Synthesis and in Vitro Evaluation of 5,6,7,8,9,10-Hexahydro-7,10-iminocyclohept[*b*]indoles: High-Affinity Ligands for the *N,N'*-Di-*o*-tolylguanidine-Labeled σ Binding Site

Richard E. Mewshaw,*,† Ronald G. Sherrill,† Rose M. Mathew,† Carl Kaiser,† Michael A. Bailey,‡ and E. William Karbon‡

Scios-Nova Inc., 6200 Freeport Centre, Baltimore, Maryland 21224-6522

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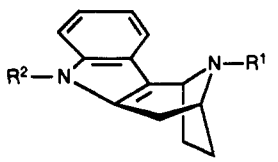
A series of 5,6,7,8,9,10-hexahydro-7,10-iminocyclo[*b*]indoles substituted at the 5 and/or 11 positions was synthesized from tropinone. Affinity for σ binding sites was determined using [^{3}H]-*N,N'*-di-*o*-tolylguanidine ([^{3}H]DTG) and [^{3}H]-(+)-3-(3-hydroxyphenyl)-*N*-1-propylpiperidine ([^{3}H]-(+)-3-PPP) and for the dopamine D_2 receptor labeled with [^{3}H]sulpiride. Nearly all compounds studied in this series possessed a higher affinity for [^{3}H]DTG than [^{3}H]-(+)-PPP-labeled σ sites, suggesting that [^{3}H]DTG and [^{3}H]-(+)-3-PPP radioligands label pharmacologically distinct σ binding sites, as reported previously. Substitution at the 11 position with side chains containing a four-carbon tether resulted in compounds having the highest affinity for the [^{3}H]DTG-labeled σ site. The most potent and selective member of this series was 11-[4-(2-furanyl)butyl]-5,6,7,8,9,-10-hexahydro-7,10-iminocyclohept[*b*]indole (**40**). Enantioselectivity was investigated by preparing the (+)- and (−)-isomers of **40**. These studies revealed that (+)-**40** was more potent at the [^{3}H]-DTG-labeled σ site whereas (−)-**40** had a higher affinity at σ sites labeled with [^{3}H]-(+)-PPP. Racemic **40** was observed to possess a higher affinity than either of its respective enantiomers at both the [^{3}H]DTG- and [^{3}H]-(+)-3-PPP-labeled sites, suggesting an allosteric interaction.

σ Antagonists have attracted considerable attention due to their therapeutic potential in treating psychiatric and neurodegenerative disorders.[1] Though their physiological role remains largely unknown, recent studies have implicated σ binding sites in the regulation of motor behavior,[2,3] enhancement of neurotransmitter release,[4] smooth-muscle contraction,[4,5] negative modulation of brain phosphoinositide metabolism,[6] and inhibition of neuronal firing rate.[7,8] First postulated by Martin et al.[9] to account for the psychotomimetic effects of *N*-allylnormetazocine (SKF 10,047, **1**), recent interest in σ sites has grown because of their ability to bind both typical and atypical antipsychotics. The potential atypical antipsychotic agents rimcazole (**2**),[10] remoxipride (**3**),[11] BMY-14802 (**4**),[12] tiosperone (**5**),[13] cinuperone (**6**),[14] gevetroline (**7**),[15] and NPC 16316 (**8**)[16,17] all possess significant affinity for σ binding sites.[18] Many of these agents have only low affinity for the dopamine D_2 receptor, suggesting that their putative antipsychotic actions are manifested through a nondopaminergic mechanism.[19] Therefore, these agents might constitute a novel class of neuroleptics which lack many of the undesirable side effects associated with classical D_2 receptor antagonists. In order to further understand the potential therapeutic effects which might be derived from blockade of σ binding sites, there is a need for high-affinity σ ligands whose functional role is not masked by cross-reactivity with other neurotransmitter receptors.

As part of an effort to discover highly selective σ ligands,[16,17] we now report the preparation and in vitro evaluation of a novel series of bridged γ-carbolines (**9**). Incorporation of an ethylene bridge within the γ-carboline nucleus not only provides a rigid skeleton, but could also impart a conformational impedement, resulting in decreased affinity at other sites, thereby generating highly selective σ ligands. The γ-carboline skeleton was focused



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upon for several reasons: (1) chemically, this nucleus possesses a 3-phenylpiperidine moiety embedded within its skeleton, a structural feature suggested as being the primary pharmacophore of σ sites;[20] (2) recently, Glennon et al.[21] provided evidence that the 2-(phenylamino)ethane moiety, also retained in γ-carbolines, serves as the common denominator among a variety of chemically distinct σ ligands; (3) the γ-carboline nucleus (e.g. gevetroline, **7**) has been demonstrated to possess affinity for σ binding sites;[1a,18] and (4) the γ-carboline skeleton conforms to some of the criteria for the σ site model proposed by Manallack et al.[22] In this report we discuss structure–activity relationships (SAR) of more than 40 members (**13–55**) of this series of bridged γ-carbolines with respect to [^{3}H]-*N,N'*-di-*o*-tolylguanidine ([^{3}H]DTG) and [^{3}H]-(+)-3-(3-hydroxyphenyl)-*N*-1-propylpiperidine ([^{3}H]-(+)-3-PPP) labeled σ sites. To evaluate selectivity with respect to the dopamine receptor, affinity for the [^{3}H]sulpiride-labeled D_2 receptor was determined. Enantioselectivity was investigated by identifying the most potent and selective racemic member of this series, preparing the enantiomers, and determining their affinity for σ and D_2 sites.

Chemistry

Synthesis. Bridged γ-carbolines **13–15** were prepared as illustrated in Scheme I. *N*-(2,2,2-Trichlorocarbethoxy)-nortropinone (**11**) was derived from commercially available tropinone (**10**).[23] Reduction of carbamate **11** with zinc in glacial acetic acid afforded nortropinone (**12**).[23] Fischer indole synthesis (method A) was achieved by initial

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.

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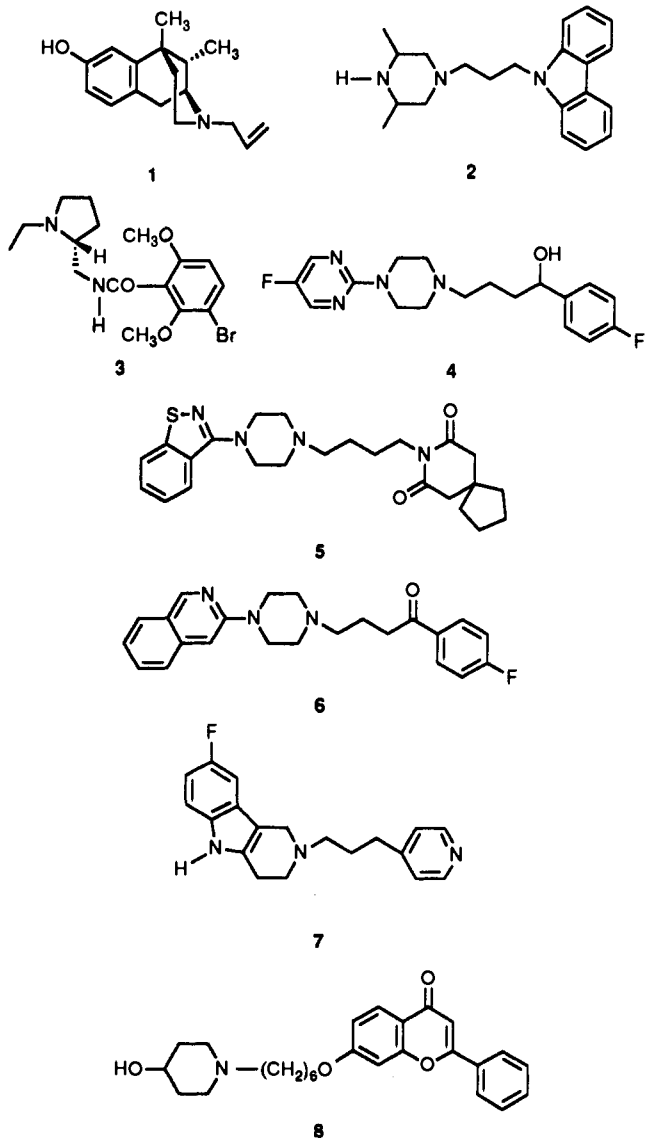
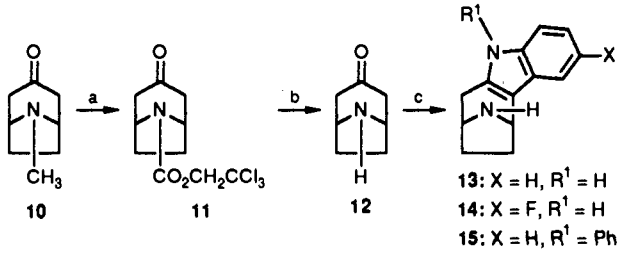
Chart I



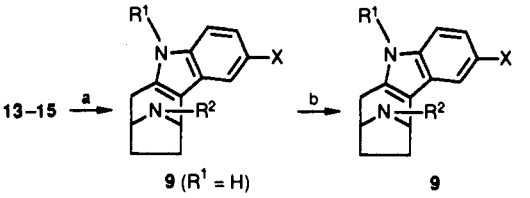
Scheme I[a]



[a] Reagents and conditions: (a) $ClCO_2CH_2CCl_3$, K_2CO_3; (b) Zn, AcOH; (c) Fischer indole synthesis (method A).

