needles (3.67 g, 66%): 264–265 °C dec. ^1H NMR (CD_3OD): δ 1.779 (s, 6 H), 2.090 (s, 6 H), 2.165 (s, 3 H) 7.168 (t, 1 H, $J = 8.1$ Hz), 7.388 (d, 1 H, $J = 8.1$ Hz), 7.503 (t, 1 H, $J = 7.8$), 8.004 (d, 1 H, $J = 7.8$ Hz). IR: 3442, 3160, 2909, 1653, 1634 cm^{-1}. Anal. ($C_{17}H_{23}ClIN_3$) C, H, N.

General Procedure for the Synthesis of Symmetrical N,N′-Disubstituted Guanidines. Method B. To a stirred solution of the appropriate amine (10 mmol) in EtOH (3–5 mL) at 0 °C was carefully added a solution of BrCN (11 mmol, 1.1 eq) in EtOH (1–2 mL). After the exotherm subsided, the reaction mixture was allowed to warm to 25 °C and was then heated at 150 °C for 15–30 min, while N_2 was swept through the flask to completely remove the boiling solvent. The fused reaction mixture was allowed to cool to 25 °C, and the resulting glassy solid was taken up in hot EtOH (10–15 mL), treated with decolorizing charcoal (50–60 mg), and filtered through Celite. The filtrate was diluted with aqueous 1 N NaOH (10–20 mL), and the precipitated guanidine free base was filtered off. The analytical sample was obtained by repeated crystallizations from aqueous EtOH, as described in Method A.

***N,N′*-Bis(3-ethylphenyl)guanidine (13). Method B.** A solution of BrCN (650 mg, 6.14 mmol) in Et_2O (1 mL) was added to neat 3-ethylaniline (1.42 g, 11.7 mmol). After the exothermic reaction subsided, the resulting viscous oil was heated under a stream of N_2 at 150 °C for 15 min and then was allowed to cool to 25 °C. The resulting solid was dissolved in EtOH (20 mL), and 10% NaOH (20 mL) was added. A white precipitate was filtered off and recrystallized twice from aqueous 50% EtOH, to give **13** (620 mg, 20%) as white needles, mp 96–98 °C. ^1H NMR ($CDCl_3$): δ 1.216 (t, 6 H, $J = 7.5$), 2.608 (q, 4 H, $J = 7.5$), 6.937 (m, 6 H), 7.222 (t, 2 H, $J = 7.8$ Hz). IR ($CDCl_3$): 2971, 1629, 1589, 1490, 1417, 1217 cm^{-1}. Anal. ($C_{17}H_{21}N_3$) C, H.

Preparation of *N,N′*-Dicyclohexyl-*N″*-substituted-guanidines. Method C. To a stirred solution of dicyclohexylcarbodiimide (10 mmol) in THF (10 mL) under N_2 was added the appropriate amine (9.8 mmol). The resulting solution was stirred at 25 °C for several days and then evaporated. The residue was taken up in absolute EtOH (15 mL). Excess ethanolic HCl was added, and any precipitated dicyclohexylurea was filtered off. The filtrate was evaporated, and the residue was crystallized from EtOH/Et_2O as described in Method A.

Radioligand Binding Assays. Frozen whole guinea pig brains (Pel-Freez, Rodgers, AR, and Biotrol, Indianapolis, IN) were homogenized in 10 volumes (w/v) of ice-cold 0.32 M sucrose with use of a Polytron (Brinkman). The homogenate was centrifuged at 1,000*g* for 20 min at 4 °C. The homogenate was then centrifuged again at 20000*g* for 20 min at 4 °C. The resulting pellet was resuspended in 10 volumes of 50 mM Tris–HCl buffer (pH 7.4) and centrifuged at 20000*g* for 20 min at 4 °C. The resulting pellet was then resuspended in 5 volumes of 50 mM Tris–HCl (pH 7.4), and the final volume was adjusted to yield a protein concentration of 3 mg/mL, as determined by dye-binding protein assay (Biorad); 20-mL aliquots were stored at −70 °C until used.

For [^3H]-**3**, [^3H]-**4**, and [^3H]-**5** radioligand binding assays, 20-mL aliquots of the frozen membrane suspension were thawed and diluted 1:3 in 50 mM Tris–HCl (pH 7.4). To 12 × 75-mm polystyrene test tubes were added 0.8 mL of diluted membrane suspension, 0.1 mL of [^3H]-**3** (52 Ci/mmol)[21] or [^3H]-**4** (104 Ci/mmol, New England Nuclear) or [^3H]-**5** (100 Ci/mmol, New England Nuclear) to yield a final concentration of 1.4, 0.96, or 1.8 nM, respectively, and 0.1 mL of unlabeled compound or buffer. The protein content in the 1-mL final incubation volume was 800 μg, corresponding to 32 mg of brain tissue (original wet weight) and to a tissue concentration within the linear range for specific binding. Nonspecific binding for both [^3H]-**3** and [^3H]-**4** assays was defined as that remaining in the presence of 10 μM haloperidol, and for [^3H]-**5** in the presence of 10 μM PCP. Specific binding constituted 92.1 ± 0.4% SEM ($n = 7$) of total [^3H]-**3** binding, 91.5 ± 0.4% SEM ($n = 4$) of total [^3H]-**4** binding and 94.6 ± 0.8% ($n = 6$) of total [^3H]-**5** binding. Incubations were terminated after 90 min (45 min for [^3H]-**5**) at room temperature by addition of 4 mL of 50 mM Tris–HCl (pH 7.4) and rapid filtration of the membrane suspension through Whatman GF/B glass-fiber filters (or Schleicher & Schueller No. 32 filters) under vacuum, using a 48-well cell harvester (Brandel, Gaithersburg, MD). The filters were washed two times with 4 mL of 50 mM Tris–HCl (pH 7.4). Total filtration and washing time was less than 10 s. Each filter was suspended in 10 mL of Cytoscint (Westchem, Sand Diego, CA), and radioactivity was measured by liquid scintillation spectrometry at a counting efficiency of approximately 50%. Saturation data were evaluated by Scatchard analysis using the EBDA (MacPherson, 1983) data analysis program on an IBM PC-AT. IC_{50} values were determined by interpolation from displacement-curve plots on semilogarithmic graph paper.

[^3H]-**6** (97 Ci/mmol)[67] radioligand assays were performed in a fashion similar to [^3H]-**3**, [^3H]-**4**, and [^3H]-**5** radioligand assays but with the following modifications. Final concentration of [^3H]-**6** used was 1 nM and protein concentration was 150 μg/mL. Tris-HCl (5 mM; pH 7.4) was used as assay buffer and for filtration. Incubation time was 4 h at 25 °C. Nonspecific binding was defined as that remaining in the presence of 10 μM **5** or **6** and was ≤10% of total binding.

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