Pharmacological and Behavioral Analysis of the Effects of Some Bivalent Ligand-Based Monoamine Reuptake Inhibitors

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Novel piperidine-based bivalent ligands were prepared in enantiomerically pure form and evaluated for their ability to inhibit reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) into rat brain nerve endings (synaptosomes). In this study, we have succeeded in using (1) the length of the linking chain connecting the two piperidine-based monomer units and (2) the absolute configuration of the piperidine monomer as a means to tailor activity and selectivity at the three monoamine transporters tested. In this series, the bivalent ligand **16**, comprised of two (+)-*trans*-piperidine units linked by a pentamethylene spacer, exhibits a combination of high DA transporter (DAT) and 5-HT transporter (SERT) activity (K_i = 39 nM and 7 nM, respectively). Piperidine **16** is capable of reducing cocaine's locomotor effects in mice while not having any effect on locomotion when tested alone. Additionally, compound **16** (1−10 mg/kg) does not substitute for cocaine in drug discrimination studies in rats. However, the analogous bivalent ligand **15** comprised of two (−)-*trans*-piperidine units, which is SERT selective, was less effective in antagonizing cocaine's locomotor stimulant activity. The piperidine-based bivalent inhibitors described herein constitute a new class of monoamine reuptake inhibitors that exhibit varying levels of monoamine transporter activity and selectivity, and these ligands may serve as lead candidates in the discovery of new therapeutics to treat a range of neurological disorders including cocaine addiction.

Introduction

Cocaine abuse is one of the major concerns of our society as it is coupled with substantial crime-related costs both in the United States and abroad.[1] Various studies have shown that the ability of cocaine to bind to the dopamine (DA) transporter (DAT) and to inhibit the reuptake of DA is responsible for the reinforcing properties of this drug.[1c] While several strategies have been examined in the discovery of medications for cocaine addiction, most of this work has focused on the development of either dopamine-sparing cocaine antagonists[2] or high-affinity DAT-selective agents that may function as partial agonists. In this regard, a large number of dopamine reuptake inhibitors have been developed over the past decade,[3] most of which belong to six distinct classes of compounds (Chart 1), namely analogues of cocaine (**1**), benztropine (**2**),[4] WIN 35,065-2 (**3**),[5] GBR 12909 (**4**),[6] methylphenidate (**5**),[7] and mazindol (**6**).[8] Despite extensive work on these compounds and their analogues, to date no suitable medications for the treatment of cocaine abuse and addiction have emerged.

To develop effective treatments for cocaine abuse, it is desirable to have a better understanding of the complex changes in neurophysiology that are associated with withdrawal from cocaine. To identify effective medications, it may be necessary to define the exact mix of monoaminergic properties necessary to treat, in particular, both the anhedonia and craving that accompanies withdrawal from cocaine. As studies using knockout mice have demonstrated that cocaine provides its rewarding cues to humans through its effects on several different systems, and not just the dopaminergic system, it is likely that the development of a medication will require a drug that targets more than one transporter.[9] Although selective inhibitors of DA, 5-HT, and NE transport have been developed to treat a variety of neurological and psychiatric disorders,[10] less is known about the neurochemical and physiological actions of compounds that exhibit selectivity for the DAT and the SERT (or DAT and NET) in the context of a cocaine abuse medication.

DA reuptake inhibition is needed to alleviate the anhedonia that is associated with the transient decreases in dopaminergic neurotransmission following cessation of cocaine use.[11] Additional inhibitory activity at the serotonin transporter (SERT) may serve to counteract the increase in craving associated with the administration of a DA reuptake inhibitor.[12] This strategy is supported by the reported success of a combination of the 5-HT releaser fenfluramine with the DA releasers phentermine[13] or pemoline[14] in pilot studies for cocaine addiction treatment. Accordingly, 5-HT-

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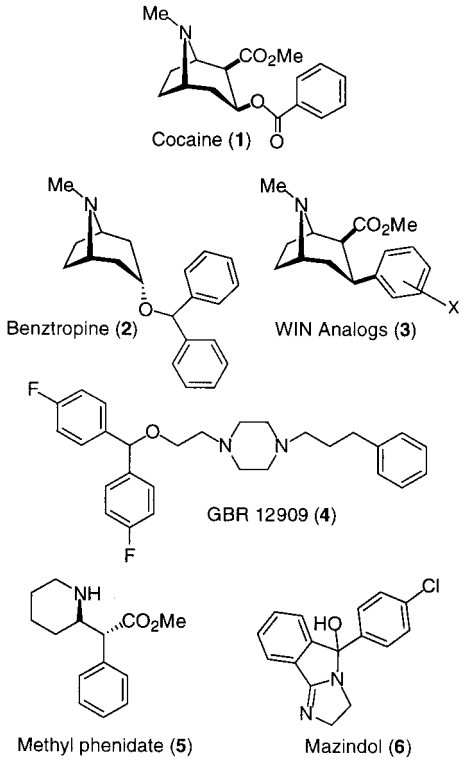
Chart 1



based agents are being investigated as possible medications for the treatment of cocaine abuse as well.[15,16] Interestingly, SERT inhibitors lacking dopaminergic activity do not produce reward or euphoria in primates.[17]

Further rationale for the utility of DAT/SERT-selective inhibitors comes from studies of craving, subjective ratings of cocaine effects, and effects on self-reports of drug use as well as on quantitative urinalysis. It has been reported that there is a significant correlation between regional brain metabolism in the orbitofrontal and prefrontal cortices and cocaine craving in abstinent patients.[18] Recent studies have shown increases in metabolism in these areas following treatment with the DAT inhibitor methylphenidate that were associated with an increase in craving in cocaine addicts.[19] This suggests that the use of selective DAT inhibitors alone may not be effective for the treatment of cocaine withdrawal. Such agents may help to relieve the anhedonia resulting from the putative DA deficits but also could serve as the interoceptive cue that enhances craving and reinstates self-administration.[20] On the other hand, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been shown to diminish subjective ratings of cocaine effects[21] but has had inconsistent effects in outpatient cocaine abusers.[22] These inconsistencies could be related to dose, trial length, or patient heterogeneity. Nevertheless, these data suggest that SSRIs alone will not produce a robust positive effect in cocaine-dependent patients. However, DAT/SERT-selective inhibitors could overcome the apparent shortcomings of both DAT-selective and SERT-selective inhibitors.