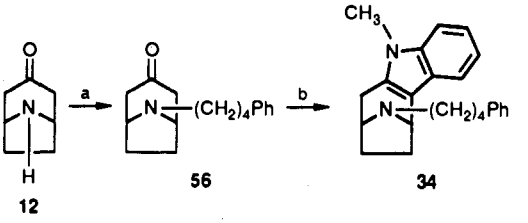
formation of the hydrazone in 2-propanol followed by exposure to HCl gas.[24] The γ-carboline intermediates could be isolated without chromatography. Substitution at the N-11 position was achieved by reacting indoles **13–15** with the appropriate alkyl bromides or chlorides (in the presence of NaI) in DMF as described in the Experimental Section (Scheme II, method B). Substitution at the N-5 position was achieved by initial deprotonation using excess sodium hydride followed by the addition of the appropriate alkyl halide (method C). γ-Carboline **16** (Table I) was prepared directly from tropinone using Fischer indole conditions. Compound **34** (Scheme III)

Scheme II[a]



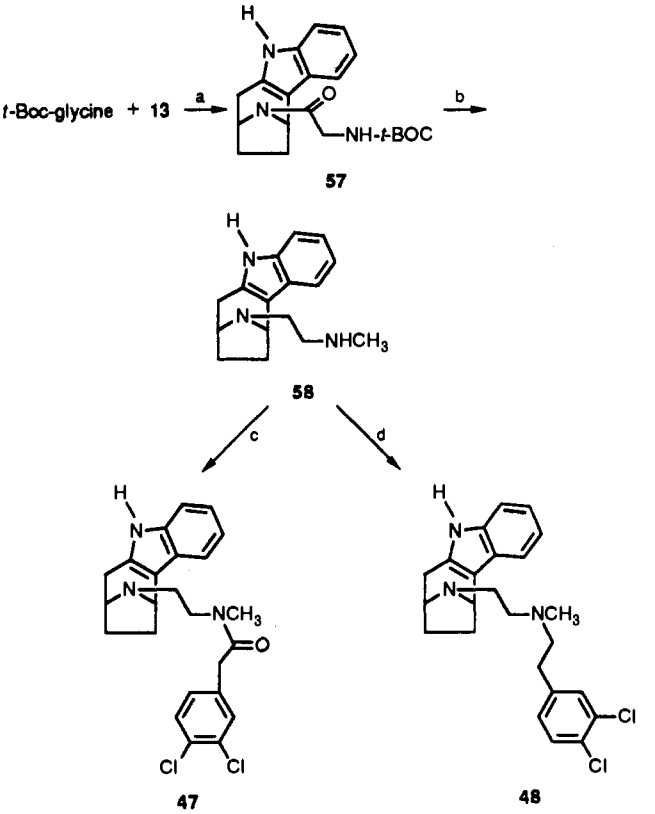
[a] Reagents and conditions: (a) R^2X, K_2CO_3, DMF (method B); (b) NaH, R^1X, DMF (method C).

Scheme III[a]



[a] Reagents and conditions: (a) $Ph(CH_2)_4Br$, K_2CO_3, DMF; (b) $PhNHMeNH_2$, HCl.

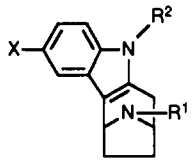
Scheme IV[a]



[a] Reagents and conditions: (a) EDC; (b) LAH (method D); (c) 3,4-Cl_2PhCH_2COCl; (d) 3,4-$Cl_2PhCH_2CH_2OTs$ (method B).

was prepared by N-alkylation of nortropinone (**12**) according to general method B, followed by the Fischer indole methodology (method A). Dichloride **55** (Table VII) was prepared from 2-(3,4-dichlorophenyl)ethyl tosylate[25] (available from borohydride reduction of 3,4-dichlorophenylacetic acid followed by tosylation) using method B (Scheme II). Compound **57** was synthesized by DIC coupling of **13** with *N*-(*tert*-butoxycarbonyl)glycine, which was subsequently reduced with lithium aluminum hydride (method D) to afford **58** (Scheme IV).[25] Diamine **58** was acylated with dichlorophenylacetyl chloride to afford **47**. Treatment of **58** with 2-(3,4-dichlorophenyl)ethyl tosylate afforded **48**. Compound **53** (Table VII) was obtained by

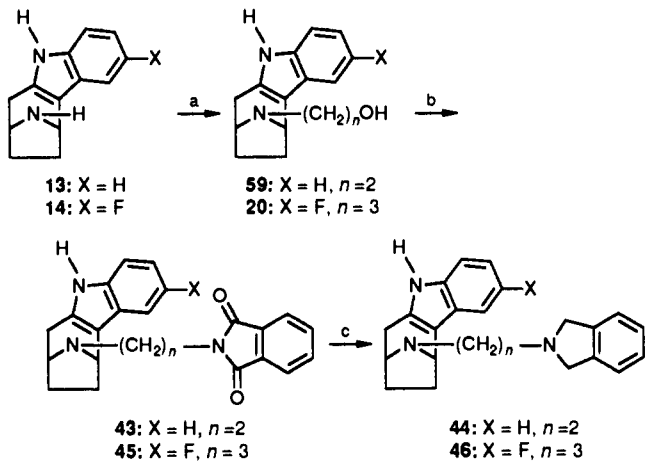
Table I. Binding Affinities of γ-Carbolines[a]



compd[a]	X	R^1	R^2	σ (IC_{50}, nM) [^{3}H]DTG[b]	σ (IC_{50}, nM) [^{3}H]-(+)-3-PPP[b]	D_2 (K_i, μM) [^{3}H]sulpiride[b]
13	H	H	H	5000	3590 (±1410)	>100
14	F	H	H	1473 (±83)	1212 (±178)	36.6
15	H	H	Ph	1895	6605	10.0 (±0.1)
16	H	Me	H	2650 (±1150)	2005 (±1095)	16.6 (±6.0)
17	H	Et	H	3560 (±1830)	3840	>10.0
18	H	n-Pr	H	1084 (±43)	1276 (±724)	11.2 (±4.1)
19	H	1-butenyl	H	683 (±284)	1763 (±306)	0.71
20	F	$(CH_2)_3OH$	H	317 (±49)	1382 (±188)	37.3 (±12.7)

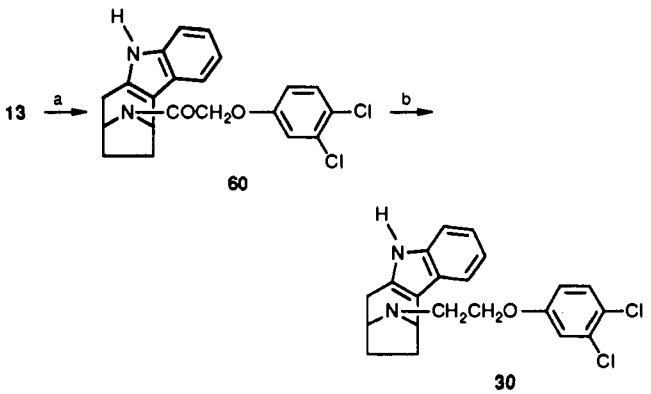
[a] The compounds presented here are racemates unless indicated. [b] The IC_{50} and K_i binding data for Tables I–VII were generated as described in Experimental Section. All values are the mean of at least two separate determinations followed by ±SEM. Values having no error limits are the result of only one experiment.

