

# Synthesis and Structure-Activity Studies of *N,N*-Diarylguanidine Derivatives. *N*-(1-Naphthyl)-*N'*-(3-ethylphenyl)-*N'*-methylguanidine: A New, Selective Noncompetitive NMDA Receptor Antagonist

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Diarylguanidines, acting as NMDA receptor ion channel site ligands, represent a new class of potential neuroprotective drugs. Several diarylguanidines structurally related to *N,N*-di-*o*-tolylguanidine (DTG), a known selective  $\sigma$  receptor ligand, were synthesized and evaluated in *in vitro* radioligand displacement assays, with rat or guinea pig brain membrane homogenates, using the NMDA receptor ion channel site specific radioligand [<sup>3</sup>H]-(+)-5(*S*)-methyl-10(*R*),11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine (MK-801, 3), and the  $\sigma$  receptor-specific radioligand [<sup>3</sup>H]-di-*o*-tolylguanidine (DTG, 5). This paper presents the structure-activity relationships leading to novel tri- and tetrasubstituted guanidines, which exhibit high selectivity for NMDA receptor ion channel sites and weak or negligible affinity for  $\sigma$  receptors. The *in vitro* binding results from symmetrically substituted diphenylguanidines indicated that compounds having ortho or meta substituents (with respect to the position of the guanidine nitrogen) on the phenyl rings showed greater affinity for the NMDA receptor ion channel site compared with para-substituted derivatives. Among the group of ring substituents studied for symmetrical diarylguanidines, an isopropyl group was preferred at the ortho position and an ethyl group was preferred at the meta position. Several unsymmetrical guanidines containing a naphthalene ring on one nitrogen atom and an ortho- or a meta-substituted phenyl ring on the second nitrogen atom, e.g., *N*-1-naphthyl-*N'*-(3-ethylphenyl)guanidine (36), showed a 3-5-fold increase in affinity for the NMDA receptor ion channel site and no change in  $\sigma$  receptor affinity compared to the respective symmetrical counterparts. Additional small substituents on the guanidine nitrogen atoms bearing the aryl rings resulted in tri- and tetrasubstituted guanidine derivatives which retained affinity for NMDA receptor ion channel sites but exhibited a significant reduction in their affinities for  $\sigma$  receptors. For example, *N*-1-naphthyl-*N'*-(3-ethylphenyl)-*N'*-methylguanidine (40) showed high affinity for the NMDA receptor ion channel site (IC<sub>50</sub> = 36 nM vs [<sup>3</sup>H]-3) and low affinity for  $\sigma$  receptors (IC<sub>50</sub> = 2540 nM vs [<sup>3</sup>H]-5). Selectivity for the NMDA receptor ion channel sites over  $\sigma$  receptors appears to be dependent upon the structure of the additional substituents on the guanidine nitrogen atoms bearing the aryl groups. Methyl and ethyl substituents are most preferred in the tri- and tetrasubstituted diarylguanidines. The trisubstituted guanidine, *N*-1-naphthyl-*N'*-(3-ethylphenyl)-*N'*-methylguanidine (40) and its close analogues showed good *in vivo* neuroprotection and are potential neuroprotective drug candidates for the treatment of stroke and other neurodegenerative disorders.

## Introduction

The *N*-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptor, may play a pivotal role in many brain disorders.<sup>1,2</sup> Excessive stimulation of NMDA receptors has been implicated in nerve cell death in stroke, brain, or spinal cord trauma and in some neurodegenerative disorders such as Alzheimer's disease and Huntington's disease.<sup>3,4</sup> Compounds which specifically antagonize the actions of the neurotransmitter glutamate at the NMDA receptor through an interaction at its ion channel binding site (also commonly known as the PCP site or PCP receptor) offer a novel approach to treating these disorders. Compounds that bind at this site inhibit glutamate responses noncompetitively by blocking the open ion channel of the NMDA receptor.<sup>5</sup> In recent years much research has focused on developing new ligands that

interact at the NMDA receptor ion channel site.<sup>6-8</sup> Known ligands for the NMDA receptor ion channel site include *N*-(1-phenylcyclohexyl)piperidine (PCP, 1),<sup>9</sup> *N*-[1-(2-thienyl)cyclohexyl]piperidine (TCP, 2),<sup>10</sup> (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine (MK-801, 3),<sup>11</sup> and (+)-10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (4).<sup>12</sup>

Many ligands that interact at NMDA receptor ion channel sites also bind to  $\sigma$  receptors in mammalian brain membrane suspensions.<sup>7,13</sup> Notable exceptions to this observation are compounds 3 and 4.  $\sigma$  receptors do not appear to be associated with NMDA receptor ion channels, and their physiological function is still unknown. In our earlier studies, we have described a highly potent series of  $\sigma$  receptor ligands based on *N,N*-di-*o*-tolylguanidine (DTG, 5).<sup>14</sup> Many of these compounds show negligible affinity for the NMDA receptor ion channel site. Because of the extensive cross-reactivity of many  $\sigma$  receptor ligands with the NMDA receptor ion channel site<sup>7,15,16</sup> (and vice versa), we reasoned that chemical alterations to the DTG

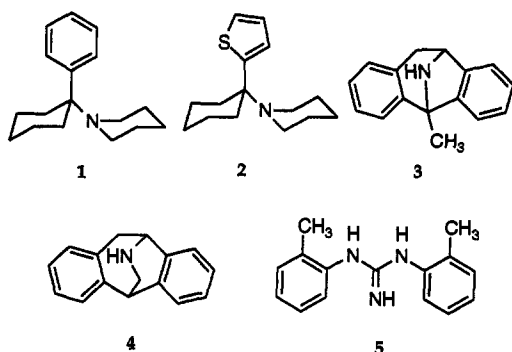
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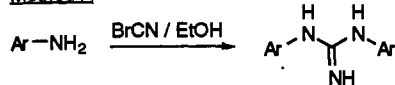
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Chart 1