During our efforts to discover ligands of possible use as medications,[23] we recently identified a rather interesting aspect of the SERT structure−activity relationships (SAR), namely that significant selectivity and potency for the SERT can be achieved through the incorporation of certain (−)-*trans*-piperidine units into bivalent ligands.[24] On the other hand, as some of these piperidine building blocks in the (+)-enantiomeric series were found to show partial cocaine-like effects in vivo, we decided to apply this bivalent ligand concept to the (+)-series. One of these piperidines, namely (+)-methyl 4β-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylate,[25] was therefore chosen as the starting monomer for the assembly of bivalent ligands that were anticipated to exhibit potent and selective SERT and DAT activity. The present SAR studies in this series of bivalent piperidines has led us to the identification of novel ligands that indeed exhibit potent inhibitory activity at the SERT and DAT (Table 1). Herein, we describe the synthesis, monoamine uptake activity, and preliminary behavioral studies of these bivalent compounds.

Chemistry

Scheme 1 delineates the chemistry used to prepare the compounds in this series. Briefly, the individual enantiomers of the *trans*-piperidines, **7** and **8**, were prepared using a previously reported procedure.[25] The esters **7** and **8** were hydrolyzed and converted to the corresponding acid chlorides in two steps, and these acid chlorides were then reacted without purification with the desired bis-nucleophile to afford the bivalent reuptake inhibitors **11**−**22**. The structure of (+)-**14** was confirmed by crystallographic methods (Figure 1).[26] Reaction of the (+)-acid chloride with mono-*N*-FMOC protected 1,5-diaminopentane hydrochloride gave the *N*-FMOC protected monomer (structure not shown) which was deprotected in situ and reacted with the appropriate acid chloride to give the unsymmetrical ligands **23**−**25** (Scheme 2). Other compounds shown in Table 1 were prepared according to previously described procedures.[24,25,27]

Pharmacological Results

All final compounds were tested for their ability to inhibit high-affinity uptake of DA, 5-HT, and NE into the nerve endings (synaptosomes) and to displace [^{3}H]-mazindol binding on the DAT using established protocols.[27] The binding and the uptake data are listed in Table 1.

In general, none of the (−)-bivalent ligands exhibited high affinity for the DAT. On the other hand, the (+)-bivalent ligands exhibit nanomolar affinity (K_i = 8−920 nM) for the mazindol binding site on the DAT and act as potent inhibitors of DA reuptake (K_i = 14−341 nM). Comparative data for the monomeric esters and amides (**7**−**10**) are also provided in Table 1, and as is readily apparent, the amides **9** and **10** are DAT inactive while the esters **7** and **8** are more potent.

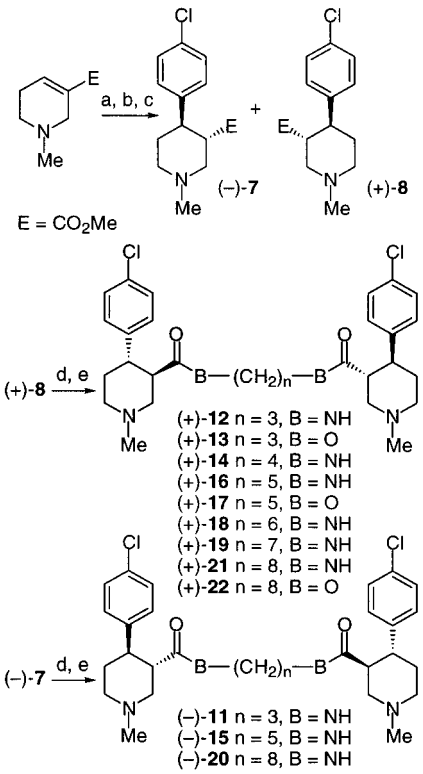
As the number of the methylene groups in the linking chain increases from 3 to 8 for the (+)-bivalent ligands, the ability of these compounds to inhibit DA reuptake decreases in a gradual fashion (Figure 2). The same trend is observed in the inhibition of the NET. However, this is not the case for the SERT. Among the (+)-bivalent ligands, compound **16**, with five methylene groups in the linking chain, is the most potent com-

Table 1. Activity of Bivalent Inhibitors at the Monoamine Transporters, $K_i \pm$ SE (nM)