Scheme V[a]



[a] Reagents and conditions: (a) $BrCH_2(CH_2)_nOH$, (method B); (b) DEAD, PPh_3, phthalimide; (c) LAH, reflux.

Scheme VI[a]

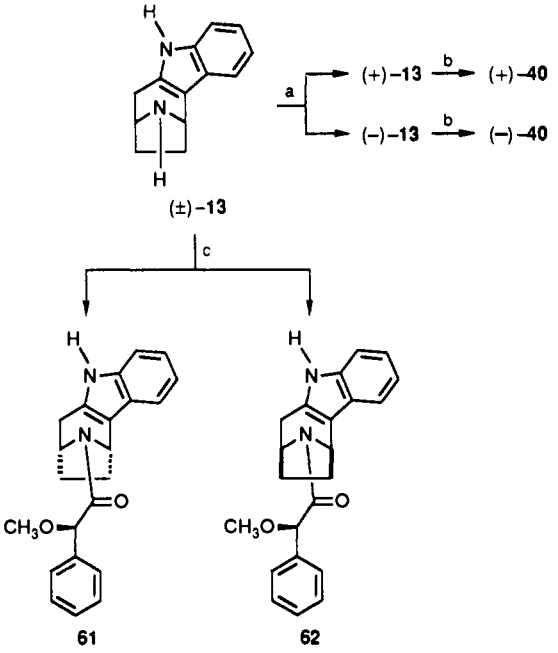


[a] Reagents and conditions: (a) 3,4-Cl_2PhOCH_2COCl, TEA; (b) AlH_3/THF.

treatment of the γ-carboline **14** with the requisite pyridinylalkyl bromide[15] using general method B. Phthalimides **43** and **45** and isoindoles **44** and **46** were prepared as depicted in Scheme V (methods E and F). Compound **30** was prepared from **13** in two steps as shown in Scheme VI (method G). General methods (A–G) of synthesis, physical, and spectroscopic properties of **13–55** are tabulated in Table VIII.

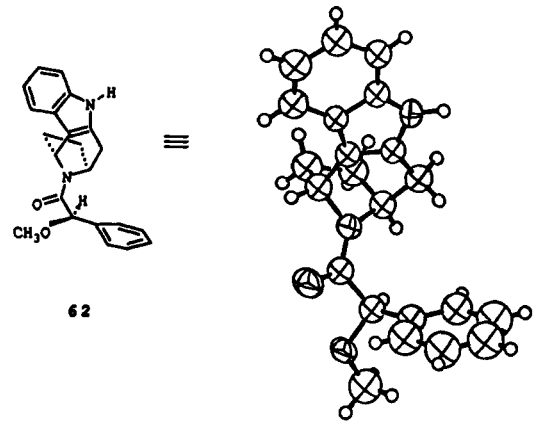
Resolution and Determination of Optical Purity. Racemic **13** was converted to its tartrate salts and resolved through fractional crystallization of the diastereomeric salts from water. An HPLC method was used to estimate the optical purities of enantiomerically enriched samples of **13**.[26] Coupling of the liberated free bases with (*R*)-(+)-*O*-methylmandelic acid (Aldrich, >99.5 ± 0.5% optically pure) afforded the corresponding *O*-methylmandeloylamides, **61** and **62** (Scheme VII). Purification by HPLC (reverse phase, C_{18} column, 40% acetonitrile–60% water) enabled separation and isolation of the two diastereomeric amides having retention times of approximately 16.6 and 19.3 min.[27] The enantiomeric excess of (−)-**13** derived from the classical resolution was determined to be >98% ee, while (+)-**13** was observed to be >99% ee. Both enantiomers, (+)-**13** and (−)-**13**, were then N-alkylated to afford (+)-**40** and (−)-**40**, respectively (Scheme VII).

Scheme VII[a]



[a] Reagents and conditions: (a) classical resolution; (b) 2-furanylbutyl bromide, K_2CO_3, DMF (method B); (c) EDC, (*R*)-(−)-methoxyphenylacetic acid; HPLC separation.

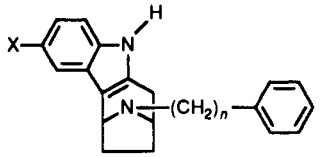
X-ray Crystallography. The absolute configuration of (+)-**13** and (−)-**13** was established by single crystal X-ray crystallographic analysis of (+)-**13** derivatized as its (*R*)-*O*-methylmandeloylamide **62**. The structure was solved according to the direct method[30] and refined by full-matrix



62

Figure 1. ORTEP drawing of 62 as determined by X-ray analysis.

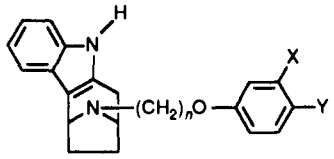
Table II. Binding Affinities of γ-Carbolines



compd[a]	X	n	σ (IC_{50}, nM) [^{3}H]DTG[b]	σ (IC_{50}, nM) [^{3}H]-(+)-3-PPP[b]	D_2 (K_i, μM) [^{3}H]sulpiride[b]
21	F	1	86 (±14)	908 (±222)	2.42 (±1.32)
22	H	1	345 (±85)	2750 (±550)	3.65 (±0.25)
23	H	2	234 (±6)	1280 (±300)	0.84
24	H	3	81 (±13)	368 (±60)	2.6
25	H	4	25 (±3)	114 (±25)	0.733
26	H	5	107 (±59)	348 (±70)	0.677 (±0.164)
27	F	4	38 (±3)	178 (±16)	0.769 (±0.208)

[a,b] See footnotes of Table I.

Table III. Binding Affinities of γ-Carbolines



compd[a]	X	Y	n	σ (IC_{50}, nM) [^{3}H]DTG[b]	σ (IC_{50}, nM) [^{3}H]-(+)-3-PPP[b]	D_2 (K_i, μM) [^{3}H]sulpiride[b]
28	H	H	2	110 (±8)	534 (±40)	2.60
29	H	Cl	2	251 (±28)	4876 (±2308)	0.53
30	Cl	Cl	2	400 (±93)	782 (±12)	0.65
31	H	H	3	132 (±16)	262 (±18)	1.28 (±0.26)
32	H	F	3	55 (±9)	148 (±12)	2.10 (±0.77)
33	H	H	4	88 (±15)	205 (±57)	0.10

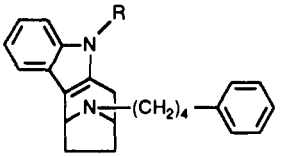
[a,b] See footnotes of Table I.

least squares and difference Fourier methods. The oxygen and nitrogen atoms were refined anisotropically. The carbon atoms were refined isotropically because of the low reflection to parameter ratio. The hydrogen atom attached to the nitrogen atom was located from a difference Fourier map and refined isotropically. The positions of the remaining hydrogen atoms were calculated assuming ideal geometries. The space group was determined to be $P2_12_12_1$. The cell parameters and characteristics are shown in Table IX. The ORTEP drawing of **62** is shown in Figure 1. As a consequence, the stereocenters of (+)-**13** and (−)-**13** are 7*S*,10*R* and 7*R*,10*S*, respectively.

Results and Discussion

σ Site Affinity. All compounds were examined for their affinity at σ sites labeled with [^{3}H]DTG and [^{3}H]-(+)-3-PPP in guinea pig brain membranes (Tables I–VI). The unsubstituted γ-carbolines and lower-alkyl substituted γ-carbolines (**13–20**, Table I) had little affinity for the σ sites. Affinity increased dramatically upon substitution of the 11 position with phenylalkyl side chains (Table II). Increasing the length of the alkyl spacer between the basic amine and the phenyl group from one to four methylene units (**22–25**) resulted in a progressive increase in affinity. However, when the chain length was increased further by

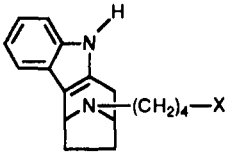
Table IV. Binding Affinities of N-Substituted Derivatives of **25**

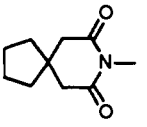


compd[a]	R	σ (IC_{50}, nM) [^{3}H]DTG[b]	σ (IC_{50}, nM) [^{3}H]-(+)-3-PPP[b]	D_2 (K_i, μM) [^{3}H]sulpiride[b]
25	H	25 (±3)	114 (±25)	0.73 (±0.01)
34	Me	116 (±6)	281 (±99)	1.82 (±0.08)
35	*i*-Pr	231 (±35)	705 (±20)	2.64 (±0.27)
36	Ph	212 (±14)	1210 (±150)	1.57 (±0.34)
37	Bn	267 (±87)	396 (±92)	1.83 (±0.14)

[a,b] See footnotes of Table I.