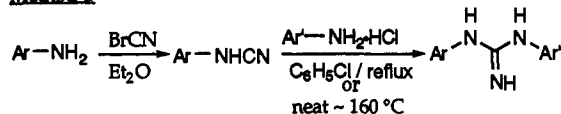


Scheme 1

## Method A

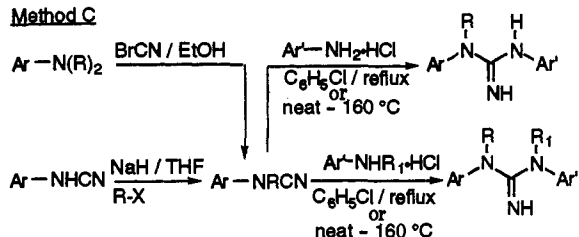


## Method B



Scheme 2

## Method C



(5) molecule might generate compounds that are selective for the NMDA receptor ion channel site over the  $\sigma$  receptor.

Herein, we report the preparation of more than 50 guanidines (Tables 1–4) along with their affinities for both the NMDA receptor ion channel site and the  $\sigma$  receptor. We also discuss structure-activity and structure-selectivity relationships for affinities of these guanidines for the NMDA receptor ion channel site and the  $\sigma$  receptor.

## Chemistry

Symmetrical *N,N'*-disubstituted guanidines were synthesized (Scheme 1, method A) by directly reacting 2 equiv of the amine with 1 equiv of cyanogen bromide (BrCN) either in ethanol or without solvent.<sup>14</sup> Unsymmetrical *N,N'*-disubstituted guanidines were prepared (Scheme 1, method B) by reacting arylcyanamides with the appropriate amine hydrohalide salts in refluxing chlorobenzene<sup>17</sup> or directly in a 1:1 melt without solvent.<sup>18</sup> The requisite cyanamides were synthesized from the corresponding amines by treatment with cyanogen bromide in ether.<sup>17,18</sup>

*N,N,N'*-trisubstituted or *N,N,N',N'*-tetrasubstituted guanidines were synthesized (Scheme 2, method C) by reacting *N*-alkyl-*N*-arylcyanamides with appropriate amine hydrohalide salts in refluxing chlorobenzene<sup>17</sup> or directly in a 1:1 melt without solvent.<sup>18</sup> The starting cyanamides were synthesized either (a) from a reaction of BrCN with *N,N*-dialkyl-*N*-arylamines in refluxing ethanol<sup>19</sup> or (b) by an alkylation of an arylcyanamide with sodium hydride/alkyl halide in THF.

## Binding Studies

*In vitro* radioligand binding assays were performed using [<sup>3</sup>H]-3 and rat brain membrane suspensions for the NMDA receptor ion channel site and [<sup>3</sup>H]-5 and guinea pig brain membrane suspensions for the  $\sigma$  receptor.<sup>20,21</sup> Relative affinities of compounds were determined as IC<sub>50</sub> values from displacement curves. The results are presented in Tables 1–4. The guanidines are classified according to their chemical structures: symmetrically substituted diphenylguanidines and related *N*-alkyl analogs (Table 1), dinaphthylguanidines and related analogs (Table 2), *N*-naphthyl-*N'*-phenylguanidines and related *N*-alkyl, *N*-aryl, and *N,N'*-dialkyl analogs (Table 3), and miscellaneous guanidines (Table 4).

## Results and Discussion

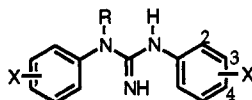
Table 1 shows the relative affinities of *N,N'*-diphenylguanidine derivatives for the NMDA receptor ion channel site and  $\sigma$  receptor. The data indicate that the affinity for the NMDA receptor ion channel site is a sensitive function of the substitution pattern on the phenyl rings of the guanidines. In virtually every example of symmetrical diphenylguanidines, para-substituted (relative to the position of guanidine nitrogen) derivatives (19–22) exhibited markedly reduced affinity for the NMDA receptor ion channel site compared to analogous ortho- or meta-substituted derivatives.

In addition to the relative position of substituents on the phenyl rings in symmetrical diphenylguanidines, the size of the substituents also appears to be important for the NMDA receptor ion channel site affinity. For example, the affinity of compounds for the NMDA receptor ion channel site improves as the size of the substituent at the ortho-position is increased: *cf.* methyl (5) vs ethyl (7) vs isopropyl (8). But an increase in size beyond that of the isopropyl group at the ortho position sharply decreases the affinity of the compound for the NMDA receptor ion channel site, *e.g.*, *tert*-butyl (9) and phenyl (12). In meta-substituted diphenylguanidines, an ethyl substituent (14) appears to be optimal and any group beyond the size of ethyl decreases the affinity of compounds for the NMDA receptor ion channel site: *e.g.*, *m*-isopropyl (15) vs *m*-*n*-propyl (16) vs *m*-iodo substituents (17).

In summary, among the substituents studied in the symmetrical diphenylguanidines, an isopropyl or an iodo substituent is preferred at the ortho position while an ethyl substituent is preferred at the meta position. Substituents were poorly tolerated at the para position. Thus, the substitution pattern as well as the size of the substituents are important determinants of the potency of these compounds.

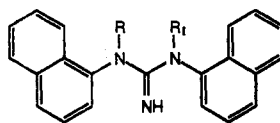
The synthesis of *N,N'*-di-1-naphthylguanidine (26, Table 2) was based on the rationale that the molecule shares the positive structural features of both ortho- and meta-substituted diphenylguanidines. Guanidine 26 emerged as a good NMDA receptor ion channel site ligand (IC<sub>50</sub> = 330 nM vs [<sup>3</sup>H]-3). The corresponding *N,N'*-ditetralin (33) and diindan (34) guanidines had much lower affinities for the NMDA receptor ion channel site (IC<sub>50</sub> = 1570 and 506 nM, respectively, vs [<sup>3</sup>H]-3), suggesting that the extended planarity characteristic of the naphthalene ring system is associated with high affinity in the guanidines.