compd	B	spacer	stereochemistry	mazindol binding K_i (nM)	[^{3}H]DA[a] uptake K_i (nM)	[^{3}H]NE[a] uptake K_i (nM)	[^{3}H]5-HT[a] uptake K_i (nM)
cocaine				230 ± 16	423 ± 147	108 ± 3.5	155 ± 0.4
7[b]	OMe		(−)-*trans*	1770 ± 180	2890 ± 250	242 ± 3.0	3600 ± 410
8[b]	OMe		(+)-*trans*	248 ± 18	228 ± 30	90 ± 5.2	5880 ± 440
9[c]	NHMe		(−)-*trans*	>39000	>70000	3110 ± 530	>10000
10[c]	NHMe		(+)-*trans*	>12000	>9000	4380 ± 1100	>53000
11[c]	NH	$-(CH_2)_3-$	(−)-*trans*	>6500	5090 ± 90	373 ± 55	342 ± 6.0
12	NH	$-(CH_2)_3-$	(+)-*trans*	8.4 ± 0.7	14 ± 2.9	146 ± 8.4	566 ± 4.1
13	O	$-(CH_2)_3-$	(+)-*trans*	68 ± 1.1	108 ± 9.5	340 ± 2.1	730 ± 68
14	NH	$-(CH_2)_4-$	(+)-*trans*	81 ± 3.5	33 ± 6	104 ± 7.6	534 ± 41
15[c]	NH	$-(CH_2)_5-$	(−)-*trans*	1440 ± 130	1960 ± 200	393 ± 6.7	1.2 ± 0.1
16	NH	$-(CH_2)_5-$	(+)-*trans*	103 ± 2.9	39 ± 4.3	158 ± 15	7.0 ± 0.6
17	O	$-(CH_2)_5-$	(+)-*trans*	64 ± 2.8	56 ± 4.7	182 ± 8.0	25 ± 5.4
18	NH	$-(CH_2)_6-$	(+)-*trans*	402 ± 37	75 ± 8	579 ± 28	60 ± 2.0
19	NH	$-(CH_2)_7-$	(+)-*trans*	348 ± 21	190 ± 1.9	394 ± 18	40 ± 4.6
20[c]	NH	$-(CH_2)_8-$	(−)-*trans*	NT	3184 ± 213	1037 ± 62	2.1 ± 0.1
21	NH	$-(CH_2)_8-$	(+)-*trans*	294 ± 19	341 ± 0.2	1980 ± 220	56 ± 12
22	O	$-(CH_2)_8-$	(+)-*trans*	920 ± 50	142 ± 3.7	658 ± 88	175 ± 3.7
23	NH		(+)-*trans*	409 ± 75	465 ± 64	1200 ± 190	494 ± 29
24	NH		(+)-*trans*	194 ± 24	256 ± 13	551 ± 34	159 ± 2.0
25	NH		(+)-*trans*	246 ± 5.0	253 ± 5.0	1080 ± 80	133 ± 21

[a] Data are presented as the mean ± standard error of at least three experiments. [b] Data taken from ref 27a. [c] Data taken from ref 24a.

Scheme 1[a]



[a] (a) 4-ClPhMgBr, ether, −10 °C; (b) dibenzoyl-D-tartaric acid, MeOH; or dibenzoyl-L-tartaric acid, MeOH; (c) NaOMe, MeOH; (d) HCl (6 N), reflux; $(COCl)_2$, CH_2Cl_2; (e) diamine or diol, Et_3N, CH_2Cl_2.

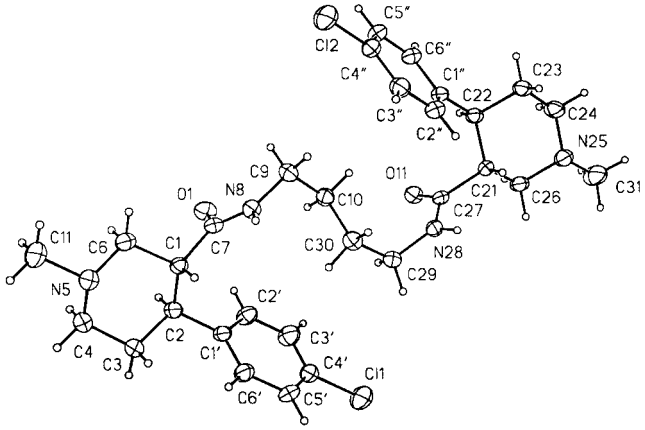
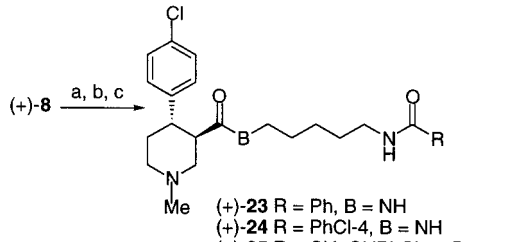


Figure 1. ORTEP drawing of piperidine (+)-**14**.

Scheme 2[a]



[a] (a) HCl (6 N), reflux; $(COCl)_2$, CH_2Cl_2; (b) FMOC-NH-$(CH_2)_5$-NH_2·HCl, Et_3N, CH_2Cl_2; (c) Et_3N, DMF, 12 h; RC(O)Cl, CH_2Cl_2.

pound at the SERT. Compounds with fewer methylene groups in the linker (**12** and **14**, $n = 3-4$) show a reduced ability ($K_i \sim 550$ nM) to inhibit the SERT. Similarly, compounds with greater than five methylene units (**18**, **19**, and **21**, $n = 6-8$) in the linker also have diminished activity ($K_i \sim 50$ nM). This is consistent with our previous observation in which (−)-*trans*-piperidine dimers with varying linker chain lengths were used to probe the SERT.[24] In that study, as in the present one, a methylene chain length of five units was optimal for the inhibition of reuptake at the SERT. This finding strongly suggests that a second binding site resides within the same SERT polypeptide chain or on a nearby polypeptide chain in a SERT oligomeric complex, and that the distance between these sites coincides with the optimal distance (5 methylene units) between the dimer headgroups. If the dimer is too short to bridge both sites, the potency is weaker. In the case where the dimer is longer than optimal, the headgroups can still bind to both sites, but the potency is reduced, presumably as a result of the entropy loss associated with the adoption of the requisite connecting chain conformation.