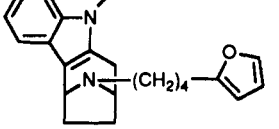
Table V. Binding Affinities of γ-Carbolines



compd[a]	X	σ (IC_{50}, nM) [^{3}H]DTG[b]	σ (IC_{50}, nM) [^{3}H]-(+)-3-PPP[b]	D_2 (K_i, μM) [^{3}H]sulpiride[b]
25	Ph	25 (±3)	114 (±25)	0.73 (±0.01)
38	4-FC_6H_4	37 (±8)	107 (±5)	1.16 (±0.01)
39		21 (±6)	98 (±24)	0.62 (±0.11)
40[c]		28 (±7)	105 (±8)	1.27 (±0.39)
41[c]		66 (±29)	136 (±54)	2.23 (±0.77)
42		54 (±4)	988 (±152)	3.00 (±0.91)

[a,b] See footnotes of Table I. [c] See refs 40 and 41.

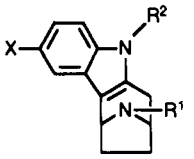
Table VI. Binding Affinities of Enantiomers of **40**

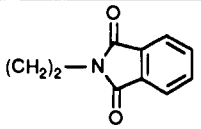
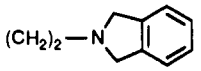
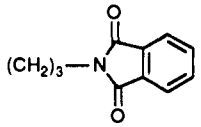
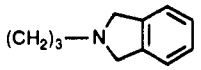
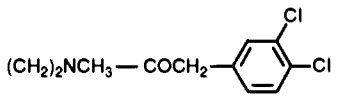
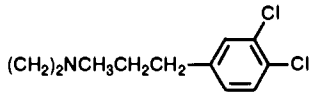
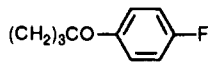
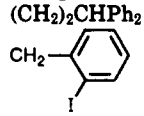
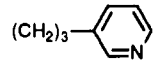
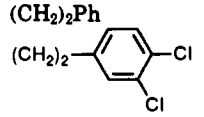


compd	σ (IC_{50}, nM) [^{3}H]DTG[a]	σ (IC_{50}, nM) [^{3}H]-(+)-3-PPP[a]	D_2 (K_i, μM) [^{3}H]sulpiride[a]
(±)-**40**	28 (±7)	105 (±8)	1.27 (±0.39)
(+)-**40**[b]	46 (±13)	482 (±51)	0.33 (±0.10)
(−)-**40**[c]	170 (±12)	108 (±1)	3.15 (±0.13)

[a] The IC_{50} and K_i binding data were generated as described in Experimental Section. All values are the mean of at least three separate determinations. [b] $[\alpha]_D^{24}$ +11° (*c* = 1, CH_2Cl_2). [c] $[\alpha]_D^{24}$ −10° (*c* = 1, CH_2Cl_2).

Table VII. Binding Affinities of Miscellaneous γ-Carboline Derivatives



compd[a]	R^1	R^2	X	σ (IC_{50}, nM) [^{3}H]DTG[b]	σ (IC_{50}, nM) [^{3}H]-(+)-3-PPP[b]	D_2 (K_i, μM) [^{3}H]sulpiride[b]
43		H	H	8085 (±1915)	>10000	52.1
44		H	H	141 (±22)	85 (±18)	2.0 (±0.2)
45		H	F	836 (±333)	3332 (±1808)	12.3 (±1.7)
46		H	F	54 (±18)	76 (±20)	1.78 (±0.62)
47		H	H	1612 (±660)	>10000	3.79
48		H	H	509 (±63)	474 (±140)	2.53 (±0.15)
49		H	H	129 (±55)	283 (±50)	0.27 (±0.01)
50	*t*-$CH_2CH{=}CHPh$	H	H	133 (±9)	517 (±119)	2.46
51	$(CH_2)_2CHPh_2$	H	H	1483 (±34)	4007 (±1599)	4.52
52		H	F	3044 (±574)	>10000	5.31 (±0.98)
53		H	F	44 (±11)	114 (±10)	12.2 (±4.7)
54	$(CH_2)_2Ph$	Bn	H	482 (±72)	487 (±182)	1.62
55		H	H	702 (±66)	>10000	3.43
7	gevetroline			182 (±19)	282 (±12)	0.006 (±0.002)

[a,b] See footnotes of Table I.

one methylene unit (e.g. **26**), affinity decreased. Very little effect on affinity was observed when an oxygen atom was incorporated in the side-chain spacer between the phenyl group and amine (**24** vs **28**, **25** vs **31**, **26** vs **33**, **27** vs **32**). In all cases, substitution of chlorine in the phenyl rings resulted in a decrease in affinity (**23** vs **55**, **24** vs **29** or **30**). Substituting fluorine for hydrogen (**31** vs **32**) resulted in a 2-fold increase in affinity in the phenoxy series (Table III). However, this was not observed in the phenylalkyl-substituted series (**25** vs **27**). Substitution on the indole nitrogen in all cases (**25** vs **34–37**, Table IV) resulted in lower affinity ligands. Compounds **43**, **45**, and **47** all had lower affinity than their respective reduced analogues, **44**, **46**, and **48** (Table VII). These results support the earlier suggestion that binding sites for two basic nitrogens may exist within the σ site.[25] Incorporation of the previously reported[25] σ potent side chains [e.g. (3,4-dichlorophenyl)-acetamide and 2-(3,4-dichlorophenyl)ethyl groups] into the γ-carboline nucleus resulted in ligands having low affinity for the σ sites. The conformationally restricted gevetroline analogue **53** (Table VII) had a 4- and 2.5-fold higher affinity than gevetroline (**7**) at [^{3}H]DTG and [^{3}H]-(+)-3-PPP sites, respectively. Compounds possessing the highest affinity at σ binding sites (Table V) all have in common a four-carbon tether; however, very little difference in affinity was observed for these derivatives (Table V).

σ/D_2 Selectivity. The bridged γ-carboline series described above was observed to have a higher affinity for the [^{3}H]DTG-labeled σ binding site than the dopamine D_2 receptor. However, lower selectivity was observed between the [^{3}H]-(+)-3-PPP-labeled σ binding site and the D_2 receptor. In fact, compound **33** had higher affinity for the D_2 receptor (K_i = 100 nM) than the [^{3}H]-(+)-3-

PPP labeled site (IC_{50} = 205 nM). Data presented in Table III indicate that as the chain length increases between the basic nitrogen and phenoxy group, so too does D_2 affinity (i.e. **33** > **31** > **28**). Though incorporation of an ethylene bridge (e.g. **53**) into the γ-carboline skeleton of gevetroline (**7**) increased affinity at both σ binding sites, potency at the D_2 receptor was greatly reduced (K_i = 12.2 μM vs 6.0 nM).

σ Site Selectivity and Enantioselectivity. Several lines of evidence now suggest the existence of pharmacologically distinct σ binding sites.[31-35] One of these sites (termed σ_1) is preferentially labeled by [^{3}H]-(+)-3-PPP and [^{3}H]-(+)-pentazocine, exhibits high affinity for (+)-benzomorphans and dextromethorphan, and is allosterically modulated by phenytoin and guanine nucleotides.[36] The other binding site (termed σ_2) can be selectively labeled by [^{3}H]DTG once the σ_1 site is blocked by pentazocine, exhibits low affinity for (+)-benzomorphans and dextromethorphan, and is insensitive to phenytoin and guanine nucleotides.[36] A σ binding site with pharmacological properties similar to those of the σ_2 binding site in brain has been identified on PC12 cells and in rat liver membranes.[31] In general, most σ ligands reported so far possess higher affinity for the [^{3}H]-(+)-3-PPP (σ_1) binding site.[1a,33,34] However, as indicated in Tables I–VII, virtually all the γ-carbolines in this series exhibited higher affinity for the σ binding site labeled with [^{3}H]DTG than [^{3}H]-(+)-3-PPP, suggesting that this series of γ-carbolines has a higher affinity for the σ_2 binding site. Highest selectivity for the [^{3}H]DTG binding site, observed for **29** (19-fold), can be attributed to the detrimental effect of the chlorine atom (**28** vs **29**, Table III) on the [^{3}H]-(+)-3-PPP-labeled site. The reduced sensitivity of the [^{3}H]-(+)-3-PPP binding site to this series of compounds supports the notion that [^{3}H]DTG and [^{3}H]-(+)-3-PPP are labeling pharmacologically distinct σ binding sites.