Based on the weak affinity of *N,N'*-di-2-naphthylguanidine (35) for the NMDA receptor ion channel site, we

**Table 1.** Physical Properties and Binding Affinities of Symmetrical *N,N'*-Diphenylguanidines and Related *N*-Alkyl Analogs for the NMDA Receptor Ion Channel Site and the  $\sigma$  Receptor

compd <sup>b</sup>	X	R	mp, °C	method (% yield) <sup>c</sup>	formula <sup>d</sup>	IC <sub>50</sub> (nM) against <sup>a</sup>	
						[ <sup>3</sup> H]-3	[ <sup>3</sup> H]-5
5	2-CH <sub>3</sub>	H	176–178	e	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub>	9120 ± 770	31 ± 3
6	H	H	148–150	e	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub>	3450 ± 320	397 ± 21
7	2-C <sub>2</sub> H <sub>5</sub>	H	158–161	A (59)	C <sub>17</sub> H <sub>21</sub> N <sub>3</sub>	820 ± 66	14 ± 1
8	2-CH(CH <sub>3</sub> ) <sub>2</sub>	H	175–177	A (53)	C <sub>19</sub> H <sub>23</sub> N <sub>3</sub>	217 ± 23	88 ± 13
9	2-C(CH <sub>3</sub> ) <sub>3</sub>	H	204–205	A (33)	C <sub>21</sub> H <sub>25</sub> N <sub>3</sub>	38300 ± 14900	356 ± 63
10	2-I	H	161–162	A (39)	C <sub>13</sub> H <sub>11</sub> I <sub>2</sub> N <sub>3</sub>	228 ± 38	13 ± 1
11	2-OCH <sub>3</sub>	H	117–119	A (35)	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	1600 ± 30	1990 ± 270
12	2-C <sub>6</sub> H <sub>5</sub>	H	181–182	A (62)	C <sub>25</sub> H <sub>21</sub> N <sub>3</sub>	10000 ± 100	8110 ± 40
13	3-CH <sub>3</sub>	H	105–107	A (38)	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub>	335 ± 25	43 ± 5
14	3-C <sub>2</sub> H <sub>5</sub>	H	96–98	A (20)	C <sub>17</sub> H <sub>21</sub> N <sub>3</sub>	168 ± 38	8 ± 2
15	3-CH(CH <sub>3</sub> ) <sub>2</sub>	H	118–119	A (32)	C <sub>19</sub> H <sub>23</sub> N <sub>3</sub>	407 ± 51	96 ± 18
16	3-(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	H	69–70	A (20)	C <sub>19</sub> H <sub>25</sub> N <sub>3</sub>	2000 ± 70	42 ± 4
17	3-I	H	172–173	A (15)	C <sub>13</sub> H <sub>11</sub> I <sub>2</sub> N <sub>3</sub>	1100 ± 10	125 ± 1
18	3-OCH <sub>3</sub>	H	134–135	A (55)	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	493 ± 35	351 ± 39
19	4-CH <sub>3</sub>	H	168–170	A (20)	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub>	13300 ± 3300	535 ± 62
20	4-C <sub>2</sub> H <sub>5</sub>	H	136–138	A (38)	C <sub>17</sub> H <sub>21</sub> N <sub>3</sub>	10300 ± 600	245 ± 38
21	4-CH(CH <sub>3</sub> ) <sub>2</sub>	H	137–139	A (27)	C <sub>19</sub> H <sub>23</sub> N <sub>3</sub>	23200 ± 9900	242 ± 27
22	4-Br	H	166–168	A (27)	C <sub>13</sub> H <sub>11</sub> Br <sub>2</sub> N <sub>3</sub>	34000	33 ± 3
23	2-CH <sub>3</sub>	CH <sub>3</sub>	154–156	C (24)	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> -PTSA	10000 ± 100	6280 ± 360
24	3-CH <sub>3</sub>	CH <sub>3</sub>	69–70	C (53)	C <sub>16</sub> H <sub>19</sub> N <sub>3</sub> -HBr	1990 ± 150	247 ± 17
25	3-C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	oil	C (57)	C <sub>18</sub> H <sub>23</sub> N <sub>3</sub>	214 ± 36	82 ± 10

<sup>a</sup> [<sup>3</sup>H]-3, [<sup>3</sup>H]-(-)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine; [<sup>3</sup>H]-5, [<sup>3</sup>H]-*N,N'*-di-*o*-tolylguanidine. IC<sub>50</sub> values are mean ± SEM and are the results of a minimum two determinations; no SEM indicates a single determination. <sup>b</sup> Compounds 5–17 and 19–22 are reported in ref 14. <sup>c</sup> Yields refer to analytically pure products. <sup>d</sup> All new compounds were analyzed either for C, H, and N analyses or by high-resolution mass spectroscopy (HRMS). In the case of HRMS, the purity of the compound was determined by HPLC. <sup>e</sup> Purchased from Aldrich Chemical Co.