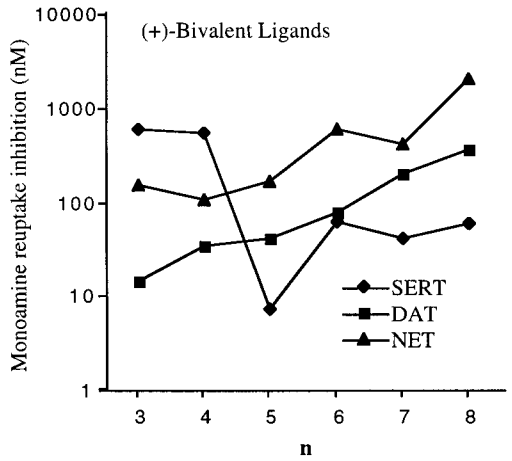


Figure 2. Monoamine reuptake inhibitory activity (K_i, nM) as a function of the number of methylene units (n) in the linking chain.

Overall, compounds **16** and, to a lesser extent, **18** and **19** in the (+)-bivalent series show selectivity for the SERT and the DAT, while compound **14** exhibits some selectivity for the DAT and the NET. However, compounds **15** and **20** in the (−)-bivalent series are potent and selective serotonin reuptake inhibitors. In this series, the DAT vs SERT selectivity is apparently dictated by the absolute stereochemistry of the piperidine building blocks. Piperidines **23**−**25**, which are nonsymmetrical versions of **16**, also exhibit the same dual selectivity for the DAT and SERT relative to NET, but the degree of selectivity is reduced. However, the nonsymmetrical compounds are, in general, less potent than the parent compound **16** at all three monoamine transporters, suggesting that the second piperidine unit is playing more than just a bystander role.

Behavioral Studies

Locomotor activity of male Swiss−Webster mice was recorded using Truscan activity monitors (Coulbourn Instruments, Allentown, PA) and a computer according to the procedure described elsewhere.[27b] Following 1 h of habituation to test arenas, several groups of mice were injected intraperitoneally (ip) with different doses of test drugs or appropriate vehicles. Locomotor activity was then measured in 10 min bins, and the bin with the greatest activity over the 2 h session for each dose of each drug was expressed as the percent of its corresponding vehicle control response and used in plotting the dose−response curves. For pretreatment studies, different groups of mice were injected with different doses of test drugs or appropriate vehicle (0.1 M tartaric acid) 20 min prior to 20 mg/kg cocaine injection.

Cocaine (3−30 mg/kg) produced dose-dependent enhancements in the distance traveled and stereotypic movements in mice (Figure 3). Unlike cocaine, the compounds **15** (10−56 mg/kg) and **16** (1−56 mg/kg) lacked locomotor stimulant effects. Neither compound was found to cause any statistically significant behavioral disruption at doses up to 56 mg/kg. However, pretreatment of mice with **16** dose-dependently antagonized cocaine-induced locomotor activation (Figure 4). Compound **15** also produced a moderate, but not statistically significant, reduction in cocaine-induced locomotor activation. Neither **15** nor **16** completely prevented cocaine-induced locomotor activity, even at the highest doses tested. The ability of **15** and **16** to blunt cocaine-induced locomotor activity demonstrates that these compounds penetrate the mouse blood-brain barrier, thereby arguing that their inactivity when administered alone is not due to a lack of access to the central nervous system.

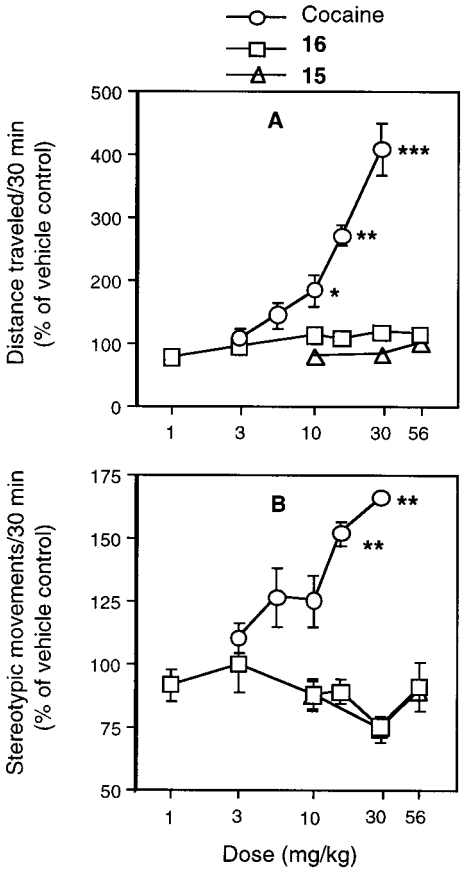


Figure 3. Locomotor effects of cocaine (circles) and compounds **15** (triangles) and **16** (squares) in male Swiss−Webster mice. Cocaine, but not compounds **15** and **16**, produced significant and dose-dependent increases in the distance traveled (A) ($F_{5,74} = 30.5$, $P < 0.001$) and in stereotypic movements (B) ($F_{5,74} = 8.3$, $P < 0.001$) as compared to the saline control group. The distance traveled and the stereotypic movement responses in the saline control group were 3517 ± 35 cm and 1299 ± 71, respectively. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ as compared to the corresponding responses in the vehicle control group by Tukey's post hoc test.