Recent investigations have shown that enantioselectivity is observed within the benzomorphan class of σ ligands.[1a,33,34] Furthermore, the (+)-isomers of pentazocine, cyclazocine, SKF 10047, and 3-PPP possessed a higher affinity for the [^{3}H]-(+)-3-PPP labeled site than their respective (−)-isomers. However, these σ ligands retained a reduced enantioselectivity for the [^{3}H]DTG labeled site. In order to further discern the binding properties within this class of γ-carbolines, enantioselectivity was investigated by examining one of the most potent and selective σ ligands in Table V (i.e. **40**). As shown in Table VI, (+)-**40** had a higher affinity for the [^{3}H]DTG-labeled binding site, whereas (−)-**40** possessed a higher affinity for the [^{3}H]-(+)-3-PPP-labeled site. Thus, an opposite stereoselectivity was observed at the [^{3}H]DTG- and [^{3}H]-(+)-3-PPP-labeled binding sites, providing further evidence for the existence of pharmacologically distinct σ binding sites. Interestingly, (±)-**40** had equal or slightly higher affinity for both [^{3}H]DTG- and [^{3}H]-(+)-3-PPP-labeled sites than either one of its enantiomers. An allosteric-type of model could explain our results, in which both enantiomers of **40** are capable of increasing each other's affinity for the [^{3}H]-DTG- and [^{3}H]-(+)-3-PPP-labeled σ sites. Allosteric coupling effects have been reported to be associated with the σ binding site.[1a,33,34] Rothman and co-workers recently reported that several σ ligands are capable of accelerating the dissociation of [^{3}H]DTG from its binding sites and termed this conceptualization the "pseudoallosteric model".[37] Additional experiments are necessary to more clearly define this phenomenon.

In summary, a novel series of rigid γ-carbolines has been identified. This series includes some of the most potent ligands for the [^{3}H]DTG-labeled σ binding site reported to date. The results from this radioligand binding study provide further evidence to support the existence of σ binding site subtypes. Comparison of the present series of conformationally rigid compounds with other σ ligands may provide insight into the requirements for the development of more potent and selective σ_2 ligands to probe further the functional role of this binding site.

Experimental Section

Chemistry. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C spectra were recorded with a General Electric QE300 spectrometer or Bruker AC 400-MHz spectrometer using tetramethylsilane as an internal standard. IR spectra were obtained on a Beckman FT 1300 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc. of Atlanta, GA. Specific rotation determinations at the sodium D line were obtained on a Perkin-Elmer 241-MC polarimeter at 24 °C. Single-crystal X-ray analysis of **62** was carried out by the Molecular Structure Corp. of The Woodlands, TX. Thin-layer chromatography (TLC) was performed using fluorescent 0.25-mm silica gel plates (Merck, Kieselgel 60 F-254). Tropinone was purchased from Lancaster Synthesis Inc. Many of the compounds described in this paper, particularly oxalate salts, were obtained as partial hydrates despite drying in vacuo. Hydration was confirmed by Karl Fischer determination in several cases. Shown below is an example of each method described in Table VIII.

Nortropinone Hydrochloride (12).[23] To a slurry of zinc dust (64.7 g, 0.99 g-atom) in glacial acetic acid (50 mL) under argon at 60 °C was slowly added dropwise over 1 h a solution of 2,2,2-trichlorocarboxynortropinone[23] (75 g, 0.25 mol) in glacial acetic acid (100 mL). The temperature was maintained above 60 °C during the course of the addition by the heat of reaction. After the addition was completed, the reaction temperature was maintained at 60 °C until gas evolution had ceased. The reaction mixture was allowed to stir at room temperature and then it was filtered using a small quantity of acetic acid. The filter cake was washed with water, and the filtrates were combined and passed slowly through a column packed with 375 g of Amberlyst 15 (prewashed with water). The column was washed sequentially with water, methanol, and finally 10% aqueous ammonium hydroxide in methanol. The combined eluents were concentrated in vacuo to an oil which was dissolved in methylene chloride, dried over anhydrous sodium sulfate, filtered, and concentrated to an oil. The oil was dissolved in ether (100 mL), and 1 N HCl in ether (500 mL) was added dropwise. After the resulting slurry was stirred vigorously for 15 min, it was filtered and dried under vacuum to afford colorless crystals: yield 31.4 g (78%); mp 192–199 °C dec (lit.[23] mp 190–199 °C dec).

General Methods. Method A. 5,6,7,8,9,10-Hexahydro-7,-10-iminocyclohept[*b*]indole Fumarate (13). Nortropinone hydrochloride (10.0 g, 61.9 mmol) and phenylhydrazine (7.7 g, 71.2 mmol) were heated for 30 min at reflux in anhydrous 2-propanol (175 mL). The reaction mixture was allow to cool to ambient temperature and then saturated with hydrogen chloride and heated to reflux for an additional 10 h. The resulting solution was concentrated under reduced pressure to give a dark residue which was dissolved in methanol. Amberlite IRA-400 resin (prewashed with methanol) was added to pH >10. The mixture was filtered and the resin washed with hot methanol. The filtrate was concentrated in vacuo to give an oil which was diluted with methanol. The resulting solution was heated to reflux and treated with 15 g of Norite activated charcoal. After filtration through a pad of diatomaceous earth, the pad was washed with hot methanol, followed by hot 2-propanol. Concentration of the filtrate in vacuo afforded an oil. The crude product was diluted with methylene chloride (50 mL) and stored in a freezer overnight. The precipitate was filtered, washed with methylene chloride