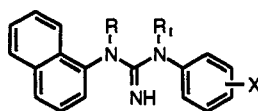
**Table 2.** Physical Properties and Binding Affinities of *N,N'*-Dinaphthylguanidines and Related Analogs for the NMDA Receptor Ion Channel Site and the  $\sigma$  Receptor

compd <sup>b</sup>	R	R <sub>1</sub>	mp, °C	method (% yield) <sup>c</sup>	formula <sup>d</sup>	IC <sub>50</sub> (nM) against <sup>a</sup>	
						[ <sup>3</sup> H]-3	[ <sup>3</sup> H]-5
26	H	H	210–211	A (30)	C <sub>21</sub> H <sub>17</sub> N <sub>3</sub>	330 ± 76	165 ± 28
27	H	CH <sub>3</sub>	249–250	C (10) <sup>e</sup>	C <sub>22</sub> H <sub>19</sub> N <sub>3</sub> ·HCl	115 ± 11	4800 ± 130
28	H	C <sub>2</sub> H <sub>5</sub>	84–86	C (56)	C <sub>23</sub> H <sub>21</sub> N <sub>3</sub> ·HCl 0.5 H <sub>2</sub> O	117 ± 27	6130 ± 470
29	H	C <sub>6</sub> H <sub>5</sub>	194–198	C (43)	C <sub>27</sub> H <sub>21</sub> N <sub>3</sub> ·HCl <sup>f</sup>	484 ± 104	7930 ± 1490
30	CH <sub>3</sub>	CH <sub>3</sub>	258–260	C (21)	C <sub>23</sub> H <sub>21</sub> N <sub>3</sub> ·HCl	69 ± 14	10700 ± 1400
31	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	135–137	C (1) <sup>g</sup>	C <sub>24</sub> H <sub>23</sub> N <sub>3</sub> ·HCl <sup>f</sup>	53 ± 12	8480 ± 890
32	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	270–272	C (3)	C <sub>28</sub> H <sub>23</sub> N <sub>3</sub> ·HCl <sup>f</sup>	470 ± 93	11000 ± 700
33			217–218	A (48)	C <sub>21</sub> H <sub>25</sub> N <sub>3</sub>	1570 ± 210	59 ± 3
34			197–199	A (10) <sup>h</sup>	C <sub>19</sub> H <sub>21</sub> N <sub>3</sub> <sup>f</sup>	506 ± 99	29 ± 8
35			203–204	A (57)	C <sub>21</sub> H <sub>17</sub> N <sub>3</sub>	12700 ± 3800	92 ± 9

<sup>a,c,d</sup> See footnotes in Table 1. <sup>b</sup> Compounds 26 and 33 were reported earlier, ref 14. <sup>e</sup> For the preparation of *N*-methyl-*N*-1-naphthylcyanamide, see ref 19. <sup>f</sup> Analyzed by HRMS as the corresponding free base and by HPLC for purity. <sup>g</sup> For the preparation of *N*-alkyl-1-naphthylamine, see ref 25. <sup>h</sup> Starting material 4-aminoindan was prepared from 4-nitroindan.

concluded that ring annelation in diphenylguanidines involving the meta and para positions was less desirable compared to the ortho and meta positions (compounds 26 vs 35). This is in agreement with our earlier observation that the para-substituted diphenylguanidines were poor NMDA receptor ion channel site ligands.

The best of the symmetrical diphenyl- and dinaphthylguanidine series of ligands showed an IC<sub>50</sub> of about 200 nM for NMDA receptor ion channel site. Thus a significant improvement in affinity has been achieved compared with DTG, which has an IC<sub>50</sub> of only 10 000 nM for the same site. However, all compounds discussed thus

**Table 3.** Physical Properties and Binding Affinities of *N*-Naphthyl-*N'*-phenylguanidines and Related *N*-Alkyl and *N,N'*-Dialkyl Analogs for the NMDA Receptor Ion Channel Site and the  $\sigma$  Receptor

compd	X	R	R <sub>1</sub>	mp, °C	method (% yield) <sup>c</sup>	formula <sup>d</sup>	IC <sub>50</sub> (nM) against <sup>a</sup>	
							[ <sup>3</sup> H]-3	[ <sup>3</sup> H]-5
36	3-C <sub>2</sub> H <sub>5</sub>	H	H	99–101	B (38)	C <sub>19</sub> H <sub>19</sub> N <sub>3</sub>	39 ± 7	54 ± 5
37	2-CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	175–177	B (44)	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub>	102 ± 22	91 ± 9
38	2-I	H	H	154–155	B (33)	C <sub>17</sub> H <sub>14</sub> N <sub>3</sub> I	209 ± 50	40 ± 7
39	3-CH <sub>3</sub>	H	H	116–117	B (77)	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> ·HCl·0.25H <sub>2</sub> O	192 ± 16	75 ± 12
40	3-C <sub>2</sub> H <sub>5</sub>	H	CH <sub>3</sub>	223–225	C (37)	C <sub>20</sub> H <sub>20</sub> N <sub>3</sub> ·HCl	36 ± 7	2540 ± 670
41	3-C <sub>2</sub> H <sub>5</sub>	H	C <sub>2</sub> H <sub>5</sub>	89–91	C (18)	C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> ·2.5 H <sub>2</sub> O <sup>j</sup>	73 ± 11	2190 ± 360
42	3-C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H	56–66	C (41) <sup>e</sup>	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> ·HCl <sup>f</sup>	537 ± 48	1000 ± 60
43	2-CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	H	231–232	C (46)	C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> ·HCl <sup>f</sup>	859 ± 62	7250 ± 640
44	3-CH <sub>3</sub>	H	CH <sub>3</sub>	123–124	C (45)	C <sub>19</sub> H <sub>18</sub> N <sub>3</sub> ·HCl	85 ± 7	1860 ± 180
45	3-NO <sub>2</sub>	H	CH <sub>3</sub>	134–136	C (25)	C <sub>18</sub> H <sub>16</sub> N <sub>3</sub> O <sub>2</sub> ·HCl <sup>f</sup>	87 ± 9	6260 ± 700
46	3-NH <sub>2</sub>	H	CH <sub>3</sub>	<i>k</i>	(86) <sup>h</sup>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> ·2HCl <sup>f</sup>	2070 ± 300	2700
47	3-N <sub>3</sub>	H	CH <sub>3</sub>	72–74	(80) <sup>i</sup>	C <sub>18</sub> H <sub>16</sub> N <sub>6</sub> <sup>f</sup>	65 ± 3	3020 ± 20
48	3-NO <sub>2</sub>	CH <sub>3</sub>	H	258–259	C (44)	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> ·HCl	2800	2640 ± 370
49	3-NH <sub>2</sub>	CH <sub>3</sub>	H	261–262	(74) <sup>h</sup>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> ·2HCl	10000 ± 100	13000 ± 300
50	3-N <sub>3</sub>	CH <sub>3</sub>	H	165–167	(51) <sup>i</sup>	C <sub>18</sub> H <sub>16</sub> N <sub>6</sub> ·HCl <sup>f</sup>	1690 ± 240	2740 ± 220
51	H	H	CH <sub>3</sub>	oil	C (39)	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> <sup>f</sup>	1030 ± 240	2900
52	3-C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	128–29	C (56)	C <sub>27</sub> H <sub>29</sub> N <sub>3</sub> ·HCl	100 ± 13	1210 ± 60
53	3-C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	oil	C (36) <sup>e</sup>	C <sub>22</sub> H <sub>25</sub> N <sub>3</sub> <sup>f</sup>	97 ± 5	2290 ± 160

