3-Substituted, 3-(4-Pyridinylmethyl)-1,3-dihydro-1-phenyl-2*H*-indol-2-ones as Acetylcholine Release Enhancers: Synthesis and SAR

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A series of 3-substituted, 3-(4-pyridinylmethyl)-1,3-dihydro-1-phenyl-2*H*-indol-2-ones was synthesized and found to enhance the stimulus-induced release of neurotransmitter acetylcholine (AcCh), and by doing so, might be useful in treating cognitive disorders where the level of this neurotransmitter may be diminished in the brain, as in Alzheimer's disease. An attempt has been made to correlate the structure of the 3-substitution with the ability of the compounds to enhance the release of AcCh from the striatum region of rat brain preparations.

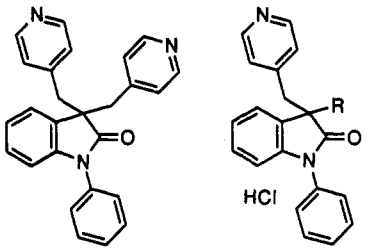
Introduction

Alzheimer's disease (AD) is a disease of the aged, generally being diagnosed after the age of 56, and affecting up to 10% of the population over the age of 65. The disease affects 30% or more of the population over the age of 80. In the developed world, AD is the fourth major cause of death after cardiovascular disease, cancer, and cerebral accidents. With an increase in life expectancy due to medical advances in the treatment of the above diseases, the number of AD patients is anticipated to increase dramatically.

The etiology of AD is not known, however, the biochemical and pathophysiological findings are presently unmistakable. Post mortem findings for AD patients and normal-aged subjects have shown qualitative and quantitative changes in the cholinergic system and brain structures.[1] The available data would suggest that the degree of cholinergic dysfunction can be correlated with the degree of cognitive deterioration; learning and memory deficits can be produced in humans by experimental cholinergic blockade. It is these neurochemical and histopathological findings in the AD population that have stimulated research efforts to develop treatments for AD, and have lead to the cholinergic hypothesis[2-5] of aging and dementia.

A number of drugs are presently in clinical trials for the treatment of AD,[6] and among the best known of these are the acetylcholinesterase inhibitors tacrine, velnacrine, E-2020, and huperzine A and the neurotransmitter release enhancer DuP996 (**I**) Figure 1. The intended action of these drugs is to increase the level of the neurotransmitter acetylcholine (AcCh) in the brain. The use of chemical entities to increase the levels of AcCh in the brain results from the post mortem findings of significantly lower levels of this neurotransmitter in the brains of AD patients when compared to that found in the normal-aged brain. Compound **I** is a 1-phenyl-3,3-bis(4-pyridylmethyl)oxindole that is in phase III clinical trials for the treatment of mild to moderate forms of AD. Synthetic approaches to **I** and similar compounds have been reported by Myers and Nickolson[7,8] and Bryant and Huhn,[9] and the biochemistry and pharmacology have been reported elsewhere.[6,10-24]

The purpose of this study was to develop a better understanding of the structure–activity relationships (SAR) associated with **I** and possibly to identify better AcCh releasers that might be useful in treating cognitive disorders such as AD.



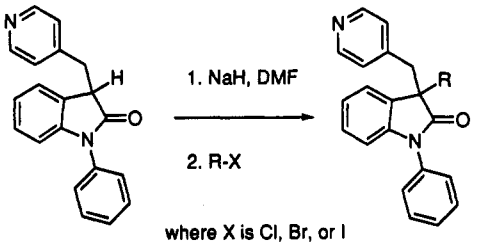
I II

8, R = $(CH_2)_3CO_2Et$

13, R = $(CH_2)_4CN$

Figure 1. Structure of **I** and two of its most active analogues, **II**.

Scheme I



Chemistry

Generally, the compounds (**II**) were synthesized by treating 1,3-dihydro-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one[9] (**1**, R = H) with 1.1 equiv of NaH, followed by reaction with an appropriate alkylating agent (Method A). Typically, **1** was alkylated with ethyl bromoacetate or ethyl 4-bromobutyrate to give the corresponding esters **2** or **8**, respectively. Such an approach was used to synthesize the nitriles **11-15**. This approach was not successful in the attempt to prepare the nitrile where R was CH_2CH_2CN. TLC showed the disappearance of starting materials, and mass spectral analysis of the reaction mixture showed the presence of the desired product. However, workup of the reaction mixture did not produce the desired nitrile. It is believed that the β-nitrile underwent a retro-Michael reaction to give the starting oxindole (**1a**) and acrylonitrile. Contrastly, **1a** was alkylated with methyl acrylate to produce the cor-

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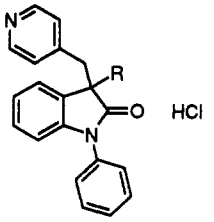
Table I. Physical and Biochemical Data for Compounds 1-28



compd	R	% yield	mp, °C	formula[a]	% AcCh Rel[b] (SD)	ClogP[d]	CMR[d]	D, Å
1a	H	98.5	100–102	$C_{20}H_{16}N_2O$	0.0 (3.6)	2.40	9.12	nd
2	CH_2CO_2Et	66	170–173	$C_{24}H_{22}N_2O_3$·HCl	21.0 (1.5)	3.22	11.16	2.92
3	CH_2CO_2H	74	172 dec	$C_{22}H_{18}N_2O_3$·HCl	−2.0 (0.2)	2.23	10.23	2.95
4	$(CH_2)_2OH$	55	193 dec	$C_{22}H_{20}N_2O_2$·HCl	12.0 (0.1)	1.46	10.20	3.80
5	$(CH_2)_2NMe_2$·HCl	55	foam	$C_{24}H_{25}N_3O$·2HCl	3.0 (0.3)	2.12	11.34	3.87
6	$(CH_2)_2CO_2Me$	76	197–198	$C_{24}H_{22}N_2O_3$·HCl	51.0 (1.0)	2.37	11.16	4.41
7	$(CH_2)_2CO_2Et$	94	181–182	$C_{25}H_{24}N_2O_3$·HCl	57.0 (6.0)	2.90	11.63	4.41
8	$(CH_2)_3CO_2Et$	86	182–183	$C_{26}H_{26}N_2O_3$·HCl	99.0 (7.8)	3.43	12.09	5.26
(+)-8	$(CH_2)_3CO_2Et$	100	foam	$C_{26}H_{26}N_2O_3$·HCl	109.0 (7.6)	3.43	12.09	
(−)-8	$(CH_2)_3CO_2Et$	94	foam	$C_{26}H_{26}N_2O_3$·HCl	3.0 (0.3)	3.43	12.09	
9	$(CH_2)_3CO_2H$	98	265–267	$C_{24}H_{22}N_2O_3$·HCl	0.0 (0.1)	2.52	11.16	5.31
10	$(CH_2)_4CO_2Et$	83	172–174	$C_{27}H_{28}N_2O_3$·HCl	3.0 (0.1)	3.96	12.55	6.80
11	CH_2CN	82	221 dec	$C_{27}H_{17}N_3O$·HCl	11.0 (0.8)	2.11	10.06	3.49
12	$(CH_2)_3CN$	41	185–187	$C_{24}H_{21}N_3O$·HCl	74.0 (6.1)	2.36	10.99	6.03
13	$(CH_2)_4CN$	93	164–165	$C_{25}H_{23}N_3O$·HCl	133.0 (11.0)	2.89	11.45	7.421
14	$(CH_2)_5CN$	42	191–192	$C_{26}H_{25}N_3O$·HCl	74.0 (5.1)	3.42	11.91	8.57
15	$(CH_2)_6CN$	25	190–192	$C_{27}H_{27}N_3O$·HCl	19.0 (1.08)	3.95	12.38	9.90
16	$CH_2CH{=}CHCO_2Et$	56	oil	$C_{26}H_{24}N_2O_3$·HCl	41.0 (6.0)	3.50	12.14	5.14
17	$(CH_2)_2CO(4\text{-F-}C_6H_4)$	65	184 dec	$C_{29}H_{23}N_2O_2F$·HCl	11.0 (2.1)	4.03	13.07	4.32
18	$(CH_2)_3CO(4\text{-F-}C_6H_4)$	46	205 dec	$C_{30}H_{25}N_2O_2F$·HCl	29.0 (4.5)	3.78	13.73	5.23
19	$(CH_2)_3COCH_3$	44	193 dec	$C_{25}H_{24}N_2O_2$·HCl	18.0 (3.2)	2.49	11.47	5.25
20	$(CH_2)_3CONH_2$	72	232 dec	$C_{24}H_{23}N_3O_2$·HCl	26.0 (2.8)	1.52	11.38	5.26
21	$(CH_2)_4OAc$	87	170–172	$C_{26}H_{26}N_2O_3$·HCl	27.0 (2.0)	3.43	12.09	7.67
22	$(CH_2)_4OH$	30	196–197	$C_{24}H_{24}N_2O_2$·HCl	29.0 (3.6)	2.52	11.13	6.30
23b	$(CH_2)_4OC_2H_5$	73	95–97	$C_{26}H_{28}N_2O_2$·HCl	17.0 (3.6)	3.63	12.05	6.30
24	$(CH_2)_4SC_3H_7$	81	149–150	$C_{27}H_{30}N_2OS$·HCl	24.0 (1.0)	5.18	13.17	6.65
25[e]	$(CH_2)_4SO_2C_3H_7$	70	197–199	$C_{27}H_{29}N_2O_3SCl$·HCl	8.0 (1.0)	3.78	13.73	6.89[c]
26	$(CH_2)_3OH$	50	146–147	$C_{23}H_{22}N_2O_2$·H_2O	27.0 (1.2)	1.99	10.66	4.98
27	OH	–	201–202	$C_{20}H_{16}N_2O_2$	8 (0.9)	1.93	9.29	1.41
28	$(CH_2)_5CH_3$	90	127–128	$C_{26}H_{28}N_2O$	6 (0.8)	4.34	12.09	nd
I	CH_2(4-Pyr)				100	2.86	11.88	5.12