Table VIII. Physical and Chemical Data

compd	formula[a]	mp, °C	recryst solvent	method[b]	% yield
13	$C_{13}H_{14}N_2 \cdot 0.5C_4H_4O_4$	208–209[i]	EtOH	A	69
14	$C_{13}H_{13}FN_2 \cdot C_4H_4O_4$[c]	145[i]	THF	A	75
15	$C_{19}H_{16}N_2 \cdot HCl$[c]	262–264[i]	H_2O	A	66
16	$C_{14}H_{16}N_2 \cdot 0.1H_2O$	158–161	Et_2O	A	32
17	$C_{15}H_{18}N_2 \cdot C_2H_2O_4$[c]	88–92[i]	EtOH/Et_2O	B	82
18	$C_{16}H_{20}N_2 \cdot C_2H_2O_4$	187–188[i]	acetone	B	83
19	$C_{17}H_{20}N_2 \cdot C_2H_2O_4$	179.5–182	EtOH	B	68
20	$C_{16}H_{19}FN_2O \cdot C_2H_2O_4$	158–159.5	acetone	B	75
21	$C_{20}H_{19}FN_2$	170–172	EtOAc/hex	B	69
22	$C_{20}H_{20}N_2$	198–199.5	EtOAc	B	72
23	$C_{21}H_{22}N_2 \cdot C_2H_2O_4$	176–181[i]	THF	B	82
24	$C_{22}H_{24}N_2 \cdot C_2H_2O_4$[d]	149–152	THF	B	64
25	$C_{23}H_{26}N_2 \cdot HCl$[c]	*h*	Et_2O	B	88
26	$C_{24}H_{28}N_2 \cdot C_2H_2O_4$	106–109	THF	B	75
27	$C_{23}H_{25}FN_2 \cdot C_2H_2O_4$	161–161.5	THF/EtOAc	B	58
28	$C_{21}H_{22}N_2O \cdot C_2H_2O_4$	169–170.5	THF	B	50
29	$C_{21}H_{21}ClN_2O \cdot C_4H_4O_4$	198–199[i]	THF	B	49
30	$C_{21}H_{20}Cl_2N_2O \cdot C_4H_4O_4$	182–183	acetone	G	60
31	$C_{22}H_{24}N_2O \cdot C_2H_2O_4$	164–167[i]	THF	B	56
32	$C_{22}H_{23}FN_2O \cdot C_2H_2O_4$	174–175.5[i]	EtOH	B	84
33	$C_{23}H_{26}N_2O \cdot C_4H_4O_4$	135–138	THF	B	93
34	$C_{24}H_{28}N_2 \cdot C_2H_2O_4$	170–171	IPA	A	50
35	$C_{26}H_{32}N_2 \cdot C_2H_2O_4$	178–180	acetone	C	58
36	$C_{29}H_{30}N_2 \cdot C_2H_2O_4$	131–132	THF/Et_2O	B	93
37	$C_{30}H_{32}N_2 \cdot 1.5C_2H_2O_4$	181–183	IPA	C	34
38	$C_{23}H_{25}FN_2 \cdot C_2H_2O_4$	120–121	acetone	B	56
39	$C_{21}H_{24}N_2S \cdot C_2H_2O_4$[c]	118–120	THF	B	74
40	$C_{21}H_{24}N_2O \cdot C_2H_2O_4$[c]	86–88[i]	THF/Et_2O	B	66
(+)-40	$C_{21}H_{24}N_2O \cdot C_2H_2O_4$[f]	108–112	THF	B	58
(−)-40	$C_{21}H_{24}N_2O \cdot C_2H_2O_4$	108–112	THF	B	54
41	$C_{20}H_{23}N_3S \cdot 2C_2H_2O_4$[e]	54–58[i]	EtOH/Et_2O	B	58
42	$C_{26}H_{33}N_3O_2$[c]	149–152	EtOAc	B	51
43	$C_{23}H_{21}N_3O_2 \cdot C_2H_2O_4$[c]	163–165[i]	THF	E	82
44	$C_{23}H_{25}N_3 \cdot 1.5C_2H_2O_4$[c]	154–158[i]	EtOH	F	35
45	$C_{24}H_{22}FN_3O_2 \cdot C_2H_2O_4$	155–160	IPA	E	82
46	$C_{24}H_{26}N_3F \cdot 1.5C_2H_2O_4$[d]	162–165	EtOH	F	88
47	$C_{24}H_{25}Cl_2N_3O \cdot C_2H_2O_4$	132–137	EtOAc/THF	D	97
48	$C_{24}H_{27}Cl_2N_3 \cdot 2C_2H_2O_4$	137–139[i]	THF	B	72
49	$C_{23}H_{23}FN_2O$	166–168	Et_2O	B	58
50	$C_{22}H_{22}N_2$[f]	211–212	acetone	B	80
51	$C_{28}H_{28}N_2 \cdot HCl$	202–203	EtOAc	B	86
52	$C_{20}H_{19}FN_2 \cdot C_2H_2O_4$[g]	132–138	IPA	B	52
53	$C_{21}H_{22}FN_3 \cdot C_4H_4O_4$	154–156	acetone	B	67
54	$C_{28}H_{28}N_2 \cdot C_2H_2O_4$[f]	170–172	THF	C	37
55	$C_{21}H_{20}Cl_2N_2 \cdot C_2H_2O_4$	183.5–184.5[i]	acetone	B	67

[a] $C_4H_4O_4$ represents fumaric acid, $C_2H_2O_4$ represents oxalic acid. All new compounds analyzed correctly (±0.4%) for C, H, N. [b] Method of preparation; see Experimental Section. [c] Hemihydrate. [d] Hydrate. [e] Sesquihydrate. [f] 0.25-Hydrate. [g] 0.5*i*-PrOH. [h] Amorphous solid. [i] Decomposes.

(25 mL), and dried to afford a yellow solid; yield 8.4 g (69%). An analytical sample was prepared as the fumarate salt in THF and recrystallized from ethanol to afford a white crystalline solid: mp 208–209 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.63 (1 H, m), 1.90 (1 H, m), 2.15–2.19 (2 H, m), 2.68 (1 H, d, *J* = 16.4 Hz), 3.31 (1 H, dd, *J* = 16.6, 4 Hz), 4.20 (1 H, bs), 4.84 (1 H, d, *J* = 4 Hz), 6.35 (1 H, s, fumarate), 6.93–7.04 (2 H, m), 7.28 (1 H, d, *J* = 8 Hz), 7.46 (1 H, d, *J* = 8 Hz), 11.10 (1 H, s). Anal. ($C_{13}H_{14}N_2 \cdot 0.5C_4H_4O_4$) C, H, N.

2-Fluoro-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indole fumarate (14) was similarly prepared using *p*-fluorophenylhydrazine to afford the free base as a yellow crystalline solid: yield 75%; mp 188–189 °C (free base, CH_2Cl_2). An analytical sample was prepared as the white solid fumarate salt: mp 145 °C dec (fumarate, amorphous solid); ^{1}H NMR (DMSO-d_6, fumarate) δ 1.71–1.78 (1 H, m), 1.95–1.98 (1 H, m), 2.19–2.22 (2 H, m), 2.79 (1 H, d, *J* = 17 Hz), 3.36 (1 H, dd, *J* = 17, 4.4 Hz), 4.33 (1 H, bs), 5.00 (1 H, d, *J* = 4.2 Hz), 6.43 (2 H, s, CH = CH), 6.84–6.91 (1 H, m), 7.28–7.36 (2 H, m), 11.30 (1 H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 29.38, 33.63, 36.66, 51.00, 52.29, 101.57 (d, *J* = 23.2 Hz), 107.21 (d, *J* = 25.7 Hz), 111.35 (d, *J* = 9.9 Hz), 116.72 (d, *J* = 4.6 Hz), 124.68 (d, *J* = 10.0 Hz), 132.03, 133.52, 156.70 (d, *J* = 230.3 Hz). Anal. ($C_{13}H_{13}FN_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

Method B. General Procedure for N-Alkylation of γ-Carbolines 13–15. 11-(4-Phenoxybutyl)-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indole (33). 1-Bromo-4-phenoxybutane (694 mg, 3.03 mmol), **13** (400 mg, 2.02 mmol), potassium carbonate (418 mg, 3.03 mmol), and DMF (5 mL) are stirred together at 60 °C for 4 h. The mixture was cooled and diluted with 200 mL of ethyl acetate and 30 mL of water. The organic layer was separated, washed with 20 mL of saturated aqueous brine solution, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography (methylene chloride/methanol, 95:5) afforded a tan oil; yield 610 mg (91%). An oxalate was prepared in THF (Table VIII). (Note: A catalytic amount of potassium iodide was added when using alkyl chlorides or tosylates as alkylating agents.)

Method C. General Procedure for Alkylation of Indole Nitrogen. 11-(4-Phenylbutyl)-5,6,7,8,9,10-hexahydro-5-isopropyl-7,10-iminocyclohept[*b*]indole (35). A mixture of 11-(4-phenylbutyl)-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]-indole (**25**) (670 mg, 2.03 mmol), sodium hydride (200 mg), and 20 mL of dimethylformamide was stirred for 30 min at room temperature. After isopropyl bromide (3 equiv) was added, the mixture was stirred for 4 h. The reaction was diluted with ethyl acetate (200 mL) and water (50 mL). The organic layer was washed with water (2 × 30 mL), dried over anhydrous sodium sulfate, concentrated, and chromatographed (flash silica, CH_2Cl_2/CH_3OH, 95:5) to afford a tan oil; yield 440 mg (58%). An oxalate was prepared in acetone; mp 178–180 °C (Table VIII).