<sup>a,c,d</sup> See footnotes in Table 1. <sup>e,f</sup> See footnotes in Table 2. <sup>h</sup> Yield based on nitro precursor. <sup>i</sup> Yield based amino precursor. <sup>j</sup> H: Calcd, 7.78; found, 7.13. <sup>k</sup> Hygroscopic.

far exhibited good to moderate affinity for the  $\sigma$  receptor. The task at hand was to retain or enhance affinities for the ion channel site while suppressing  $\sigma$  affinity. At this stage, synthesis of unsymmetrical diarylguanidines from 1-aminonaphthalene and ortho or meta-substituted anilines were considered for two reasons. First, the corresponding symmetrical guanidines (*N,N'*-bis(1-naphthyl)guanidine and *N,N'*-bis(*o*- or *m*-substituted phenyl)guanidine) showed good affinity for the NMDA receptor ion channel sites. Second, the unsymmetrical guanidines may have different conformational preferences from the symmetrical guanidines, which could affect the relative ease of fit of compounds for the receptors involved.

The first unsymmetrical diarylguanidine synthesized, *N*-1-naphthyl-*N'*-(*m*-ethylphenyl)guanidine (36) exhibited a 5-fold greater affinity (IC<sub>50</sub> = 39 nM vs [<sup>3</sup>H]-3) for the NMDA receptor ion channel site than either of its symmetrically substituted analogs. Subsequently, a series (Table 3) of unsymmetrical guanidines (37–39) was synthesized, and each showed a similar trend of increased affinity toward the NMDA receptor ion channel site relative to the symmetrical analogs. However these unsymmetrical guanidines still possessed a high  $\sigma$  receptor affinity.

The focus of further synthetic efforts was therefore to improve the compounds' selectivity for the NMDA receptor ion channel site over the  $\sigma$  receptor, without adversely affecting the NMDA receptor ion channel site affinity. Structural changes, particularly substitutions on the nitrogens bearing the aryl groups, were considered for the following reasons. Substitution on the guanidine nitrogen bearing the aryl group would be expected to decrease the degree of conformational flexibility of the guanidine relative to its "parent" diarylguanidine. This additional N-substitution might also lead to a different set of preferred conformations, and these changes in conformation might influence the affinity of the compound for the NMDA receptor ion channel site and/or  $\sigma$  receptor site. It is relevant to note that *N*-methylbenzanilide exists predominantly in a *cis* amide conformation in solution

and in the crystal, while benzanilide exists in a *trans* conformation.<sup>22</sup> *N,N'*-diphenylguanidine is a strong organic base (pK<sub>a</sub> 10.0),<sup>23</sup> and at physiological pH of 7.4 it exists predominantly as the cationic species. It is likely that the diarylguanidines would also be extensively protonated at physiological pH and hence the N-substitution will change the guanidine nitrogen from an H-bond donor and/or acceptor into a relatively hindered H-bond acceptor. This change might illustrate the importance of the state of the nitrogen with regard to the affinity of the molecule for the NMDA receptor ion channel site or  $\sigma$  receptor.

The first *N*-alkyl-*N,N'*-diarylguanidine, *N,N'*-di-1-naphthyl-*N'*-methylguanidine (27, Table 2), exhibited a markedly lower affinity for the  $\sigma$  receptor (IC<sub>50</sub> = 4800 nM vs [<sup>3</sup>H]-5) than its disubstituted counterpart 26 (IC<sub>50</sub> = 165 nM vs [<sup>3</sup>H]-5). Most importantly, the NMDA receptor ion channel site affinity was mildly enhanced in this case. This discovery led to the subsequent syntheses of *N*-alkyl derivatives of both symmetrical (23–25 in Table 1; 28, 29 in Table 2) and unsymmetrical (40–51 in Table 3) diarylguanidines. The binding studies of these compounds confirmed that the N-alkylation markedly reduces the affinity of substituted diarylguanidines for  $\sigma$  receptors. Among the substituents studied for N-alkylation of *N,N'*-diarylguanidines, guanidines containing methyl (27) and ethyl (28) groups have possessed essentially similar NMDA receptor ion channel site affinity (IC<sub>50</sub> = 115 and 117 nM, respectively, vs [<sup>3</sup>H]-3), whereas a guanidine containing a phenyl (29) group showed a 4-fold reduction in affinity for the same site. We therefore conclude that both size and electronic effect of the N-substituent can influence a compound's affinity for the NMDA receptor ion channel site. In all the cases studied, further N-alkylation or N-arylation of *N,N'*-diarylguanidines markedly reduced the affinity of the resulting trisubstituted guanidines for the  $\sigma$  receptors.