[a] All compounds assayed for C, H, and N, and S where appropriate with assay values being within ±0.4% of theoretical values. [b] Normalized ACh release from the striatum region of the rat brain using eq 1. [c] Average of values for the sulfone oxygens. [d] Medchem Software v3.0, Pomona College, Claremont, CA. [e] This compound is different from other members of the series in that it is a 5-chlorooxindole.

responding methyl ester **6**. Depending on the purity, the compounds were recrystallized from an appropriate solvent or further purified by column chromatography. The free base was dissolved in an appropriate solvent and treated with HCl/Et_2O to form the HCl salt.

Other representative compounds of this series were synthesized by converting one R group to another which could be transformed to another R group. In such a case, the ester **8** was saponified to give the acid **9**, which was reduced to the alcohol **22**. This approach was also used to convert the ester **2** to the acid **3**, which was reduced to the alcohol **4**. Alternatively, the ester **8** was directly reduced to the alcohol **22** with BH_3. The reverse ester **21** was prepared by alkylating the sodium anion of **1** with 4-bromobutyl acetate. Nitrile **12** was converted to the corresponding amide **20** using the procedure described by Noller.[25] Compound **1** was reacted with 1-bromo-4-chlorobutane to give the corresponding alkyl chloride, which was reacted with potassium ethoxide to give the ethyl ether **23**, or with sodium thiopropoxide to give the propyl thioether **24**. The oxidation of 1,3-dihydro-1-phenyl-3-[4-(propylthio)butyl]-3-(4-pyridinylmethyl)-2*H*-indol-2-one hydrochloride (**24**) with Oxone did not yield the desired product, but the unexpected 5-chloro-1,3-dihydro-1-phenyl-3-[4-(propylsulfonyl)butyl]-3-(4-pyridinylmethyl)-2*H*-indol-2-one which was isolated as the hydrochloride (**25**). We propose that the Oxone oxidizes the HCl to produce HOCl, which then reacts with the oxindole in the 5-position to effect an electrophilic substitution resulting in **25**.[26]

During the course of some of the alkylations of **1**, a small amount (<10%) of a byproduct was formed, as evidenced by chromatographic methods and mass spectral analysis, and this was subsequently identified as the alcohol **26**. We propose that the alcohol resulted from the reaction of the tertiary carbanion with oxygen in the non-degassed solvent to form the hydroperoxide, which decomposed on workup to give the alcohol.[27] When the anion of **1** was deliberately exposed only to air, **26** was formed quantitatively. Alcohol **26** is the major product from the Aldol condensation of 4-picoline with 1-phenylisatin.

The compounds were isolated as racemic mixtures. However, **8** was resolved through fractional crystallization of the diastereomeric salts of (+)- and (−)-*O,O'*-*p*-toluyltartaric acid to give (+)-**8** and (-)-**8**, respectively (method B). Table I contains the physical and biochemical data for the compounds of this investigation.

Biology

The compounds were assayed for their ability to enhance stimulated release of AcCh from brain slices (slice assay or technique) at least twice, as described by Nickolson et

Table II. Statistical Description of the Enhanced Stimulated AcCh Release[a] Caused by I in Rat Brain Slices

observations	33[b]	standard error	23.3
minimum, %	148.0	variance	17978.3
maximum, %	675.0	standard deviation	134.1
range, %	527.0	coefficient of variation	39.7
median, %	314.0	skewness	0.9031
mean, %	337.4	kurtosis	0.0963

[a] %ACh Rel = (% measured release − % vehicle release). [b] Observation were taken over a 10-month span.

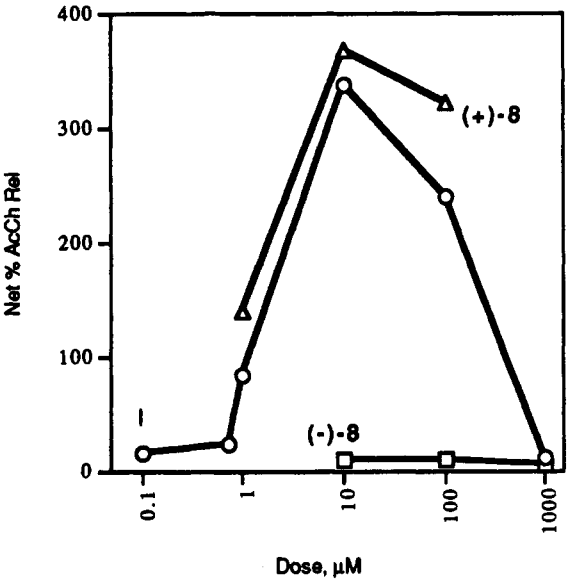


Figure 2. Dose–response curves of I (○), (+)-8 (△), and (−)-8 (□).

al.[13] The results (averages) are reported as the *amount of AcCh release caused by 10 μmol of a compound relative to a standard (I)*. Because of the day-to-day variability in the assay results (see Table II), each release was normalized according to eq 1, and the results are listed in Table I.

$$\text{normalized AcCh release} = \left[\frac{(\text{compd \% release at 10 } \mu\text{M}) - \text{control}}{(\text{I \% release at 10 } \mu\text{M}) - \text{control}}\right] \times 100 \quad (1)$$

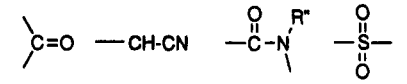
The slice assay for AcCh release has another limitation. Very active compounds have a tendency to produce "inverted U-shaped" dose–response curves as illustrated in Figure 2 for I. This limitation is further magnified in the "one-point" slice assay. However, because of the resources required for a "3-point" dose–response curve, this approach was not applied routinely.

The passive avoidance hypoxia induced amnesia assay (PA) in rats was used to determine cognitive enhancement,[12,14] and, indirectly, the brain bioavailability of 8.

Computer Methods and Statistics

Distances (*D*) for the R group [R = $(CH_2)_mY$] were measured from the oxindole 3-position (Ox) to the hydrogen bonding moiety Y on energy-minimized structures using CSC Chem3D Plus v3.1 by Cambridge Scientific Computing, Inc., Cambridge, MA. Graphs and statistical presentations were obtained using CA-Cricket Graph III v1.0 by Computer Associates International, Inc., Islandia, NY, and StatView II v1.03 by Abacus Concepts, Inc., Berkeley, CA. Computer-generated ClogP and CMR were obtained using Medchem Software v3.0, Pomona College, Claremont, CA, or calculated as described by Hansch and Leo.[28]

Chart I. Carbonyl Group Isosteres[a]



[a] Taken in part from Thornber.[29]

Discussion

Our initial attempts to understand the SAR associated with I centered on the requirements of the substitutions (pendant groups) at the 3-position of the oxindole core. The 4-pyridylmethyl groups were assumed to form hydrogen bond(s) or salt bridges with the binding site, and the question was the necessity of both for good activity. In an attempt to answer this question, a small series of compounds (II) was synthesized where one of the CH_2(4-Pyr) groups had been replaced by nonheterocyclic moieties (R). Compounds **2-5** were synthesized and evaluated for their ability to enhance the release of AcCh as compared to I. The acid **3**, the alcohol **4**, and the amine **5** were all inactive, while only the ester **2** showed any significant activity. Having established **2** as a "lead", a homologous series of esters [$(CH_2)_mCO_2Et$] was synthesized and evaluated. Progressing from $m = 1$ for compound **2** to $m = 2$ for **7**, and $m = 3$ for **8** showed an increase in AcCh release activity while compound **10** ($m = 4$) showed a decrease in activity. Clearly, the racemic ethyl butyrate **8** was as active as I. The activity may be a function of the distance between Ox and the potential hydrogen bonding moiety Y [R = $(CH_2)_mY$].

On the basis of the results seen with the esters, a small series of alcohols (**4**, **22**, **26**, **27**) was synthesized and evaluated. The alcohols differed only in the number of methylenes in R, where R = $(CH_2)_nOH$ and $n = m + 1$. As seen with the ester, increasing from $n = 0$ for **27** to $n = 4$ for **22** resulted in an increase in activity from 8% to 49%, respectively. Though the alcohols were less active than the corresponding esters, the observed trend was the same: increased *n* resulted in increased activity. However, increasing the number of methylenes for the acid **3** from $n = 1$ to $n = 4$ for **9** did not result in improved activity.