Table IX. Cell Parameters and Experimental Details X-ray Analysis of 62

Crystal Data	
empirical formula	$C_{22}H_{22}N_2O_2$
formula weight	346.43
crystal color, habit	colorless, needle
crystal dimensions (mm)	0.450 × 0.100 × 0.050
no. of reflections used for unit cell determination (2θ range)	15 (30.7–48.5°)
θ scan peak width at half-height	0.54
lattice parameters	
a	10.29 (1) Å
b	21.86 (3) Å
c	8.39 (2) Å
V	1888 (4) Å^3
space group	$P2_12_12_1$
R	0.0630
Z value	4
D_{calc}	1.219 g/cm^3
*F*000	736
μ (CuKα)	5.90 cm^{-1}
Intensity Measurements	
diffractometer	Rigaku AFC5R
radiation	Cu Kα (λ = 1.54178 Å)
temperature	23 °C
attenuators	Zr foil (factors: 3.7, 13.1, 46.6)
take-off angle	6.0°
detector aperture	6.0 mm horizontal 6.0 mm vertical
crystal to detector distance	40 cm
scan type	$\omega - 2\theta$
scan rate	8.0°/min
scan width	1.37° + 0.30 tan θ
$2\theta_{max}$	119.9°
no. of reflections	1646

1-Aza-4-oxo-1-(4-phenylbutyl)bicyclo[3.2.1]octane (56) was prepared by alkylation of **12** with 1-bromo-4-phenylbutane as described in method B and isolated as its hydrochloride salt in 56% yield; mp 178–180 °C (2-propanol). Anal. ($C_{17}H_{23}NO\cdot HCl$) C, H, N.

11-(4-Phenylbutyl)-5,6,7,8,9,10-hexahydro-5-methyl-7,10-iminocyclo[*b*]indole (34) was prepared by treatment of amine **56** to the conditions described in method A using *N*-methyl-*N*-phenylhydrazine (Table VIII).

Method D. 11-[2-[[(3,4-Dichlorophenyl)methyl]-*N*-methylcarboxamido]ethyl]-5,6,7,8,9,10-hexahydro-7,10-iminocyclo[*b*]indole (47). To a suspension of **13** in anhydrous methylene chloride (20 mL) at 0 °C were added *N*-(*tert*-butoxycarbonyl)-glycine (1.0 g, 5.7 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.09 g, 5.7 mmol), and 4-(dimethylamino)pyridine (40 mg). After the reaction was allowed to slowly warm to ambient temperature while stirring overnight, it was poured into water (30 mL) and extracted with ethyl acetate (100 mL). The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated. The resulting oil was chromatographed (flash silica, ethyl acetate/hexanes, 50:50) to afford **57** as a white solid: yield 1.38 g (77%); mp 213.5–214.5 °C (ethyl acetate). Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

To a suspension of **57** (1.17 g, 3.2 mmol) in anhydrous THF (25 mL) at 0 °C was slowly added 15 mL of a 1 M solution of lithium aluminum hydride in THF over 10 min. The reaction was allowed to warm to room temperature and then heated to reflux for 2 h. The reaction was cooled to 0 °C, and then added sequentually were 1 mL of water, 1 mL of 10% aqueous NaOH, and 1 mL of water. The salts were filtered and washed with warm THF (100 mL), and the solvent was evaporated. Water was azeotroped using benzene to afford **58** as a yellow oil: yield 796 mg (98%); ^{1}H NMR ($CDCl_3$) δ 1.50–1.95 (3 H, m), 2.10–2.41 (3 H, m), 2.45 (3 H, s), 2.55–2.75 (4 H, m), 3.3 (1 H, m), 3.65 (1 H, bs), 4.30 (1 H, bs), 7.10–7.50 (4 H, m), 8.42 (1 H, bs).

Diamine **58** was dissolved in anhydrous methylene chloride (5 mL) containing triethylamine (2 equiv) and the solution was added to a solution of 3,4-dichlorophenylacetyl chloride (1.2 equiv, prepared from the corresponding acid and oxalyl chloride in methylene chloride). After being stirred for 1 h, the reaction was poured into 10% aqueous NaOH (25 mL) and methylene chloride (100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. Chromatography (flash silica, CH_3OH/CH_2Cl_2, 5:95) afforded a white foam; yield 810 mg (97%). An oxalate was prepared in THF (Table VIII).

Method E. 2-Fluoro-11-(3-phthalimidopropyl)-5,6,7,8,9,-10-hexahydro-7,10-iminocyclohept[*b*]indole Oxalate (45). To a solution of alcohol **20** (630 mg, 2.30 mmol, prepared according to method B) was added phthalimide (340 mg, 2.31 mmol), triphenylphosphine (665 mg, 2.54 mmol), and anhydrous THF (20 mL), followed by the slow addition of diethyl azodicarboxylate (442 mg, 2.54 mmol). The reaction was stirred for 12 h, poured into methylene chloride (100 mL), and extracted with water (25 mL). The organic layer was separated and dried over anhydrous sodium sulfate and filtered and the solvent removed in vacuo. The crude product was chromatographed (flash silica, CH_2Cl_2/MeOH, 9:1) to afford a foam; yield 760 mg (82%). An oxalate was prepared in 2-propanol (Table VIII).

11-(2-Phthalimidoethyl)-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indole (43) was prepared using alcohol **59** (method B, 37%) according to method E in 68% yield and converted into an oxalate (Table VII).

Method F. 2-Fluoro-11-(3-isoindolinylpropyl)-5,6,7,8,9,-10-hexahydro-7,10-iminocyclohept[*b*]indole Oxalate (46). To a solution of **45** (390 mg, 0.97 mmol) in anhydrous THF (5 mL) was slowly added a 1 M solution of lithium aluminum hydride in THF (4.5 mL). The reaction was heated to reflux for 3 h then allowed to cool to room temperature and treated sequentually with water (0.2 mL), 1 N NaOH (0.2 mL), and water (0.2 mL). After the reaction was stirred for 10 min, the resulting precipitate was filtered and washed with THF (20 mL). The solvent was evaporated in vacuo and the resulting oil chromatographed (flash silica, MeOH/CH_2Cl_2, 5:95) to afford a white foam: yield 320 mg (88%). An oxalate was prepared in ethanol using 2 equiv of oxalic acid (Table VIII).

Method G. 11-[2-(3,4-Dichlorophenoxy)ethyl]-5,6,7,8,9,-10-hexahydro-7,10-iminocyclo[*b*]indole (30). To a suspension of 3,4-dichlorophenoxyacetic acid (1.34 g, 6.05 mmol) in methylene chloride (10 mL) at 0 °C was slowly added oxalyl chloride (922 mg, 7.26 mmol). The reaction was allowed to warm to room temperature and stirred for another 2 h. Volatiles were removed under vacuum to afford the acid chloride as a yellow oil. To a suspension of **13** (1.0 g, 5.04 mmol) in methylene chloride (10 mL) at 0 °C was added triethylamine (765 mg, 7.56 mmol) followed by the previously prepared acid chloride in methylene chloride (10 mL). After the reaction was stirred for 1 h, it was poured into aqueous sodium bicarbonate (25 mL) and methylene chloride (75 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and filtered, and the solvent removed under reduced pressure. Purification by flash chromatography (ethyl acetate/hexane, 50:50) afforded 11-[2-(3,4-dichlorophenoxy)-1-oxoethyl]-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[*b*]indole (**60**) as a white solid: yield 1.37 g (68%); mp 198.5–199.5 °C (ethyl acetate). Anal. ($C_{21}H_{18}Cl_2N_2O_2$) C, H, N.

To a solution a **60** (500 mg, 1.25 mmol) in THF (6 mL) was added 8 mL of a 0.66 M solution of AlH_3 in THF.[25] After 15 min, the reaction mixture was poured into 10% aqueous sodium hydroxide (25 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to afford a brown oil: yield 426 mg (88%). A fumarate was prepared in acetone as a white crystalline solid (Table VIII).

Resolution of (+)-5,6,7,8,9,10-Hexahydro-7,10-iminocyclohept[*b*]indole (13). To a solution of L-tartaric acid (41.1 mmol) in water (45 mL) was added (±)-**13** (8.15 g, 41.1 mmol). The mixture was heated until a homogeneous solution was formed. The solution was allowed to stand at room temperature for 18 h. The resulting crystalline tartrate (4.8 g) was filtered and washed with 20 mL of water. This material was recrystallized three times from water (4 mL/g) to a constant rotation: $[\alpha]^{24}_D$ −7.10° (c = 1.1, H_2O). The free base was regenerated from an aqueous solution of the salt with excess ammonium hydroxide and extracted with 2% methanol in methylene chloride. The solvent was evaporated to afford 890 mg of crystalline (−)-**13**: mp 215–216 °C; $[\alpha]^{24}_D$ −40.0° (c = 1, MeOH). The optical purity of (−)-**13** was estimated by first preparing the *O*-methylmande-

loylamides using (R)-(+)-methoxyphenylacetic acid according to the procedure described in method H and observing the ratios of the diastereomeric amides by HPLC, which revealed an enantiomeric excess of >98% ee.