Further structure-affinity studies of trisubstituted diarylguanidines were undertaken to study the effect on NMDA receptor ion channel affinity of different groups

in place of the 3-ethyl substituent in the phenyl ring of *N*-(1-naphthyl)-*N'*-(3-ethylphenyl)-*N'*-methylguanidine (40). Replacement of the ethyl substituent by nitro (45) or azido (47) groups led to a slight reduction in their NMDA receptor ion channel site affinity.<sup>24</sup> However, when the ethyl group was replaced with an amino group (46), the compound affinity for this site was reduced substantially ( $IC_{50} = 2070$  nM vs [<sup>3</sup>H]-3). Replacement of the ethyl group of 40 with a hydrogen atom (51) caused a 30-fold loss in affinity, demonstrating the preference of a hydrophobic substituent at the 3-position. Collectively, these results suggest that the electronic and steric effect of groups at the 3-position of the phenyl ring markedly influences the affinity of the compound for the NMDA receptor ion channel site.

Since trisubstituted guanidines showed good selectivity and affinity for the NMDA receptor ion channel site over the  $\sigma$  receptor, the effect of further N-substitutions was investigated. This substitution further reduces the H-bond donor capacity of the guanidine and increases its rigidity relative to trisubstituted counterpart. Thus several *N,N'*-disubstituted *N,N'*-diarylguanidines (30, 31, 32 in Table 2; 52, 53 in Table 3) were synthesized. In general these ligands possessed equal or greater affinity and selectivity for the NMDA receptor ion channel site over the  $\sigma$  receptor compared to their trisubstituted counterparts (*cf.* compound 30 vs 27). The *N*-phenyl-*N'*-alkyl-*N,N'*-diarylguanidine (32) showed reduced affinity for the NMDA receptor ion channel site similar to its trisubstituted counterpart (29). We conclude that the protons attached to the guanidine nitrogens bearing the aryl groups are not required for interaction with NMDA receptor ion channel site but may be of importance for its interaction with the  $\sigma$  receptor.

During the course of above synthetic studies, several semirigid guanidines were prepared. The relative affinities of these guanidines for the NMDA receptor ion channel site and the  $\sigma$  receptor are presented in Table 4. The markedly low affinity of guanidines 57–60 for the NMDA receptor ion channel sites may be because of the lack of planarity of one of the N-substituents. This is in agreement with our earlier observation that planarity of the N-substituents is associated with high affinity in the diarylguanidines.

## Conclusions

More than 50 diarylguanidines have been synthesized in an effort to find high-affinity ligands for the binding site associated with the ion channel of the NMDA receptor-channel complex. The synthesis of these guanidines utilized known, straightforward methodology. The symmetrically substituted diphenylguanidines and unsymmetrical *N*-naphthyl-*N'*-phenylguanidine analogs exhibited good to moderate affinities for the NMDA receptor ion channel sites, but also comparable affinities for the  $\sigma$  receptors. The tri- and tetrasubstituted versions of *N,N*-dinaphthyl- and *N*-naphthyl-*N'*-(3-substituted phenyl)-guanidines exhibited a remarkably high affinity and selectivity for the NMDA receptor ion channel site over the  $\sigma$  receptor. Certain of the tri- and tetrasubstituted guanidines merit consideration for development as potential neuroprotective drugs and may be useful for further pharmacological and biochemical characterization of the NMDA receptor. One of the trisubstituted guanidines, *N*-1-naphthyl-*N'*-(3-ethylphenyl)-*N'*-methylguanidine (40)

has been selected as a clinical candidate for development as an acute treatment to limit the extent of brain damage in stroke and traumatic head injury.<sup>27</sup>

## 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<sub>254</sub> (0.2 mm) or Baker-flex 1B2-F silica gel plates. Guanidines were visualized on TLC with 254-nm UV light or as a blue spot with bromocresol spray reagent (Sigma Chemical Co.). Preparative TLC was performed on Analtech GF precoated silica gel (1000  $\mu$ m) glass-backed plates (20  $\times$  20 cm). The IR and <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds were consistent with their assigned structures. NMR spectra were recorded on a General Electric QE-300, and the chemical shifts were reported in ppm ( $\delta$ ) relative to the residual signal of the deuterated solvent (CHCl<sub>3</sub>,  $\delta$  7.26; CHD<sub>2</sub>OD,  $\delta$  3.30). Infrared spectra were recorded in CHCl<sub>3</sub> (unless otherwise noted) on a Nicolet 5DXB FT-IR or Perkin-Elmer Model 1420. All new compounds were analyzed either by C, H, and N elemental analyses or by exact mass determination. Compounds for which exact mass was employed were further analyzed by HPLC for homogeneity. Elemental analyses were performed by Desert Analytics (Tucson, AZ) or Galbraith Laboratories (Knoxville, TN). High-resolution mass spectra (HRMS) were recorded on a Finnegan MAT 90. HPLC was performed on a C18 reverse-phase column using 50:50 (in most cases) water/acetonitrile with 0.1% TFA as the mobile phase. BrCN (caution! Toxic) was obtained from Aldrich Chemical Co., and was used as received. All starting amines were obtained from commercial sources and were purified by standard procedures before use, or they were prepared, where noted, by published procedures. Chlorobenzene was used after freshly distilling over CaH<sub>2</sub>. Ether (Et<sub>2</sub>O) and tetrahydrofuran (THF) were refluxed over sodium/benzophenone ketyl and freshly distilled under N<sub>2</sub> before their use. Anhydrous quality (Sure Seal) solvents (chlorobenzene, ether, and THF) supplied by Aldrich were also used. All other solvents were reagent grade. Alkyl- and arylcyanamides were prepared according to published procedures by reaction of the amines with BrCN in ether.<sup>17,18</sup>

**General Procedure for Synthesis of Symmetrical *N,N'*-Diarylguanidines (Method A).** 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 equiv) in EtOH (1–2 mL). After the exothermic reaction subsided, the reaction mixture was allowed to warm to 25 °C and then heated at 150 °C for 15–30 min, while N<sub>2</sub> 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 solution (10–20 mL), and the precipitated guanidine free base was filtered off. The analytical sample was obtained by repeated crystallizations from 95% EtOH (20–30 mg/mL), followed by slow addition of H<sub>2</sub>O (30–50% volume). Typically, the guanidine salts were crystallized inside a closed Et<sub>2</sub>O chamber containing a solution of the guanidine salt in absolute EtOH (20–40 mg/mL).