Using the teachings of Thornber,[29] and the references therein on isosterism, a limited investigation of the isosteres of the ester carbonyl was undertaken (Chart I). A series of nitriles [R = $(CH_2)_mCH_2CN$] was synthesized and evaluated. Progressing from $m = 0$ for **11** to $m = 3$ for **13** resulted in increased activity, while further increases to $m = 4$ for **14** and $m = 5$ for **15** resulted in decreased activity. The relationship between the number of methylenes in R and activity was similar to that of the esters and alcohol: increasing *m* to some point resulted in increased activity, while further increases resulted in diminished activity. Clearly the racemic nitrile derivative (**13**) is a better releaser of AcCh than the ester **8** or the (4-Pyr)CH_2 of I.

Changes in chain length of some R-substituted oxindoles, whether represented by *m* or *n*, resulted in changes in the ability of the compounds to enhance the release of AcCh. These changes resulted in changes in lipophilicity, as can be represented by ClogP; molecular size or bulk, by molar refractivity (CMR) or molecular weight; and distance geometry, by D or *m*.[30] Unfortunately, the colinearity between this set of parameters did not indicate which one

Table III. Equations and Statistics for the Nitriles 11–15 as a Consequence of Homology[a]

$$\log(1/\text{AcCh Rel}) = 1.117(\text{Mol ClogP})^2 - 6.783(\text{Mol ClogP}) + 8.144 \quad (2)$$

$$\log(1/\text{AcCh Rel}) = 0.490(\text{R ClogP})^2 - 1.750(\text{R ClogP}) - 0.459 \quad (3)$$

$$\log(1/\text{AcCh Rel}) = 0.653(\text{MR})^2 - 14.783(\text{MR}) + 81.620 \quad (4)$$

$$\log(1/\text{AcCh Rel}) = 0.086D^2 - 1.197D + 2.117 \quad (5)$$

$$\log(1/\text{AcCh Rel}) = 0.141m^2 - 1.046m - 0.110 \quad (6)$$

eq	n	r^2	adj r^2	SE	F	probability of $>F$
2	5	0.888	0.776	0.215	7.925	0.112
3	5	0.973	0.946	0.106	36.088	0.027
4	5	0.972	0.943	0.109	34.122	0.028
5	5	0.972	0.943	0.107	35.151	0.028
6	5	0.971	0.942	0.109	33.704	0.029

[a] SE, standard error of estimate; Mol ClogP, computer-calculated molecular log P; R ClogP, calculated log P for the R group; CMR, computer calculated molar refractivity; D, distance from the 3-position of the oxindole to the nitrogen of the cyano group taken from low-energy conformer; m, number of methylenes between the oxindole ring and the cyano group.

Table IV. Correlation Table for the Parameters for the Nitriles

	Mol ClogP	R ClogP	CMR	D	m
Mol ClogP	1.000	0.955	0.960	0.959	0.960
R logP		1.000	0.997	0.997	0.996
CMR			1.000	1.000	1.000
D				1.000	1.000
m					1.000

parameter or combination of parameters contributed most to activity (Tables III and IV and eqs 2–6). In an attempt to gain further understanding of the relationship between lipophilicity and molecular size and activity, **28** [R = $(CH_2)_5CH_3$)] was synthesized and assayed for AcCh releasing activity. Though **28** is more lipophilic (ClogP = 4.34) than **8** (ClogP = 3.43) and **13** (ClogP = 2.89), its molar refractivity (CMR = 12.09) is not significantly different from that of **8** (CMR = 12.09) or **13** (CMR = 11.45). Since **28** was inactive, the data would suggest that CMR is not a major contributor to activity. Unfortunately, the probe did not lead to the same conclusion for ClogP. Of the four categories of compounds investigated, the valeronitrile **13** [R = $(CH_2)_3CH_2CN$] and the ethyl butyrate **8** [R = $(CH_2)_3CO_2Et$] demonstrated remarkable activity. Like the pyridyl group of **I**, the CO_2Et and CN moieties are H-bond acceptors while the CO_2H and OH moieties can be both H-bond acceptors or donors. The alkyl group of **28** is neither, suggesting that hydrogen bonding property of Y was important to activity.

As a result of the findings with the alcohols, ester, nitriles, and **I** and the concept of isosterism (Chart I), a limited number of compounds was synthesized and evaluated based on distance geometry, lipophilicity, and H-bonding properties. The α,β-unsaturated ethyl ester (**16**) corresponding to **8** was synthesized and found to be half as active as **8**. The diminished activity may be associated with the unsaturation (slightly smaller **D**) or the "dilution" caused by the cis–trans isomerism (see NMR of Experimental Section). None of the ketones (**17-19**) showed any appreciable activity, however **18** [$(CH_2)_3CO$] was significantly more active than **17** [$(CH_2)_2CO$]. The amide (**20**) of **8** was prepared and found to be relatively inactive. The amide **20** has the same D (5.26 Å) as the ester (**8**) but half the lipophilicity (Mol ClogP = 1.52 vs 3.43). None of the ethers (OR′ or SR′) was very active, and the sulfone (**25**) was less active than the parent thioether (**24**). None of these compounds added significantly to or clarified the SAR. It should be kept in mind that the slice technique is a whole cell assay possibly requiring cell penetration, thus the ability of the compounds to enter the cell may contribute to their weak activity.

Table V. Rat Passive Avoidance Hypoxia Induced Amnesia (PA) for **8**

doses, sc, mg/kg	n	median retention latencies,[a] S
no hypoxia	60	300.0
vehicle	59	15.0
0.1	12	79.5
0.3	12	37.5
1.0	24	89.5
3.0	36	112.0**
10.0	23	136.0**
30.0	13	201.0*
100.0	10	34.0

[a] Significantly different from vehicle, Mann–Whitney U test: $^*p < 0.05$, $^{**}p < 0.025$.

In an attempt to determine if this type of compound caused a stereospecific or selective release of AcCh, compound **8** was resolved into its enantiomers (+)-**8** and (−)-**8**. Compound (−)-**8** resulted in only 3% of the AcCh release caused by **I** at the same dose while (+)-**8** caused a 109% release. It is not known why the relative increase in AcCh release caused by (+)-**8** was not significantly greater than that observed for the racemate **8**. The available data on **8** and similar compounds (unreported) would suggest that the wrong isomer (−)-**8** does not act as an antagonist to AcCh release.

A number of animal models have been used in an attempt to develop chemical entities for the treatment of AD and other cognitive disorders of man.[31-33] The operating principle in this laboratory is that there is presently no animal model for human AD. As a result of this thinking, the strategy was to propose a biochemical hypothesis, demonstrate the hypothesis *in vitro*, and ensure that the chemical entity is accessible to the brain, and relatively nontoxic. To this end, a passive avoidance hypoxia induced amnesia model (PA) was used.[12,14] The model is CNS based, and as such, activity in the model is a measure of bioavailability in the brain. Compound **8** was dosed sc and found to be active in PA as shown in Table V. No overt signs of toxicity were observed.

Conclusion

On the basis of the results of this study, the following limited SAR was observed for AcCh release for the R substitution of 3-R-3-(4-pyridylmethyl)-1-phenyloxindoles: $(CH_2)_4CN > (CH_2)_3CO_2Et > CH_2(4\text{-Pyr}) > (CH_2)_3CH_2OH > (CH_2)_3CO_2H$. The data would further suggest that the R group is an H-bond acceptor, where the position and nature of the H-bond acceptor Y [R = $(CH_2)_mY$] is important for activity. The importance of distance geometry, lipophilicity, and the quantitative nature of H-bonding for activity have not been fully elucidated. Compounds like **8** and **13** enhance the stimulated release of AcCh in whole cell brain preparations, and as demonstrated in PA, **8** was active and bioavailable in a dose-dependent manner with no overt signs of toxicity. Consequently, compounds **8** and **13** are as good as, or superior to **I** as AcCh release enhancers and may be useful in treating AD and other CNS-related diseases caused by diminished levels of AcCh in the brain.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded with an IBM/Bruker WPS 200 spectrometer, IR spectra were recorded with a Perkin-Elmer 1600 FTIR spectrophotometer, and mass spectra were performed with a Hewlett-Packard HP5988A GC–MS system. Thin layer chromatography (TLC) was performed on silica gel plates. Chiral HPLC analysis was conducted on a Varian 2510 using a Diacel OD column, flow rate of 1.0 mL/min, EtOH–hexane (50:50), UV detector at 210 nm.