The drug discrimination study was conducted using male Sprague−Dawley rats according to the procedure described elsewhere.[27b] Rats were trained to discriminate 10 mg/kg ip cocaine from saline. All drugs were administered 10 minutes prior to the testing. The response rate on both keys and the percent cocaine lever-appropriate responding were calculated for each rat. The response rates following the test drug injections were presented as the percent of its corresponding vehicle control response rates. Cocaine (3−10 mg/kg) produced dose-dependent and full substitution for cocaine in cocaine-trained animals. In contrast, compound **16** (1−10 mg/kg) did not substitute for cocaine (Figure 5). Both cocaine and compound **16** did not alter the response rates (Figure 5). A total of 3 out of 7 and 5 out of 10 rats did not respond following 3 and 10 mg/kg

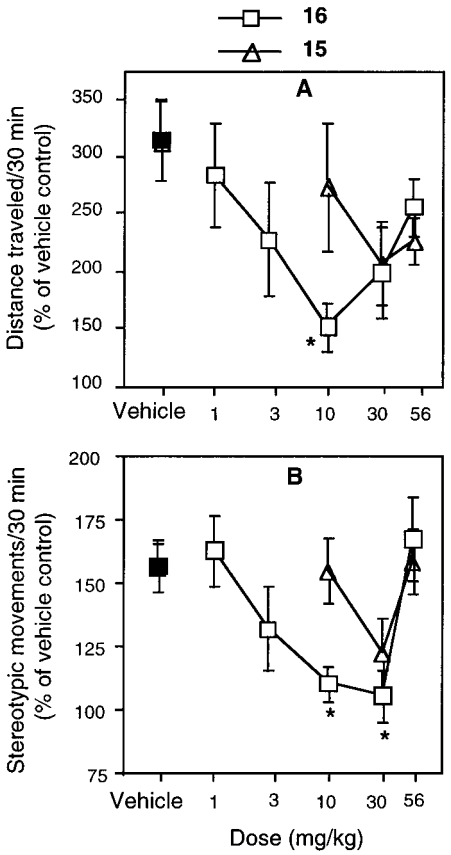


Figure 4. Effect of pretreatment with compounds **15** (triangles) and **16** (squares) on cocaine-induced (20 mg/kg ip) locomotor activation. Compound **16** (1−10 mg/kg) dose-dependently prevented the cocaine-induced increases in the distance traveled ($F_{5,87} = 2.52$, $P < 0.05$) and stereotypic movements ($F_{5,87} = 3.91$, $P < 0.01$) in male Swiss−Webster mice (A and B). The distance traveled and the stereotypic movement responses for cocaine in the vehicle (0.1 M tartaric acid) pretreated control group were 4931 ± 547 cm and 1162 ± 69, respectively. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ as compared to the cocaine responses in the corresponding vehicle (0.1 M tartaric acid) pretreated control group by Tukey's post hoc test. The data points in the figure represent the mean ± SEM.

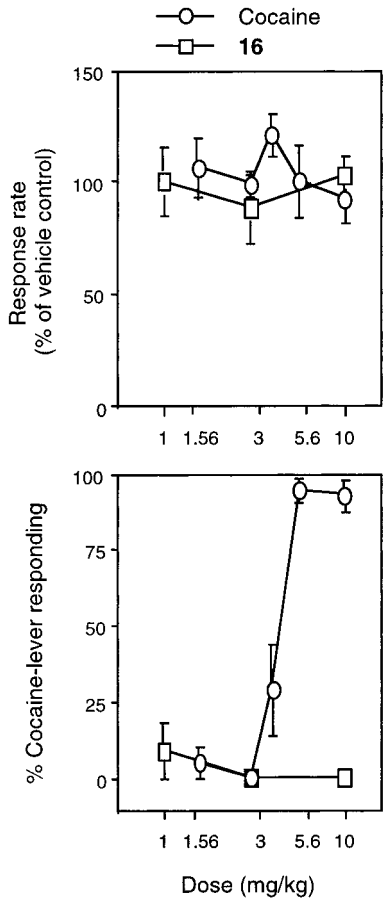


Figure 5. The discriminative stimulus effects of cocaine (circles) and compound **16** (squares) in rats ($n = 7$ to 10) trained to discriminate cocaine (10 mg/kg) from saline. The data points in the figure represent the mean ± SEM.

doses of compound **16**. These data also argue that **16** crosses the blood-brain barrier in rats as well as mice.

The primary mechanism underlying the behavioral effects of cocaine is thought to be due to its inhibitory effect on dopamine reuptake, though inhibition of serotonin uptake is also thought to be important. Compound **16** is about 5-fold and 20-fold more potent than cocaine at the DAT and SERT, respectively. Contrary to what might be expected, this compound had no cocaine-like locomotor activation or discriminative stimulus properties, yet it was able to block the locomotor effect of cocaine. On the other hand, compound **15**, the (−)-*trans* isomer, which is essentially SERT selective, also had no activity of its own but was significantly less effective as a cocaine antagonist. Although other properties, including pharmacokinetic factors, could be involved, these data imply that the reduced NET activity plays a role in the inability of **16** to produce locomotor activity and to engender a cocaine-like discriminative stimulus. However, this DAT/SERT selectivity may well underlie its ability to act as an antagonist. Additional studies, including the investigation of pharmacokinetic parameters and a thorough screening for potential activity at central nervous system neurotransmitter receptors, will be needed in order to draw more definitive conclusions regarding the behavioral activities of these interesting compounds.

Conclusions

The piperidine-based bivalent inhibitors described herein constitute a new class of monoamine reuptake inhibitors that exhibit varying levels of monoamine transporter activity and selectivity. The SAR developed for these bivalent piperidines indicates that this series of molecules can be tailored to have dual selectivity for the DAT and SERT or for the SERT exclusively. Of particular interest is the fact that one of these bivalent ligands comprised of two (+)-*trans*-piperidine units, compound **16**, is capable of blocking cocaine's locomotor effects in mice while not having any effect on locomotion when tested alone. Additionally, compound **16** (1−10 mg/kg) does not substitute for cocaine in drug discrimination studies in rats. Interestingly, this compound exhibits moderate selectivity for the DAT and SERT (39 nM and 7 nM, respectively) relative to the NET (158 nM). The behavioral data are encouraging, as they suggest that the compound is able to act in some ways as a cocaine antagonist. In comparison, the bivalent ligand **15** comprised of two (−)-*trans*-piperidine units exhibited primarily SERT activity and was less effective in antagonizing cocaine's locomotor stimulant activity.