**Method A: Example 1. *N,N'*-Bis(3-ethylphenyl)guanidine (14).** Cyanogen bromide (650 mg, 6.14 mmol) was added slowly in portions to neat stirred 3-ethylaniline (1.42 g, 11.7 mmol). After the exothermic reaction subsided, the resulting viscous oil was heated under a stream of N<sub>2</sub> 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 and was recrystallized twice from aqueous 50% EtOH to give 14 (620 mg, 20%) as white needles: mp 96–98 °C; IR (CDCl<sub>3</sub>) 2971, 1629, 1589, 1490, 1417, 1217 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.216 (t, 6 H, *J* = 7.5 Hz), 2.608 (q, 4 H, *J* = 7.5 Hz), 6.937 (m, 6 H), 7.222 (t, 2 H, *J* = 7.8 Hz). Anal. (C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>) C, H, N.

**General Procedure for Synthesis of Unsymmetrical *N,N'*-Diarylguanidines (Method B) and Their *N*-Alkyl and *N,N'*-Dialkyl Derivatives (Method C).** A stirred mixture of the appropriate cyanamide (10 mmol) and amine salt (10 mmol) in

**Table 4.** Physical Properties and Binding Affinities of Miscellaneous Guanidines for the NMDA Receptor Ion Channel Site and the  $\sigma$  Receptor

compd	structure	mp, °C	method (% yield) <sup>c</sup>	formula <sup>d</sup>	IC <sub>50</sub> (nM) against <sup>e</sup>	
					[ <sup>3</sup> H]-3	[ <sup>3</sup> H]-5
54		280–281	A (13)	C <sub>19</sub> H <sub>21</sub> N <sub>3</sub> ·HBr	2540 ± 230	1370 ± 40
55		159–160	A (6)	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> ·HCl·2H <sub>2</sub> O <sup>f</sup>	>100000	7180 ± 310
56		49–51	B (26)	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> ·HCl·0.5H <sub>2</sub> O <sup>h</sup>	1870 ± 10	341 ± 73
57		166–167	B (25)	C <sub>16</sub> H <sub>19</sub> N <sub>3</sub> ·HCl·0.5H <sub>2</sub> O <sup>i</sup>	10000 ± 100	1070 ± 260
58		194–196	B (65)	C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> ·HCl <sup>j</sup>	10000 ± 100	1410 ± 100
59		194–195	B (33)	C <sub>22</sub> H <sub>23</sub> N <sub>3</sub> ·HCl·0.25H <sub>2</sub> O	10000 ± 100	343 ± 32
60		192–194	B (58)	C <sub>20</sub> H <sub>25</sub> N <sub>3</sub> ·HCl·0.25H <sub>2</sub> O	10000 ± 100	60 ± 8
61		148–150	B (6)	C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> ·HCl <sup>k</sup>	5130 ± 640	240 ± 15
62		252–254	C (4)	C <sub>28</sub> H <sub>21</sub> N <sub>3</sub> ·HCl <sup>l</sup>	1880 ± 340	2100 ± 160
63		197–98	B (67) <sup>b</sup>	C <sub>28</sub> H <sub>21</sub> N <sub>3</sub> ·HCl·0.3H <sub>2</sub> O	2900	140 ± 13

<sup>a,c,d</sup> See footnotes in Table 1. <sup>b</sup> Reference: Klingner, R. Z. *Phys. Chem.* 1926, 155, 206–239. <sup>f</sup> See footnote in Table 2. <sup>g</sup> C: calcd, 60.80; found, 58.18. <sup>h</sup> C: calcd, 65.72; found, 65.23. <sup>i</sup> N: calcd, 14.06; found, 15.10.

chlorobenzene (30 mL) or neat was heated at 130–160 °C under N<sub>2</sub> for 2–10 h. The reaction was monitored by TLC (CHCl<sub>3</sub>/EtOH/Et<sub>3</sub>N, 75:20:5). On cooling to 25 °C, the compounds precipitated from solution as hydrohalide salts, which were filtered off and washed with dichloromethane (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 solution, and the precipitated guanidine free base was filtered off. An analytical sample was obtained by repeated crystallizations from aqueous EtOH as described in method A.

**Method B: Example 1.** *N*-(1-Naphthyl)-*N'*-(3-ethylphenyl)guanidine (36). A solution of cyanogen bromide (3.31 g, 31.26 mmol) in Et<sub>2</sub>O (25 mL) was added slowly to a stirred solution of 3-ethylaniline (6.06 g, 50 mmol) in Et<sub>2</sub>O (50 mL), and stirring continued at room temperature for 6 h. A white precipitate of 3-ethylaniline hydrobromide (4.46 g) was filtered off, and the filtrate was washed with H<sub>2</sub>O (2 × 20 mL). Evaporation of the

ether layer afforded the cyanamide (3.85 g, 96.5%) as a thick liquid. IR (film) 2225 cm<sup>-1</sup>.

A solution of (3-ethylphenyl)cyanamide (730 mg, 4.99 mmol) and 1-naphthylamine hydrochloride (900 mg, 5.01 mmol) in chlorobenzene (20 mL) was heated at 140–145 °C for 12 h. The reaction mixture was allowed to cool to room temperature and concentrated, and the residue was partitioned between dichloromethane and 10% NaOH solution. The organic layer was concentrated, and the resulting residue was recrystallized from absolute EtOH-H<sub>2</sub>O to give *N*-(1-naphthyl)-*N'*-(3-ethylphenyl)guanidine 36, (550 mg, 38%) as off-white needles: mp 96–98 °C; IR (CHCl<sub>3</sub>) 1650, 3400, 3500 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.16 (t, 3 H, *J* = 9 Hz), 2.55 (q, 2 H, *J* = 9 Hz), 4.83 (br, NH), 6.89–8.20 (m, 11 H). Anal. (C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>) C, H, N.