Chemical Synthesis. 1,3-Dihydro-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one Hydrochloride (1b). A solution of 1,3-dihydro-3-(4-pyridinylmethylene)-1-phenyl-2*H*-indole-2-one[7,8] (29.84 g, 100 mmol) in 100 mL of THF was treated with $NaBH_4$ (3.78 g, 100 mmol), stirred at room temperature for 24 h, and refluxed for 2 h. The mixture was cooled to room temperature and treated with 75 mL of acetic acid. The mixture was concentrated *in vacuo*, and the residue was made alkaline with 1 N NaOH and extracted with 200 mL of CH_2Cl_2. The extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to a thick oil which crystallized on standing at room temperature overnight. The desired product, as the free base (**1a**), was obtained in 98.5% (29.6 g) yield after recrystallization from *n*-BuCl: mp 98–100 °C; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ [3.24, 3.29 (2d, 1H), 3.42, 3.46 (2d, 1H), CH_2-Pyr], 3.96 (dd, 1H, CH), [6.65 (d, 1H), 7.06 (m, 4H), 7.18 (m, 3H), 7.4 (m, 1H), 7.48 (m, 2H), 8.44 (m, 2H), Ar]; IR (Nujol) 1719 (C=O) cm^{-1}; UV–vis (c = 0.013, MeOH) λ_{max} 247 (14 025) nm; MS (NH_3–CI) m/e 301(M + 1). Anal. Calcd for $C_{20}H_{16}N_2O$ MW 300.36: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.85; H, 5.21; N, 9.26.

The HCl salt **1b** was obtained by treating **1a** with 1 N HCl/Et_2O in quantitative yield: mp 137–140 °C; IR (Nujol): 1703 (C=O) cm^{-1}; NMR (DMSO-d_6 TMS) δ 3.61 (m, 2H, CH_2-Pyr), 4.39 (t, 1H, CH–C-Pyr), [6.66 (d, 1H), 7.07 (dd, 1H), 7.22 (dd, 1H), 7.34 (m, 3H), 7.45 (m, 1H), 7.56 (m, 2H), Ph + 1, 2-Ph], [7.91 (d, 2H), 8.82 (d, 2H), 4-Pyr]; MS m/e 301 (M + 1).

(±)-2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-butanoic Acid Ethyl Ester Hydrochloride (8). Method A. A solution of **1b** (33.7 g, 0.1 mol) in 200 mL of CH_2Cl_2 was treated with 150 mL of 1 N NaOH. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to an oil which solidified on cooling. The free base was dissolved in 150 mL of dry THF, cooled in an ice bath, treated with NaH (2.88 g, 0.12 mol), and stirred under dry nitrogen for 30 min. The mixture was treated with ethyl 4-bromobutyrate (19.5 g, 0.1 mol) in 25 mL of dry THF. The mixture was stirred in ice for 1 h and for 16 h at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between 300 mL of Et_2O and 200 mL of water. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, treated with 150 mL of 1 N HCl/Et_2O, and concentrated *in vacuo*. The residue was dissolved in 100 mL of anhydrous EtOH with warming and stirred at room temperature for 24 h. The resulting crystals were collected by filtration, washed with a small portion of cold EtOH and Et_2O, and dried *in vacuo* at 80 °C to give the desired product in 86% (38.6 g) yield: mp 182.5–183.0 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.15 (t, 3H, CH_3), 1.2, 1.3 (2m, 2H, 1′–CH_2), 2.1 (m, 2H, 2′-CH_2), 2.26 (t, 2H, CH_2CO), [3.43 (d, J = 12.0 Hz, 1H), 3.64 (d, J = 12.0 Hz, 1H), CH_2-Pyr], 4.02 (q, 2H, OCH_2), [6.54 (m, 1H), 7.2 (m, 2H), 7.5 (m, 5H), 7.68 (m, 1H), Ph], 7.10, 8.70 (2d, 4H), Pyr; IR (Nujol) 1722 (C=O), 1703 (C=O) cm^{-1}; UV–Vis (c = 0.0258, MeOH) λ_{max} 245 (14028) nm; MS (NH_3–CI) m/e 415(M + 1). Anal. Calcd for $C_{28}H_{26}N_2O_3$·HCl, MW 450.97: C, 69.25; H, 6.04; N, 6.21. Found: C, 69.02; H, 5.98; N, 6.52.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-acetic Acid Ethyl Ester Hydrochloride (2). By substituting ethyl 2-bromoacetate in Method A, the desired product was obtained in 66% yield: mp 170–173 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 0.92 (s, 3H, CH_3), [3.23 (d, 1H), 3.39 (d, 2H), 3.58 (d, 1H), CH_2-C–CH_2], [6.49 (d, 1H), 7.09 (m, 4H), 7.43 (m, 3H), 7.54 (m, 2H), 7.65 (d, 1H), 8.70 (d, 2H), Ar]; IR (Nujol) 1717 (C=O) cm^{-1}; UV–Vis (c = 0.0256, MeOH) λ_{max} 247 (12986) nm; MS (NH_3–CI) m/e 387(M + 1). Anal. Calcd for $C_{24}H_{22}N_2O_3$ HCl, MW 422.91: C, 68.16; H, 5.48; N, 6.62. Found: C, 68.12; H, 5.29; N, 6.55.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-acetic Acid Hydrochloride (3). A solution of **2** (20.0 g, 47.3 mmol) in 50 mL of water and 100 mL of dioxane was treated with NaOH (8.0 g, 200 mmol) and stirred at room temperature until no starting material was evidenced by TLC ($CHCl_3$–MeOH, 9:1). The mixture was concentrated *in vacuo* and neutralized with AcOH–H_2O. The mixture was extracted with 2 × 100 mL of CH_2Cl_2, and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to a gum. The gum was flash chromatographed over silica gel using $CHCl_3$–MeOH (9:1), and appropriate fractions were combined, concentrated, redissolved in hot benzene, and treated with 100 mL of 1 N HCl/Et_2O. The resulting crystals were collected by filtration, washed with benzene and Et_2O, and dried to give the desired product in 74% (13.9 g) yield: mp 172 °C dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.1–3.6 (2m, 4H, CH_2CCH_2), [6.44 (d, 1H), 7.06 (d, 2H), 7.07 (m, 2H), 7.39 (m, 3H), 7.5 (m, 2H), 7.62 (d, 1H), 8.67 (d, 2H), Ar]; IR (Nujol) 1715 (C=O) cm^{-1}; UV–Vis (c = 0.0256, MeOH) λ_{max} 248 (13 372) nm; MS (NH_3–CI) m/e 359 (M + 1). Anal. Calcd for $C_{22}H_{18}N_2O_3$ HCl, MW 394.86: C, 66.92; H, 4.85; N, 7.09. Found: C, 67.37; H, 4.71; N, 7.12.

1,3-Dihydro-3-(2-hydroxyethyl)-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one Hydrochloride (4). A suspension of **3** in 25 mL of dry THF was treated with 1 M BH_3–THF (60 mL, 60 mmol), stirred at room temperature for 3 h, and refluxed for 5 h. The excess borane was decomposed with MeOH, and the mixture was concentrated *in vacuo*. The residue was treated with 100 mL of 2 N HCl, heated at 80 °C for 1 h, and made alkaline with 1 N NaOH. The mixture was extracted with 200 mL of CH_2Cl_2, and the organic solution was washed with 5% $NaHCO_3$, and water and brine, dried over $MgSO_4$, filtered; and concentrated to an oil. The oil was flash chromatographed on silica gel using butyl chloride as the mobile phase. Appropriate fractions were combined, concentrated, and treated with 1 N HCl/Et_2O. The resulting solid was collected by filtration, washed with Et_2O, and dried to give the desired product in 55% (4.8 g) yield: mp 193 °C dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ [2.3 (m, 2H), 3.13 (m, 1H), 3.29 (m, 1H), CH_2CH_2], [3.42 (d, J = 12.4 Hz, 1H), 3.60 (d, J = 12.4 Hz, 1H), CH_2-Pyr]), [6.48 (m, 2H), 7.16 (m, 2H), 7.45 (m, 5H), 7.64 (m, 1H), Ar], [7.09 (d, 2H), 8.68 (d, 2H), Pyr]; IR (Nujol) 3322 (OH), 1713 (C=O) cm^{-1}; UV–Vis (c = 0.0258, MeOH) λ_{max} 290 (5828), 246 (12 040) nm; MS (NH_3–CI) m/e 345 (M + 1). Anal. Calcd for $C_{22}H_{20}N_2O_2$·HCl, MW 380.88: C, 69.38; H, 5.56; N, 7.36. Found: C, 69.25; H, 5.39; N, 7.44.