The combined mother liquors of the above tartrate were stirred in the presence of ammonium hydroxide (100 mL) and extracted with 2% methanol in methylene chloride (500 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and filtered to afford 7.1 g of free base. The free base (35.8 mmol) was dissolved in a solution of warm D-tartaric acid (5.37 g, 35.8 mmol) in water (20 mL). The solution was allowed to stand at room temperature for 24 h and the precipitate filtered to afford 8 g of tartrate. This material was recrystallized three times to a constant rotation: $[\alpha]^{24}_D$ +7.14° (c = 1.0, H_2O). The free base was regenerated with aqueous ammonium hydroxide and extracted with 2% methanol in methylene chloride (400 mL). The solvent was evaporated to afford 600 mg of crystalline (+)-13: mp 215–216 °C; $[\alpha]^{24}_D$ +40.4° (c = 1, MeOH). The enantiomeric excess was estimated to be >99% using procedure described in method H.

Method H. Preparation and Isolation of (7*R*,10*S*,α*R*)- and (7*S*,10*R*,α*R*)-11-(α-Methoxy-α-phenylacetyl)-5,6,7,8,9,-10-hexahydro-7,10-iminocyclohept[*b*]indoles (61 and 62). To a stirred solution of (±)-13 (2.50 g, 12.6 mmol) and of (R)-(−)-(α)-methoxyphenylacetic acid (2.31 g, 13.9 mmol; Aldrich; 99.5 ± 0.5% optically pure) in 100 mL of methylene chloride was added of 1-hydroxybenzotriazole hydrate (1.72 g, 12.7 mmol) followed by of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (2.44 g, 12.7 mmol). The mixture was allowed to warm to room temperature, stirred overnight, diluted with methylene chloride, washed with water, and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the resulting material was chromatographed on silica gel eluting with methylene chloride followed by 2% methanol in methylene chloride to afford the desired amide (3.56 g, 82%) as a mixture of diastereomers. The diastereomeric amides were dissolved in acetonitrile and separated using preparatory HPLC (reverse phase, C_{18}, 40% acetonitrile/60% water). Fractions containing pure diastereomeric amides were combined and isolated separately, by evaporating off most of the acetonitrile followed by extraction with methylene chloride. In each case, the organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to afford 1.06 g of the pure early eluting amide, **61** [t_R = 16.9 min; $[\alpha]^{24}_D$ +40.4° (c = 1.1, CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.53–1.66 (1 H, m), 1.75–2.15 (3 H, m), 2.52, 2.56 (1 H, app s, rotamers), 2.94, 3.12 (1 H, dd, J = 16.2, 4.5 Hz), 3.13, 3.28 (3 H, s, rotamers), 4.89 (1 H, m), 5.11, 5.16 (1 H, s, rotamers), 5.55, 5.80 (1 H, d, J = 5.2 Hz, rotamers), 6.92–7.48 (9 H, complex m), 10.67, 10.81 (1 H, s, rotamers); IR ($CHCl_3$) 3471, 3006, 1632, 1453 cm^{-1}] and 1.3 g of the pure late eluting amide, **62** [t_R = 19.4 min; $[\alpha]^{24}_D$ −96.0° (c = 1.1, CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.54–1.63 (1 H, m), 1.76–1.92 (2 H, m), 2.07–2.10 (1 H, m), 2.41–2.59 (1.5 H, complex m), 3.04, 3.29 (3 H, s, rotamers), 3.27 (0.5 H, dd, J = 16.2, 4.2 Hz, rotamers), 4.79, 4.83 (1 H, m, rotamers), 5.06, 5.14 (1 H, s, rotamers), 5.63 (1 H, m), 6.91–6.99 (2 H, m), 7.17–7.52 (7 H, m), 10.71, 10.82 (1 H, s, rotamers); IR ($CHCl_3$) 3469, 3006, 1653, 1463, 1329 cm^{-1}. Each of the purified amides showed a diastereomeric excess >99%. An analytical sample of the late eluting amide **62** for X-ray analysis was prepared by recrystallization from acetonitrile: mp 204–205 °C (CH_3CN). Anal. ($C_{22}H_{22}N_2O_2$) C, H, N.

X-Ray Crystallographic Analysis. The absolute configuration of (+)-13 was indirectly determined by an X-ray analysis of its *N*-11-(*O*-methylmandelic acid) derivative, **62**. A colorless needle-shaped crystal of $C_{22}N_{22}N_2O_2$ having approximate dimensions of 0.450 × 0.100 × 0.050 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated Cu Kα radiation and a 12KW rotating-anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 15 carefully centered reflections in the range 30.70° < 2θ < 48.50° corresponded to an orthorhombic cell with dimensions: a = 10.29 (1) Å; b = 21.86 (3) Å; c = 8.39 (2) Å; V = 1888 (4) Å^3. The space group was determined to be $P2_12_12_1$. A total of 1646 reflections were collected. The structure was solved by direct methods.[30] The non-hydrogen atoms were refined either anisotropically or isotropically. The hydrogen atoms were either refined isotropically or included in the structure factor calculation in idealized positions (d_{C-H} = 0.95 A°). The standard deviation of an observation of unit weight was 2.74. The cell parameters and characteristics are given in Table IX.

Radioligand Binding (σ Assay). The σ ligand binding studies were determined by competition studies using [^{3}H]DTG or [^{3}H]-(+)-3-PPP as previously described in detail.[33] Both assays were performed with frozen guinea pig brains, which were thawed and homogenized in 10 volumes (w/v) of ice cold 0.32 M sucrose using a motor-driven glass-fitted Teflon pestle adjusted to 600 rpm. The homogenate was centrifuged at 900*g* for 10 min (4 °C) and the resultant supernatant collected and centrifuged at 22000*g* for 20 min. The pellet obtained from the centrifugation was resuspended in 10 volumes of 50 mM Tris-HCl (pH 7.4, 25 °C) and incubated for 30 min at 37 °C. Following the preincubation, the homogenate was centrifuged at 22000*g* for 20 min and the final pellet was resuspended in the buffer solution to a protein concentration of 0.5–1.0 mg/mL for use in the assay.

The binding reactions were initiated by the addition of tissue (800 μM) to tubes containing the assay buffer, the radioligand (final concentration 1–3 nM), and the compound of interest. Final assay volume was 1 mL. Reactions were allowed to proceed for 45 min at 25 °C and terminated by rapid filtration. Filter-bound radioactivity was quantified using conventional liquid scintillation spectrometry at 55% efficiency. Specific binding was typically in the range of 70–90%. For determination of equilibrium dissociation constants (K_d), a fixed concentration of radioligand was incubated in the presence of unlabeled ligand ranging in concentration between 0.5 and 10 000 nM. The concentration of test compound causing 50% inhibition of radioligand binding (IC_{50}) was determined from concentration–response curves in which at least 14 concentrations of test compounds were examined. All assays were performed using duplicate determinations unless otherwise stated. For comparison purposes, IC_{50} values are reported rather than K_i values.

Dopamine D_2 Assay. The affinity of compounds of interest for the D_2 receptor was determined according to a previously reported method.[38] Briefly, on the day of the assay, rats were sacrificed by decapitation, the corpus striatum was dissected and homogenized in 20 volumes of 50 mM Tris-HCl (pH 7.5, 25 °C). The homogenate was centrifuged (4 °C) and the resulting pellet was resuspended in 20 volumes of fresh buffer containing 100 mM NaCl to a tissue concentration of 3.75 mg wet weight/mL. A portion of the suspension (800 μL) was added in triplicate to the tubes containing 3 nM [^{3}H]sulpiride and the test compound. The final assay volume was 1 mL; haloperidol (10 μM) was used to determine nonspecific binding. Following a 60-min incubation at 25 °C, the reactions were terminated by rapid filtration over Whatman GF/B filters which had been pretreated in a solution of 0.3% (w/v) of aqueous polyethyleneimine. Filters were washed three times using 5 mL of cold buffer and processed using standard procedures to determine radioactivity. IC_{50} values were obtained from concentration–response curves in which a number of concentrations of the test compound were examined. K_i values were determined using the Cheng–Prusoff equation.[39]

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