**Method C: Example 2.** *N*-(1-Naphthyl)-*N'*-(3-ethylphenyl)-*N*-methylguanidine Hydrochloride (40). A solution of (3-ethylphenyl)cyanamide (1.46 g, 10 mmol) and sodium hydride (480 mg, 20 mmol, prewashed three times with hexane) in anhydrous THF (10 mL) was heated at 80–85 °C for 2.5 h. After the reaction mixture was allowed to cool to room temperature,

methyl iodide (3.5 g, 25 mmol) was added, and stirring continued at room temperature for 2 h. Methanol (10 mL) followed by water (20 mL) was added, and the reaction mixture was extracted with dichloromethane (3 × 25 mL). Concentration of the organic layer followed by flash chromatography on SiO<sub>2</sub> afforded *N*-(3-ethylphenyl)-*N*-methylcyanamide (960 mg, 60%) as a colorless liquid: IR (film) 2220, 3400 cm<sup>-1</sup>.

A mixture of *N*-(3-ethylphenyl)-*N*-methylcyanamide (520 mg, 3.25 mmol) and 1-aminonaphthalene hydrochloride (508 mg, 3.25 mmol) was placed in a preheated oil bath at 160 °C for 3 h and then allowed to cool to room temperature. The resulting solid was taken up in dichloromethane and washed with 10% NaOH solution. The organic layer was concentrated, and the resulting residue was dissolved in absolute EtOH (2 mL) and treated with dilute HCl. The solution was concentrated, and the solid was twice recrystallized from absolute EtOH-Et<sub>2</sub>O to give *N*-(1-naphthyl)-*N'*-(3-ethylphenyl)-*N'*-methylguanidine hydrochloride 40 (403 mg, 37%) as off-white needles: mp 223–25 °C; IR (CHCl<sub>3</sub>) 1630, 3400 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.28 (t, 3 H, *J* = 7.9 Hz), 3.56 (s, 3 H), 7.30–8.01 (m, 11 H). Anal. (C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>Cl) C, H, N.

**Method C: Example 3. *N*-(3-Ethylphenyl)-*N'*-1-naphthyl-*N,N'*-dimethylguanidine (52).** In a 5-mL round bottom flask was placed *N*-(3-ethylphenyl)-*N*-methylcyanamide (340 mg, 2.18 mmol), *N*-methyl-1-naphthylamine hydrochloride<sup>25</sup> (440 mg, 2.28 mmol), and a stir bar. The flask was evacuated via an aspirator and flushed with N<sub>2</sub>. The reaction flask was immediately placed in a preheated (160 °C) oil bath and allowed to stir under N<sub>2</sub> for 14 h. The resulting brown glass was dissolved in methanol (5 mL) and diluted with hot distilled water (20 mL). This solution was basified with 0.1 N NaOH (25 mL) and extracted with CHCl<sub>3</sub> (5 × 20 mL) to yield a brown oil upon drying. This was purified by column chromatography with benzene as eluent. The product was eluted with benzene/EtOH (2:1) to afford the title compound 52 (380 mg, 56%) as a pale yellow oil. IR (neat): 3323 (NH), 1609–1570 cm<sup>-1</sup> (broad, C=NH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.02 (t, 3 H, *J* = 7.5 Hz), 2.35 (q, 2 H, *J* = 7.75 Hz), 2.96 (s, 3 H), 3.27 (s, 3 H), 5.70 (broad s, 1 H), 6.45–7.73 (m, 11 H, H-aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 163.4 (CN<sub>2</sub>); 145.9, 144.4, 142.5, 134.0, 129.7, 128.2, 127.8, 125.9, 125.5, 125.3, 125.1, 123.6, 123.1, 123.0, 122.5, 120.8 (Ar), 40.1 (NCH<sub>3</sub>); 39.4 (N'CH<sub>3</sub>), 28.2 (CH<sub>2</sub>), 15.0 (CH<sub>3</sub>); MS *m/e* calcd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub> 317.1892, found 317.1892.

**Radioligand Binding Assays.** [<sup>3</sup>H]-3 binding assays were performed<sup>19,21</sup> with rat brain membranes as a source of the binding sites. In brief, thawed crude synaptic membranes were incubated at 1 mg of protein/mL with 0.01% Triton X-100 for 15 min at 37 °C and then washed three times by centrifugation to reduce the endogenous amino acid concentrations; 1 μM glycine and L-glutamate were added to the binding assays to maximally stimulate ion channel site binding.

For [<sup>3</sup>H]-3 binding, 1 nM radioligand (97 Ci/mmol) was incubated with about 100 μg of membrane protein for 4 h at room temperature. Nonspecific binding was defined as that remaining in the presence of 10 μM PCP. All assays were carried out in 5 mM Tris/HCl or Tris/acetate buffer (pH 7.4 at 25 °C) and were stopped by rapid filtration through Whatman GF/B or Schleicher & Schuell no. 32 glass fiber filters (presoaked in 0.05% polyethyleneimine).

σ receptor binding assays were performed<sup>20</sup> using membrane from guinea pig brains. Thawed membrane preparations were incubated in 50 mM Tris/HCl (pH 7.4), 0.9 nM [<sup>3</sup>H]-5, and 0.8 mg protein/mL. Nonspecific binding was defined as that remaining in the presence of 10 μM haloperidol. After a 90-min incubation at room temperature, the membrane suspension was rapidly filtered under vacuum through Whatman GF/B glass fiber filters, using a Brandel harvester. The filters were washed three times with 5 mL of ice-cold 50 mM Tris/HCl buffer, and the filters were suspended in 10 mL of Cytosant (ICN, Costa Mesa, CA).

IC<sub>50</sub> values (concentrations required to inhibit 50% of specific radioligand binding) were calculated from displacement curves<sup>20</sup> or by nonlinear least squares regression analysis.<sup>28</sup>

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