3-[(Dimethylamino)ethyl]-1,3-dihydro-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one Dihydrochloride (5). By substituting chloroethyl dimethylamine hydrochloride in Method A, the desired compound was obtained in 55% yield as a hygroscopic foam: ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 2.51, 2.98 (2m, 2H, CH_2), 2.78 (s, 6H, $2CH_3$), [3.46 (m, 2H), 3.67 (d, 1H), 4.03 (m, 1H), $2CH_2$]), [6.54 (m, 1H), 7.12 (d, 2H), 7.23 (m, 2H), 7.48 (m, 1H), 7.54 (m, 2H,), 7.75 (m, 1H), Ph], 7.37, 8.63 (2d, 4H, Pyr); IR (MeOH) 1708 (C=O) cm^{-1}; UV–Vis (c = 0.0515, MeOH) λ_{max} 245 (8742) nm; MS (NH_3–CI) m/e 372 (M + 1). Anal. Calcd for $C_{24}H_{25}N_3O$·2HCl, MW 444.41: C, 64.87; H, 6.12; N, 9.46. Found: C, 64.40; H, 6.39; N, 9.14.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-propanoic Acid Methyl Ester Hydrochloride (6). A solution of **1a** (9.0 g, 29.96 mmol) in 150 mL of dry THF was cooled in an ice bath and treated with NaH (0.8 g, 32.96 mmol). The mixture was stirred in the ice bath for 45 min and treated with methyl acrylate (2.8 g, 32.96 mmol) in 25 mL of dry THF. The mixture was stirred in the ice bath for 1 h and room temperature for 16 h. The mixture was diluted with 200 mL of 5% $NaHCO_3$ and extracted with 2 × 100 mL of CH_2Cl_2. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to an oil. The impure oil was flash chromatographed on silica gel (BuCl–MeOH, 85:15), and appropriate fractions were combined, treated with 30 mL of 1 N HCl/Et_2O, and evaporated to dryness. The solid was recrystallized from EtOAc to give the desired methyl ester in 73% (9.2 g) yield: mp 197–198 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS)

δ 2.0, 2.2 (2m, 2H, 1′-CH_2), 2.4 (m, 2H, CH_2CO), 3.48 (s, 3H, CH_3), [3.48 (d, J = 12.5 Hz, 1H), 3.68 (d, J = 12.5 Hz, 1H), CH_2-Pyr], [6.54 (m, 1H), 7.2 (m, 2H), 7.5 (m, 5H), 7.68 (m, 1H), Ph], 7.18 and 8.79 (2d, 4H, Pyr); IR (Nujol) 1716 (C=O), 1732 (C=O) cm^{-1}; UV-vis (c = 0.0258, MeOH) λ_{max} 246 (13 418) nm; MS (NH_3-CI) m/e 387 (M + 1). Anal. Calcd for $C_{24}H_{22}N_2O_3$·HCl, MW 422.91: C, 68.16; H, 5.48; N, 6.62. Found: C, 67.88; H, 5.32; N, 6.50.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-propanoic Acid Ethyl Ester Hydrochloride (7). By substituting ethyl 3-bromopropionate in Method A, the desired compound was obtained in 94% yield: mp 179–181 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.11 (t, 3H, CH_3), 1.99 and 2.18 (2m, 2H, 1′-CH_2), 2.4 (m, 2H, CH_2CO), [3.36 (d, J = 12.5 Hz, 1H), 3.55 (d, J = 12.5 Hz, 1H) CH_2-Pyr], 3.94 (q, 2H, OCH_2), [6.51 (m, 1H), 7.2 (m, 6H), 7.44 (m, 1H), 7.51 (m, 2H), 7.68 (m, 1H) Ph], 7.02, 8.55 (2d, 4H, Pyr); IR (Nujol) 1707 (C=O), 1731 (C=O) cm^{-1}; UV-vis (c = 0.0255, MeOH) λ_{max} 246 (12 731) nm; MS (NH_3-CI) m/e 401 (M + 1). Anal. Calcd for $C_{25}H_{24}N_2O_3$·HCl MW 436.94: C, 68.72; H, 5.77; N, 6.41. Found: C, 69.08; H, 5.78; N, 6.32.

(+)-2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-butanoic Acid Ethyl Ester Hydrochloride [(+)-8], Method B. (±)-2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1H-indole-3-butanoic acid ethyl ester hydrochloride (8) (19.33 g, 0.043 mol) was partitioned between 200 mL of Et_2O and 200 mL of water containing $NaHCO_3$ (4.0 g, 0.048 mol). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in EtOH (100 g) and treated with *O,O′*-(−)-*p*-toluyl-L-tartaric acid monohydrate (17.33 g, 0.043 mol). The mixture was warmed at 60 °C to effect solution, and the mixture was stirred at room temperature for 24 h. The resulting crystals were collected by filtration, washed with 3 × 50 mL of cold EtOH and 2 × 50 mL of Et_2O, and dried *in vacuo* to give the salt in 24.5% (8.6 g) overall yield, which implies 48.9% of one isomer; mp 135.0–136.0 °C dec; IR (KBr): 1725, 1711 (C=O) cm^{-1}; ^1H NMR($CDCl_3$, TMS): δ 1.21 (t, 3H, CH_3), 1.38 (m, 2H, 1′-CH_2), 2.0–2.3 (m, 4H, CH_2CH_2), 2.35 (s, 6H, $2CH_3$), [3,08 (d, J = 12.1, 1H), 3.30 (d, J = 12.0, 1H) CH_2-Pyr], 4.08 (g, 2H, OCH_2), 5.92 (s, 2H, 2CHCO), [6.4 (m, 1H), 6.85 (m, 2H), 7.1 (m, 2H), 7.3(m, 2H), 7.38 (dd, 1H) Ph], [6.93 (d, 2H), 8.27 (d, 2H), Pyr], [7.15 (d, 4H), 7.95 (d, 4H) 4-Me-Ph]: MS m/e 415 (M + 1 − $C_{20}H_{18}O_8$); $[\alpha]^{25}_D$ −61.88° (c 0.6, EtOH). Anal. Calcd for $C_{26}H_{26}N_2O_3$ $C_{20}H_{18}O_8$, MW 800.87: C, 68.99; H, 5.54; N, 3.50. Found: C, 68.94; H, 5.50; N, 3.56.

The salt [2,3-dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1H-indole-3-butanoic acid ethyl ester (−)-2,3-bis(4-methylbenzoyloxy)butanedioate] (7.56 g, 0.0094 mol) was partitioned between 100 mL of Et_2O and 100 mL of 5% $NaHCO_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, treated with 15 mL of 1 N HCl/Et_2O, and concentrated *in vacuo* to a foam (4.34 g, 100%): ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.15 (t, 3H, CH_3), 1.2, 1.3 (2m, 2H, 1′-CH_2), 2.1 (m, 2H, 2′-CH_2), 2.26 (m, 2H, CH_2CO), [3.43 (d, J = 12.0 Hz, 1H), 3.64 (d, J = 12.0 Hz, 1H), CH_2-Pyr], 4.02 (q, 2H, OCH_2), [6.5 (m, 1H), 7.2 (m, 2H), 7.5 (m, 5H), 7.67 (m, 1H), Ph], 7.18, 8.70 (2d, 4H, Pyr); IR (KBr) 1716 (C=O) cm^{-1}; UV-vis (EtOH) λ_{max} 246 nm; MS (NH_3-CI) m/e 415 (M + 1); $[\alpha]^{20}_D$ +5.43 ±0.5° (c = 0.60, EtOH); Analytical chiral HPLC isomer ratio, 98.2% (+):1.8% (−). Anal. Calcd for $C_{26}H_{26}N_2O_3$·HCl MW 450.97: C, 69.25; H, 6.04; N, 6.21. Found: C, 68.94; H, 5.80; N, 6.03.

(−)-2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-butanoic Acid Ethyl Ester Dihydrochloride [(-)-8]. By substituting *O,O′*-(+)-*p*-toluyl-D-tartaric acid monohydrate in Method B, the desired salt was obtained in 56% (12.5 g) yield: mp 132.0–132.5 °C; ^1H (300 MHz, DMSO-d_6 TMS) δ 1.21 (t, 3H, CH_3), 1.4 (m, 2H, 1′-CH_2), 2.0–2.3 (m, 4H, 2′-CH_2), 2.34 (s, 6H, $2CH_3$), [3.08 (d, J = 12.0 Hz, 1H), 3.30 (d, J = 12.0 Hz, 1H) CH_2-Pyr], 4.08 (q, 2H, OCH_2), [6.4 (m, 1H), 6.85 (m, 2H), 7.1 (m, 2H), 7.3 (m, 4H) Ph], [6.93 (d, 2H), 8.27 (d, 2H), Pyr], [7.35 (d, 4H), 7.95 (d, 4H), 1,4-Ph]; MS m/e 415 (M + 1); $[\alpha]^{25}_D$ +61.44° (c 0.6, EtOH). Anal. Calcd for $C_{26}H_{26}N_2O_3$· $C_{20}H_{18}O_8$, MW 800.87: C, 68.99; H, 5.54; N, 3.50. Found: C, 69.13; H, 5.55; N, 3.61.