Therefore, the absolute stereochemistry of the piperidine ring is a major determinant of potency and selectivity of these ligands at the monoamine transporters in vitro, and this difference may be responsible for the observed differences in their behavioral effects. The present results may have implications for the design of therapeutic agents for the treatment of cocaine addiction.

Experimental Procedures

General. Reagents and solvents were obtained from commercial suppliers and used as received. All starting materials were commercially available unless otherwise indicated. Solvent removal was routinely performed on a rotary evaporator at 30−40 °C. All reactions were performed under inert atmosphere (N_2) unless otherwise noted. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Unity Inova instrument at 300 and 75.46 MHz, respectively. ^{1}H chemical shifts (δ) are reported in ppm downfield from internal TMS. Melting points were taken in Pyrex capillaries with a Thomas-Hoover Unimelt apparatus and are not corrected. For the symmetrical bivalent ligands, decomposition was observed above 220 °C, and thus proper melting points could not be recorded. Mass spectra were measured in the EI mode at an ionization potential of 70 eV. TLC was performed on Merck silica gel 60 F_{254} glass plates; column chromatography was performed using Merck silica gel (60−200 mesh). Yields are of purified product and are not optimized.

(+)-4*β*-(4-Chlorophenyl)-1-methylpiperidine-3α-carboxylic Acid Hydrochloride. A solution of (+)-methyl 4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylate ((+)-**8**; 1.0 g, 3.73 mmol) in HCl (6 N, 10 mL) was stirred at reflux for 6 h, then concentrated to give a white powder corresponding to the title compound (1.0 g, 95%): mp 77−78 °C; $[\alpha]_D$ +62° (*c* 1.0, EtOH); ^{1}H NMR (CD_3OD) δ 1.98−2.12 (m, 2H), 2.93 (s, 3H), 2.97−3.30 (m, 4H), 3.58 (d, J = 12.0 Hz, 1H), 3.75 (d, J = 11.7 Hz, 1H), 7.23 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H).

(−)-4*β*-(4-Chlorophenyl)-1-methylpiperidine-3α-carboxylic Acid Hydrochloride. A solution of (−)-methyl 4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylate ((−)-**7**; 800 mg, 2.99 mmol) in HCl (6 N, 10 mL) was stirred at reflux for 6 h, then concentrated to give a white powder corresponding to the title compound (819 mg, 95%): mp 77−78 °C; $[\alpha]_D$ -61° (*c* 1.0, EtOH); ^{1}H NMR (CD_3OD) δ 1.98−2.12 (m, 2H), 2.93 (s, 3H), 2.97−3.30 (m, 4H), 3.58 (d, J = 12.0 Hz, 1H), 3.75 (d, J = 11.7 Hz, 1H), 7.23 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H).

(+)-1,3-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]propane (12). To a stirred suspension of (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.10 g, 0.35 mmol) in CH_2Cl_2 (5.0 mL) was added oxalyl chloride (500 μL), and the suspension was stirred for 2 h after which time all of the solid had dissolved. The solvent was evaporated to give the acid chloride intermediate as a colorless solid. This material was dissolved in CH_2Cl_2 (5.0 mL) and treated with Et_3N (500 μL) followed by 1,3-diaminopropane (13 μL, 0.15 mmol), and the resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous NaOH (1 M, 2 × 10 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated to give a white solid. Flash chromatography (CH_2Cl_2/MeOH/ Et_3N, 90:5:5) gave a solid which was triturated in ether (5.0 mL) and isolated by filtration to give the title compound as a white powder (45 mg, 55%): $[\alpha]_D$ + 58° (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.0 (m, J = 6.3, 2H), 1.8−2.0 (m, 8H), 2.15 (td, J = 11, 3.6 Hz, 2H), 2.35 (s, 6H), 2.3−2.6 (m, 4H), 2.78 (m, 2H), 2.9−3.0 (m, 4H), 5.71 (br s, 2H), 7.14 (d, J = 8.7 Hz, 4H), 7.25 (d, J = 8.7 Hz, 4H). Anal. ($C_{29}H_{38}Cl_2N_4O_2$·0.25HCl) C, H, N.

(+)-1,4-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]butane (14). Following the above general procedure, (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.10 g, 0.35 mmol) and 1,4-diaminobutane (15 μL, 0.17 mmol) gave the title compound as a white solid (48 mg, 57%): $[\alpha]_D$ + 61° (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.70 (m, 4H), 1.8−2.0 (m, 8H), 2.15 (td, J = 11, 3.0 Hz, 2H), 2.49 (s, 6H), 2.3−2.6 (m, 2H), 2.78 (m, 2H), 2.9−3.1 (m, 6H), 5.29 (br s, 2H), 7.14 (d, J = 8.7 Hz, 4H), 7.25 (d, J = 8.7 Hz, 4H). Anal. ($C_{30}H_{40}N_4O_2Cl_2$) C, H, N.

(−)-1,5-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]pentane (15). Following the above general procedure, (−)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.20 g, 0.69 mmol) and 1,5-diaminopentane (43 μL, 0.36 mmol) gave the title compound as a white solid (90 mg, 43%): $[\alpha]_D$ - 56° (*c* 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.57 (m, J = 7.2 Hz, 2H), 1.06 (m, J = 7.9 Hz, 4H), 1.6−2.2 (m, 8H), 2.29 (td, J = 11.1, 3.9 Hz, 2H), 2.34 (s, 6H), 2.4−2.6 (m, 2H), 2.78 (m, 4H), 2.9−3.1 (m, 4H), 5.13 (bs, 2H), 7.13 (d, J = 8.1 Hz, 4H), 7.25 (d,, J = 8.4 Hz 4H). Anal. ($C_{31}H_{42}Cl_2N_4O_2$) C, H, N.