By substituting 2,3-dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1H-indole-3-butanoic acid ethyl ester (+)-2,3-bis-(4-methylbenzoyloxy)butanedioate in Method B, the desired product was obtained as a foam in 94% (5.3 g): ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.15 (t, 3H, CH_3), 1.2, 1.3 (2m, 2H, 1′-CH_2), 2.1 (m, 2H, 2′-CH_2), 2.27 (t, 2H, CH_2CO), [3.46 (d, J = 12.0 Hz, 1H), 3.68 (d, J = 12.0 Hz, 1H), CH_2-Pyr], 4.04 (q, 2H, OCH_2), [6.55 (m, 1H), 7.2 (m, 2H), 7.47 (m, 1H), 7.55 (m, 4H), 7.7 (m, 1H), Ph], 7.13, 8.75 (2d, 4H, Pyr); IR (KBr) 1717 (C=O) cm^{-1}; UV-vis (EtOH) λ_{max} 246 nm; MS (NH_3-CI) m/e 415 (M + 1); $[\alpha]^{20}_D$ −5.96 ±0.5° (c 0.60, EtOH). Anal. Calcd for $C_{26}H_{26}N_2O_3$ HCl: C, 69.25; H, 6.04; N, 6.21. Found: C, 69.25; H, 5.75; N, 6.21.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-butanoic Acid Hydrochloride (9). A solution of 8 (10.0 g, 22.2 mmol) in 100 mL of dioxane–water (1:1) was treated with NaOH (2.2 g, 55.4 mmol) and stirred at room temperature until no starting ester remained as evidenced by TLC ($CHCl_3$-MeOH, 9:1). The mixture was concentrated, and the oily aqueous residue was treated with 1 N HCl (56 mL, 56 mmol). The resulting aqueous solution formed crystals on standing. The crystals were collected by filtration, washed with water, and dried to give the desired acid in 98% (9.2 g) yield: mp 265–267 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.22, 1.29 (2m, 2H, CH_2), 2.16 (m, 2H, CH_2), 2.18 (t, 2H, CH_2CO), [3.44 (d, J = 12.4 Hz, 1H), 3.64 (d, J = 12.4 Hz, 1H) CH_2-Pyr], [6.5 (m, 1H), 7.2 (m, 2H), 7.5 (m, 5H), 7.6 (m, 1H) Ph], 7.19, 8.70 (2d, 4H, Pyr); IR (Nujol) 1713 (C=O) cm^{-1}; MS (NH_3-CI) m/e 387 (M + 1). Anal. Calcd for $C_{24}H_{22}N_2O_3$ HCl, MW 422.91: C, 68.16; H, 5.48; N, 6.62. Found: C, 68.25; H, 5.61; N, 6.48.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-pentanoic Acid Ethyl Ester Hydrochloride (10). By substituting ethyl 5-bromovalerate in Method A, the compound was isolated in 83% yield: mp 172–174 °C; ^1H NMR (300 MHz, $CDCl_3$ TMS) δ 1.06, 1.24 (2m Hz, 1H, 2′-CH_2), 1.20 (t, 3H, CH_3), 1.64 (m, 2H, 3′-CH_2), 2.1, 2.3 (2m, 2H, 1′-CH_2), 2.23 (t, 2H, CH_2-CO), [3.32 (d, J = 12.4 Hz, 1H), 3.55 (d, J = 12.4 Hz, 1H) CH_2-Pyr], 4.07 (q, 2H, OCH_2), [6.4 (m, 1H), 7.2 (m, 2H), 7.4 (m, 4H), 7.5 (m, 2H) Ph], 6.94, 8.43 (2d, 4H, Pyr); IR (Nujol) 1733 (C=O), 1714 (C=O) cm^{-1}; MS (NH_3-CI) m/e 429 (M + 1). Anal. Calcd for $C_{27}H_{28}N_2O_3$·HCl, MW 464.99: C, 69.74; H, 6.26; N, 6.02. Found: C, 69.46; H, 6.00; N, 5.83.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-acetonitrile Hydrochloride (11). By substituting bromoacetonitrile in Method A, the desired product was obtained in 82% yield: mp 221 °C dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.38–3.75 (m, 4H, CH_2CCH_2), [6.56 (m, 1H), 7.25 (m, 2H), 7.52 (m, 5H), 7.82 (m, 1H) Ph], 7.14 and 8.71 (2d, 4H, Pyr); IR (KBr) 2252 (CN), 1713 (C=O) cm^{-1}; MS (NH_3-CI) m/e 340 (M + 1). Anal. Calcd for $C_{22}H_{17}N_3O$ HCl, MW 375.86: C, 70.30; H, 4.83; N, 11.18. Found: C, 70.03; H, 4.69; N, 11.02.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-butanenitrile Hydrochloride (12). By substituting 4-bromobutyronitrile in Method A, the desired compound was obtained in 41% yield: mp 185–187 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ [1.23, 1.39 (2m, 2H), 2.18 (m, 2H), $(CH_2)_2$], 2.50 (t, 2H, CH_2CN), [3.48 (d, J = 12.4 Hz, 1H), 3.70 (d, J = 12.4 Hz, 1H) CH_2-Pyr], [6.54 (m, 1H), 7.14 (d, 2H), 7.21 (m, 2H), 7.5 (m, 6H), 7.71 (m, 1H), 8.71 (d, 2H) Ar]; IR (KBr) 2248 (CN), 1712 (C=O) cm^{-1}; MS (NH_3-CI) m/e 368 (M + 1). Anal. Calcd for $C_{24}H_2N_3O$·HCl MW 403.91: C, 71.37; H, 5.49; N, 10.40. Found: C, 71.28; H, 5.22; N, 10.18.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-pentanenitrile Hydrochloride (13). By substituting 5-bromovaleronitrile in Method A, the desired product was obtained in 93% yield: mp 164–165 °C; ^1H NMR (300 MHz, $CDCl_3$ TMS) δ [1.23, 1.33 (2m, 2H), 1.64 (m, 2H), 2.13, 2.2 (2m, 2H), $(CH_2)_6$], 2.31 (t, 2H, CH_2CN), [3.36 (d, J = 12.4 Hz, 1H), 3.56 (d, J = 12.4 Hz, 1H) CH_2-Pyr], [6.62 (m, 1H), 7.21 (m, 2H), 7.43 (m, 6H) Ph], 6.94, 8.46 (2d Hz, 4H, Pyr); IR (Nujol) 2243 (CN), 1717 (C=O) cm^{-1}; MS (NH_3-Cl) m/e 382 (M + 1). Anal. Calcd for $C_{25}H_{23}N_3O$·HCl, MW 417.94: C, 71.85; H, 5.79; N, 10.05. Found: C, 72.21; H, 5.39; N, 9.88.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-hexanenitrile Hydrochloride (14). By substituting 6-bromocapronitrile in Method A, the compound was obtained in 42% yield: mp 191–193 °C dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ [0.96, 1.09 (2m, 2H), 1.30 (m, 2H), 1.47 (m, 2H), 2.09 (m, 2H) $(CH_2)_4$], 2.42 (t, 2H, CH_2CN), [3.44 (d, J = 12.5 Hz, 1H),

3.63 (d, J = 12.4 Hz, 1H), CH_2-Pyr], [6.53 (m, 1H), 7.18 (m, 2H), 7.58 (m, 5H), 7.68 (m, 1H), Ph], 7.12, 8.70 (2d, 4H, Pyr); IR (Nujol) 2242 (CN), 1713 (C=O) cm^{-1}; MS (NH_3-CI) m/e 396 (M + 1). Anal. Calcd for $C_{26}H_{25}N_3O$·HCl, MW 431.97: C, 72.29; H, 6.07; N, 9.73. Found: C, 72.00; H, 5.82; N, 9.41.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-heptanenitrile Hydrochloride (15). By substituting 7-bromoheptanenitrile in Method A, the desired compound was obtained in 25% yield: mp 190–192 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ [0.96, 1.06 (2m, 2H), 1.25 (m, 2H), 1.4 (m, 4H), 2.1 (m, 2H, $(CH_2)_5$], 2.43 (t, 2H, CH_2CN), [3.39 (d, J = 12.5 Hz, 1H), 3.57 (d, J = 12.5 Hz, 1H) CH_2-Pyr], [6.53 (m, 1H), 7.08 (m, 2H), 7.17 (m, 2H), 7.38 (m, 2H), 7.45 (m, 1H), 7.53 (m, 2H), 7.65 (m, 1H), 8.63 (d, 2H) Ar]; IR (KBr) 2243 (CN), 1714 (C=O) cm^{-1}; MS (NH_3-CI) m/e 410 (M + 1). Anal. Calcd for $C_{27}H_{27}N_3O$·HCl, MW 445.99: C, 72.71; H, 6.33; N, 9.42. Found: C, 72.91; H, 6.36; N, 9.43.

4-[2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indol-3-yl]-2-butenoic Acid Ethyl Ester Hydrochloride (16). By substituting ethyl 4-bromocrotonate in Method A, the desired product was obtained as an oil in 56% yield: ^1H NMR (300 MHz, $CDCl_3$ TMS) δ 1.24 (t, 3H, CH_3), 2.94 (m, 2H, CH_2CC), [3.11 (d, J = 12.0 Hz, 1H), 3.32 (d, J = 12.0 Hz, 1H), CH_2-Pyr], 4.14 (q, 2H, OCH_2), 5.90 (d, J = 16.0 Hz, 1H, C=CH-CO), 6.7 (m, 1H, CH=CCO), [6.5 (m, 1H), 6.79 (d, 2H), 6.9 (d, 2H), 7.15 (m, 2H), 7.4 (m, 4H), 8.29 (d, 2H), Ar]; IR (neat) 1718 (C=O) cm^{-1}; MS (NH_3-CI) m/e 413 (M + 1). Analysis Calcd for $C_{28}H_{24}N_2O_3$·HCl, MW 448.95: C, 69.56; H, 5.61; N, 6.24. Found: C, 69.56; H, 5.53; N, 5.94.

3-[3-(4-Fluorophenyl)-3-oxopropyl]-1,3-dihydro-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one Hydrochloride (17). By substituting 2-chloro 4-fluoropropiophenone in Method A, the desired product was obtained in 65% yield: mp 183–185 °C; IR (Nujol) 1710 (C=O), 1679 (C=O) cm^{-1}; UV-vis (c = 0.0130, MeOH) λ_{max} 245 (25 697) nm; MS (NH_3-CI) m/e 451 (M + 1). Anal. Calcd for $C_{29}H_{23}N_2O_2F$·HCl, MW 486.97: C, 71.53; H, 4.97; N, 5.75. Found: C, 71.63; H, 4.72; N, 5.70.

3-[4-(4-Fluorophenyl)-4-oxobutyl]-1,3-dihydro-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one Hydrochloride (18). A solution of **1b** (10.0 g, 29.7 mmol) in 100 mL of dry THF was cooled in an ice bath and treated with NaH (1.6 g, 66.7 mmol) and stirred for 10 min. The mixture was reacted with 4-chloro-4′-fluorobutyrophenone 2,2-dimethylpropylene ketal (8.5 g, 29.6 mmol) and KI (4.9 g, 29.7 mmol) and stirred at room temperature for 24 h. The mixture was treated with 100 mL of 6 N HCl, stirred an additional 24 h, cooled in an ice bath, and made alkaline with 3 N NaOH. The mixture was extracted with 2 × 100 mL of CH_2Cl_2, and the organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was dissolved in 50 mL of EtOH and treated with 35 mL of 1 N HCl/Et_2O. The resulting solid was collected by decanting the solvent and the amorphous solid was recrystallized from EtOH–EtOAc to give the desired product in 46% (6.8 g) yield: mp 205 °C dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ [1.35 (m, 2H), 2.15 (m, 2H), CH_2CH_2], 3.01 (t, 2H, CHCO), [3.44 (d, J = 12.4 Hz, 1H), 3.64 (d, J = 12.4 Hz, 1H) CH_2-Pyr], [6.56 (m, 1H), 7.12 (d, 2H), 7.19 (m, 2H), 7.24 (m, 2H), 7.46 (m, 5H), 7.69 (m, 1H), 8.00 (m, 2H), 8.69 (d, 2H) Ar]; IR (KBr) 1712 (C=O), 1684 (C=O) cm^{-1}; UV-vis (c = 0.0258, EtOH) λ_{max} 244 (18 133) nm; MS (NH_3-CI) m/e 465 (M + 1). Anal. Calcd for $C_{30}H_{25}N_2O_2F$·HCl, MW 501.00: C, 71.92; H, 5.23; N, 5.59. Found: C, 71.87; H, 5.22; N, 5.61.

5-[2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indol-3-yl]-2-pentanone Hydrochloride (19). By substituting 5-chloro-2-pentanone ethylene ketal in Method A, the corresponding ketal was obtained. The ketal was stirred in 150 mL of 3 N HCl for 16 h, and the mixture was adjusted to pH 7 with 3 N NaOH and extracted with CH_2Cl_2. The extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to an oil. The impure oil was dissolved in 50 mL of absolute EtOH and treated with 35 mL of 1 N HCl/Et_2O, concentrated *in vacuo* to a foam which was recrystallized from EtOH–EtOAc to give the desired ketone in 44% yield: mp 192–194 °C; ^1H NMR (300 MHz, $CDCl_3$ TMS) δ 1.4 (m, 2H, 2′-CH_2), 2.09 (s, 3H, CH_3), 2.11 (m, 2H, 1′-CH_2), 2.43 (m, 2H, 3′-CH_2), [3.34 (d, 1H), 3.53 (d, 1H) CH_2-Pyr], [6.6 (m, 1H), 6.95 (m, 2H), 7.2 (m, 2H), 7.4 (m, 6H), 8.46 (d, 2H) Ar]; IR (Nujol) 1705 (C=O) cm^{-1}; MS (NH_3 CI) m/e 385 (M + 1). Anal. Calcd for $C_{25}H_{24}N_2O_2$·HCl, MW 420.94: C, 71.33; H, 5.99; N, 6.66. Found: C, 71.12; H, 5.61; N, 6.51.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmeth-yl)-1*H*-indene-3-butanamide Hydrochloride (20). By treating **12** [R = $(CH_2)_3CN$] in the manner reported by Noller,[25] the desired product was obtained in 72% (3.0 g) yield: mp 232 °C dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ [1.2 (m, 2H), 2.0 (m, 4H), $((CH_2)_3]$, 3.4–3.6 (m, 2H) CH_2-Pyr), [6.55 (m, 1H), 7.2 (m, 2H), 7.5 (m, 5H), 7.65 (m, 1H) Ph], 6.73, 7.30 (2s, 2H, NH_2), 7.11, 8.79 (2d, 4H, Pyr); IR (Nujol) 3340, 1711 (C=O), 1672 (C=O) cm^{-1}; MS (NH_3-CI) m/e 386 (M + 1). Anal. Calcd for $C_{24}H_{23}N_3O_2$·HCl, MW 421.93: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.31; H, 5.63; N, 9.88.

2,3-Dihydro-2-oxo-1-phenyl-3-(4-pyridinylmethyl)-1*H*-indole-3-butanol Acetate Hydrochloride (21). By substituting 4-bromobutyl acetate in Method A, the desired compound was obtained in 87% yield: mp 170–172 °C; ^1H NMR (300 MHz, $CDCl_3$ TMS) δ 1.08 and 1.25 (m, 2H, 1′-CH_2), 1.63 (m, 2H, 2′-CH_2), 1.99 (s, 3H, CH_3), 2.11 and 2.26 (m, 2H, 3′-CH_2), [3.34 (d, J = 12.4 Hz, 1H), 3.57 (d, J = 12.4 Hz, 1H) CH_2-Pyr], 3.99 (t, 2H, OCH_2), [6.6 (m, 1H), 7.2 (m, 2H), 7.4 (m, 6H) Ph], 7.94, 8.48 (2d, 4H, Pyr); IR (KBr) 1732 (C=O), 1712 (C=O) cm^{-1}; UV-vis (c = 0.0253, EtOH) λ_{max} 247 (12 109) nm; MS (NH_3-CI) m/e 415 (M + 1). Anal. Calcd for $C_{26}H_{26}N_2O_3$·HCl, MW 450.97: C, 69.25; H, 6.04; N, 6.21. Found: C, 69.25; H, 5.84; N, 6.11.

1,3-Dihydro-3-(4-hydroxybutyl)-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one Hydrochloride (22). A suspension of **8** (10.0 g, 22.2 mmol) in 50 mL of dry THF was treated with excess 1 M BH_3–THF and stirred at room temperature for 3 days. The excess borane was decomposed with MeOH, and the mixture was concentrated *in vacuo*. The residue was digested with 100 mL of 1 N HCl for 3 h at 80 °C, and the solution was concentrated. The residue was partitioned between 200 mL of EtOAc and 100 mL of 5% $NaHCO_3$. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, treated with 44 mL of 1 N HCl/Et_2O, and evaporated *in vacuo*. The residue was suspended in hot CH_3CN and left standing overnight. The resulting crystals were collected by filtration, washed with Et_2O, and dried to give the product in 30% (2.72 g) yield: mp 196–197 °C; ^1H NMR (300 MHz, $CDCl_3$ TMS) δ 1.13, 1.24 (2m, 2H, 2′-CH_2), 2.51 (m, 2H, CH_2CO), 2.1–3.0 (m, 2H, 1′-CH_2), [3.40 (d, J = 12.4 Hz, 1H), 3.54 (d, J = 12.5 Hz, 1H) CH_2-Pyr], 3.48 (t, 2H, OCH_2), [6.5 (m, 1H), 7.2 (m, 2H), 7.4 (m, 6H) Ph], 6.99, 8.49 (2d, 4H, Pyr); IR (Nujol) 3356 (OH), 1709 (C=O) cm^{-1}; MS (NH_3-CI) m/e 373 (M + 1). Anal. Calcd for $C_{24}H_{24}N_2O_2$·HCl, MW 408.93: C, 70.49; H, 6.16; N, 6.85. Found: C, 70.44; H, 6.00; N, 6.67.