(+)-1,5-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]pentane (16). Following the above general procedure, (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (600 mg, 2.08 mmol) and 1,5-diaminopentane (116 μL, 0.988 mmol) gave the title compound as a white solid (530 mg, 93%): $[\alpha]_D$ + 56° (*c* 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.57 (m, J = 7.2 Hz, 2H), 1.02 (m, J = 7.9 Hz, 4H), 1.6−2.2 (m, 8H), 2.21 (td, J = 11.1, 3.9 Hz, 2H), 2.4 (s, 6H), 2.4−2.6 (m, 2H), 2.8 (m, 4H), 2.9−3.1 (m, 4H), 5.13 (br s, 2H), 7.13 (d, J = 8.1 Hz, 4H), 7.25 (d, J = 8.4 Hz, 4H). Anal. ($C_{31}H_{42}Cl_2N_4O_2$) C, H, N.

(+)-1,6-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]hexane (18). Following the above general procedure, (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.10 g, 0.35 mmol) and 1,6-diaminohexane (19 mg, 0.16 mmol) gave the title compound as a white solid (68 mg, 75%): $[\alpha]_D$ + 51° (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.78 (m, 4H), 1.02 (m, 4H), 1.8−2.0 (m, 6H), 2.15 (td, J = 11, 3.0 Hz, 2H), 2.35 (s, 6H), 2.3−2.6 (m, 2H), 2.82 (m, 4H), 2.9−3.1 (m, 6H), 5.21 (br s, 2H), 7.14 (d, J = 8.7 Hz, 4H), 7.25 (d, J = 8.7 Hz, 4H). Anal. ($C_{32}H_{44}N_4O_2Cl_2$) C, H, N.

(+)-1,7-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]heptane (19). Following the above general procedure, (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.10 g, 0.35 mmol) and 1,7-diaminoheptane (20 μL, 0.15 mmol) gave the title compound as a white solid (58 mg, 64%): $[\alpha]_D$ + 51° (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 2H), 1.07 (m, 8H), 1.8−2.0 (m, 6H), 2.15 (td, J = 11, 3.0 Hz, 2H), 2.35 (s, 6H), 2.3−2.6 (m, 2H), 2.82 (m, 4H), 2.9−3.1 (m, 6H), 5.21 (br s, 2H), 7.14 (d, J = 8.7 Hz, 4H), 7.25 (d, J = 8.7 Hz, 4H). Anal. ($C_{33}H_{46}Cl_2N_4O_2$) C, H, N.

(+)-1,8-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]octane (21). Following the above general procedure, (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.10 g, 0.35 mmol) and 1,8-diaminooctane (24 mg, 0.17 mmol) gave the title compound as a white solid (59 mg, 58%): $[\alpha]_D$ + 52° (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.8−1.2 (m, 12H), 1.83 (m, 4H), 2.13 (td, J = 9.9, 3.6 Hz, 2H), 2.35 (s, 6H), 2.3−2.6 (m, 4H), 2.8−3.2 (m, 10H), 5.15 (br s, 2H), 7.14 (d, J = 8.7 Hz, 4H), 7.25 (d, J = 8.7 Hz, 4H). Anal. ($C_{34}H_{48}Cl_2N_4O_2$) C, H, N.

(+)-1,5-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]oxy]pentane (17). To a stirred suspension of (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (376 mg, 1.29 mmol) in CH_2Cl_2 (5 mL) was added oxalyl chloride (0.23 mL, 2.64 mmol), and the suspension was stirred for 2 h after which time all of the solid had dissolved. The solvent was evaporated to give the acid chloride intermediate as a colorless solid. This material was dissolved in CH_2Cl_2 (10 mL) and treated with Et_3N (500 μL) followed by 1,5-pentanediol (54 μL, 0.52 mmol) and a catalytic amount of DMAP. The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (2 × 10 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (CH_2Cl_2/

MeOH/Et_3N, 90:5:5) gave a solid which was triturated in ether (10 mL) and isolated by filtration to give the title compound as an oil (240 mg, 81%): $[\alpha]_D$ +30° (*c* 1.65, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 0.81 (q, J = 7.5 Hz, 2H), 1.10−1.34 (m, 4H), 1.72−1.90 (m, 4H), 2.00−2.24 (m, 4H), 2.36 (s, 6H), 2.66−2.78 (m, 2H), 2.85 (dt, J = 3.9, 11.1 Hz, 2H), 2.95 (d, J = 11.4 Hz, 2H), 3.08 (dd, J = 2.1, 11.1 Hz, 2H), 3.65−3.95 (m, 4H), 7.13 (d, J = 8.4 Hz, 4H), 7.23 (d, J = 8.4 Hz, 4H). Anal. ($C_{31}H_{40}Cl_2N_2O_4$) C, H, N.

(+)-1,3-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]oxy]propane (13). Following the preceding general procedure, (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.20 g, 0.69 mmol) and 1,3-propanediol (22 μL, 0.30 mmol) gave the title compound as an oil (135 mg, 82%): $[\alpha]_D$ +40.9° (*c* 0.89, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37 (m, J = 6.3 Hz, 2H), 1.73−1.84 (m, 4H), 2.04−2.21 (m, 4H), 2.35 (s, 6H), 2.63−2.75 (m, 2H), 2.84 (dt, J = 3.6, 11.4 Hz, 2H), 2.94 (d, J = 11.4 Hz, 2H), 3.05 (dd, J = 2.1, 11.1 Hz, 2H), 3.50−3.70 (m, 4H), 7.11 (d, J = 8.4 Hz, 4H), 7.23 (d, J = 8.4 Hz, 4H). Anal. ($C_{29}H_{36}N_2O_4Cl_2$) C, H, N.

(+)-1,8-Bis[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]oxy]octane (22). Following the preceding general procedure, (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (0.20 g, 0.69 mmol) and 1,8-octanediol (44 mg, 0.30 mmol) gave the title compound as an oil (140 mg, 75%): $[\alpha]_D$ +40° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95−1.15 (m, 8H), 1.24−1.38 (m, 4H), 1.74−1.86 (m, 4H), 2.04−2.12 (m, 2H), 2.18 (t, J = 11.1 Hz, 2H), 2.35 (s, 6H), 2.67−2.78 (m, 2H), 2.86 (dt, J = 3.6, 11.1 Hz, 2H), 2.94 (d, J = 11.1 Hz, 2H), 3.09 (dd, J = 2.1, 11.1 Hz, 2H), 3.75−3.92 (m, 4H), 7.14 (d, J = 8.1 Hz, 4H), 7.24 (d, J = 8.7 Hz, 4H). Anal. ($C_{34}H_{46}N_2O_4Cl_2$) C, H, N.

(+)-1-[[4*β*-(4-Chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]-5-[[(9-fluorenylmethoxy)carbonyl]amino]-pentane. To a stirred suspension of (+)-4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylic acid hydrochloride (500 mg, 1.64 mmol) in CH_2Cl_2 (20 mL) was added dropwise oxalyl chloride (3.0 mL), and the solution was stirred for 2 h at which time all of the solid had dissolved. The solvent was evaporated to give the acid chloride intermediate as a colorless solid. This material was dissolved in CH_2Cl_2 (10 mL) and treated with Et_3N (332 μL) followed by *N*-Fmoc-1,5-diaminopentane (592 mg, 1.64 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (2 × 10 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (CH_2Cl_2/MeOH, 9:1) gave the title compound as a white solid (800 mg, 80%): mp 144−145 °C; $[\alpha]_D$ +44° (*c* 0.25, EtOH); ^1H NMR ($CDCl_3$) δ 0.8−1.4 (m, 6H), 1.67 (m, 2H), 2.24 (m, 2H), 2.50 (s, 3H), 2.73 (m, 3H), 2.87 (m, 4H), 4.2 (br m, 2H), 7.2−7.5 (m, 8H), 7.67 (d, J = 7.5 Hz, 2H), 7.88 (d, J = 7.5 Hz, 2H).

(+)-1-(Benzamido)-5-[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]pentane (23). A solution of the preceding intermediate (100 mg, 0.179 mmol) and Et_3N (2.0 mL) in DMF (4.0 mL) was stirred at room temperature for 12 h. Benzoyl chloride (25 μL, 0.215 mmol) was added, and the resulting solution was stirred at room temperature for 24 h. The solvent was evaporated to give a white solid. This material was dissolved in CH_2Cl_2 (10 mL), and the solution was washed with aqueous $NaHCO_3$ (2 × 10 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (CH_2Cl_2/MeOH, 9:1) gave a solid which was triturated in ether (10 mL) and isolated by filtration to give the title compound as a white solid (35 mg, 44%): mp 179−180 °C; ^1H NMR ($CDCl_3$) δ 1.03 (m, J = 7.2 Hz, 2H), 1.21 (m, J = 7.2 Hz, 2H), 1.50 (m, J = 7.2 Hz, 2H), 2.0−2.4 (m, 8H), 2.8−3.2 (m, 5H), 3.38 (m, 2H), 5.28 (s, 1H), 6.25 (m, 1H), 7.0−7.2 (m, 4H), 7.49 (m, 3H), 7.83 (d, 2H, J = 7.5 Hz). Anal. ($C_{25}H_{32}N_3O_2Cl$·0.2HCl) C, H, N.

(+)-1-(4-Chlorobenzamido)-5-[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]pentane (24). Following the preceding general procedure, (+)-1-[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]-5-[[(9-fluorenylmethoxy)carbonyl]amino]pentane (100 mg, 0.179 mmol) and 4-chlorobenzoyl chloride (100 mg, 0.558 mmol) gave the title compound as a white solid (38 mg, 45%): ^1H NMR ($CDCl_3$) δ 1.03 (m, J = 7.2 Hz, 2H), 1.21 (m, J = 7.2 Hz, 2H), 1.50 (m, J = 7.2 Hz, 2H), 2.0−2.4 (m, 8H), 2.8−3.2 (m, 5H), 3.38 (m, 2H), 5.28 (s, 1H), 6.25 (m, 1H), 7.0−7.2 (m, 4H), 7.43 (d, 2H, J = 7.5 Hz), 7.83 (d, 2H, J = 7.5 Hz). Anal. ($C_{25}H_{31}N_3O_2Cl_2$·0.2HCl) C, H, N.

(+)-1-[(4-Chlorocinnamoyl)amino]-5-[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]pentane (25). Following the preceding general procedure, (+)-1-[[4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carbonyl]amino]-5-[[(9-fluorenylmethoxy)carbonyl]amino]pentane (100 mg, 0.179 mmol) and 4-chlorocinnamoyl chloride (100 mg, 0.546 mmol) gave the title compound as a white solid (46 mg, 53%): mp 188−190 °C; ^1H NMR ($CDCl_3$) δ 0.98 (m, J = 7.2 Hz, 2H), 1.19 (m, J = 7.2 Hz, 2H), 1.45 (m, J = 6.9 Hz, 2H), 1.8−2.2 (m, 4H), 2.34 (s, 3H), 2.49 (m, 1H), 2.8−3.0 (m, 4H), 3.10 (m, 1H), 3.29 (m, 2H), 5.40 (br s, 1H), 6.00 (br s, 1H), 6.49 (d, J = 15.6 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 7.23 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 15.6 Hz, 1H). Anal. ($C_{27}H_{33}N_3O_2Cl_2$·0.2HCl) C, H, N.

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Supporting Information Available: Analytical data for compounds listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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