3-(4-Chlorobutyl)-1,3-dihydro-1-phenyl-(4-pyridinylmethyl)-2*H*-indol-2-one Hydrochloride (23a). A solution of **1** (8.9 g, 29.7 mmol) in 75 mL of dry THF was treated with NaH (0.86 g, 35.6 mmol) and stirred in an ice bath for 30 min. The mixture was treated with 1-bromo-4-chlorobutane (0.86 g, 35.6 mmol) in 25 mL of THF and stirred at room temperature for 24 h. The mixture was concentrated *in vacuo*, and the resulting residue was partitioned between 200 mL of CH_2Cl_2 and 100 mL of water. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was triturated with 100 mL of 1 N HCl, and the resulting solid was collected by filtration, and recrystallized from 100 mL of hot water. The desired intermediate was obtained in 82% (10.4 g) yield: mp 149–151 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.08, 1.2 (2m, 2H, 2′-CH_2), 1.66 (m, 2H, 1′-CH_2), 2.12 (m, 2H, 3′-CH_2), [3.45 (d, J = 12.5 Hz, 1H), 3.63 (d, J = 12.5 Hz, 1H) CH_2-Pyr], 3.57 (t, 2H, CH_2Cl), [6.55 (m, 1H), 7.2 (m, 2H), 7.5 (m, 5H), 7.68 (m, 1H) Ph], 7.12, 8.70 (2d, 4H, Pyr); IR (Nujol) 1712 (C=O) cm^{-1}; MS (NH_3-CI) m/e 391 (M + 1). Anal. Calcd for $C_{24}H_{23}N_2OCl$·HCl, MW 427.38: C, 67.45; H, 5.66; N, 6.55. Found: C, 67.23; H, 5.55; N, 6.36.

1,3-Dihydro-1-phenyl-3-[4-(ethyloxy)butyl]-3-(4-pyridinylmethyl)-2*H*-indol-2-one Hydrochloride (23b). A solution of **23a** (2.0 g, 4.67 mmol) in 25 mL of dry THF was treated with excess potassium ethoxide and stirred at room temperature for 24 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between 100 mL of CH_2Cl_2 and 100 mL of water.

The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was triturated with 25 mL of 1 N HCl/Et_2O, and the resulting solid was collected by filtration, washed with Et_2O, and dried to give the desired product in 73% (1.5 g) yield: mp 95–98 °C; IR (Nujol) 1714 (C=O) cm^{-1}; MS (NH_3-CI) *m/e* 401 (M + 1). Anal. Calcd for $C_{26}H_{28}N_2O_7$·HCl MW 436.98: C, 71.46; H, 6.09; N, 6.41. Found: C, 71.35; H, 6.10; N, 6.40.

1,3-Dihydro-1-phenyl-3-[4-(propylthio)butyl]-3-(4-pyridinylmethyl)-2H-indol-2-one Hydrochloride (24). A mixture of **23a** (6.0 g, 14.04 mmol) in 75 mL of dry THF was treated with NaH (0.75 g, 31.25 mmol) and stirred for 10 min under dry nitrogen. The mixture was then treated with propanethiol (1.2 g, 15.4 mmol) and stirred at room temperature for 16 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between 150 mL of CH_2Cl_2 and 100 mL of water. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, treated with 20 mL of 1 N HCl/Et_2O, and evaporated to dryness. The residue was triturated with 100 mL of hot EtOAc, cooled to room temperature, and filtered to collect the solid. The solid was dried *in vacuo* to give the product in 81% (5.3 g) yield: mp 149–150 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 0.90 (t, 3H, CH_3), 1.02, 1.18 (2m, 2H, 2′-CH_2) 1.45 (m, 4H, CH_2CSCCH_2), 2.1 (m, 2H, 1′-CH_2), 2.37 (2t, 4H, CH_2SCH_2), [3.42 (d, 1H), 3.59 (d, 1H) CH_2-Pyr], [6.53 (m, 1H), 7.19 (m, 2H), 7.44 (d, 3H), 7.53 (m, 2H), 7.65 (m, 1H) Ph], 7.10, 8.66 (2d, 4H, Pyr); IR (KBr) 1717 (C=O) cm^{-1}; MS (NH_3-CI) *m/e* 431 (M + 1). Anal. Calcd for $C_{27}H_{30}N_2OS$·HCl, MW 467.08: C, 69.43; H, 6.69; N, 6.00; S, 6.86. Found: C, 69.48; H, 6.73; N, 5.88; S, 6.77.

5-Chloro-1,3-dihydro-1-phenyl-3-[4-(propylsulfonyl)butyl]-3-(4-pyridinylmethyl)-2H-indol-2-one Hydrochloride (25). A solution of **24** (2.0 g, 4.28 mmol) in 50 mL of MeOH and 11 mL of water was treated with Oxone (monopersulfate compound, $2KHSO_5/KHSO_4/K_2SO_4$) (7.9 g, 12.85 mmol) and stirred for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between 100 mL of 1 N NaOH and 100 mL of CH_2Cl_2. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was column chromatographed on silica gel using $CHCl_3$-MeOH (10:1) as the mobile phase, and appropriate fractions were combined and concentrated to an oil. The oil was triturated with 1 N HCl/Et_2O to give a solid which was collected by filtration, washed with Et_2O, and dried *in vacuo* to give the product in 70% (1.6 g) yield: mp 197–199 °C dec; ^1H NMR (300 MHz, $CDCl_3$ TMS) δ 1.07 (t, 3H, CH_3), 1.3 (m, 2H, 2′-CH_2), 1.8 (m, 4H, CH_2CSCCH_2), 2.1, 2.3 (2m, 2H, 1′-CH_2), 2.9 (m, 4H, CH_2SCH_2), 3.3–3.6 (m, 2H, CH_2-Pyr), [6.57 (d, 1H), 7.2 (d, 1H), 7.4 (m, 6H) Ph], 6.92, 8.48 (2d, 4H, Pyr); IR (Nujol) 1711 (C=O), 1141 (SO_2) cm^{-1}; MS (NH_3-CI) *m/e* 497 (M + 1). Anal. Calcd for $C_{27}H_{30}N_2O_3SCl$·HCl, MW 534.53: C, 60.67; H, 5.85; N, 5.24; S, 6.00. Found: C, 60.39; H, 5.80; N, 5.31; S, 6.02.

1,3-Dihydro-3-(3-hydroxypropyl)-1-phenyl-3-(4-pyridinylmethyl)-2H-indol-2-one Monohydrate (26). A solution of **1b** (1.0 g, 3.0 mmol) in 50 mL of CH_2Cl_2 was treated with saturated $NaHCO_3$, and the organic phase was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was dissolved in 10 mL of dry THF and reacted with NaH (0.08 g, 3.3 mmol) while being stirred in an ice bath. The mixture was treated in one portion with 3-bromo-1-propanol (0.5 g, 3.6 mmol) and stirred at room temperature for 20 h. The reaction mixture was treated with 25 mL of saturated $NaHCO_3$ and extracted with 50 mL of Et_2O. The ether solution was washed with water and brine, dried over $MgSO_4$, filtered, concentrated, and column chromatographed on silica gel using $CHCl_3$–MeOH (9:1) as mobile phase. Appropriate fractions were combined and concentrated, and the residue was recrystallized from EtOAc to give the desired product in 50% (0.56 g) yield: mp 146–147 °C; ^1H NMR (300 MHz, $CDCl_3$ TMS) δ 1.25–1.5 (m, 2H, 2′-CH_2), [2.1 (d, J = 9.4 Hz, 1H), 2.3 (d, J = 9.4 Hz, 1H), 3.05 (d, J = 15.0 Hz, 1H), 3.25 (d, J = 15.0 Hz, 1H) CH_2CCH_2], 3.5 (m, 2H, CH_2O), [6.5 (m, 1H), 6.9 (m, 2H), 7.15 (m, 2H), 7.6 (m, 4) Ph], [6.75 (d, J = 4.0 Hz, 2H), 8.30 (d, J = 4.0 Hz, 2H), Pyr]; IR (KBr) 3500 (OH), 1700 (C=O) cm^{-1}; MS (NH_3-CI) *m/e* 359 (M + 1). Anal. Calcd for $C_{23}H_{22}N_2O_2$·H_2O, MW 376.46: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.29; H, 6.58; N, 7.06.

1,3-Dihydro-3-hydroxy-1-phenyl-3-(4-pyridinylmethyl)-2H-indol-2-one (27). A mixture of 1 (1 g, 3.3 mmol) and NaH (0.1 g, 4.2 mmol) in 25 mL of dry THF was aerated with dry air for 16 h. The reaction mixture was triturated with water, and the resulting gummy solid was collected by filtration. The gum was chromatographed on silica gel using $CHCl_3$-MeOH (9:1) as mobile phase. Appropriate fractions were combined and concentrated *in vacuo*. The residue was recrystallized from EtOAc to give the desired alcohol: mp 201–202 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.34 (dd, 2H, CH_2-Pyr), 4.34 (broad s, 1H, OH), [6.54 (d, 1H), 6.95 (d, 2H), 7.1 (m, 4H) Ar], 6.87, 8.30 (2d, 4H, Pyr); IR (Nujol) 3170 (OH), 1728 (C=O) cm^{-1}; UV–vis (c = 0.0253, MeOH) λ_{max} 244 (12 366) nm; MS (NH_3-CI) *m/e* 317 (M + 1). Anal. Calcd for $C_{20}H_{16}N_2O_2$, MW 316.36: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.12; H, 5.01; N, 8.76.

Alternatively, a mixture of *N*-phenylisatin and 4-picoline was heated at 130–140 °C for 3–4 h with vigorous stirring. The mixture was cooled to room temperature and triturated with CH_2Cl_2. The resulting solid was collected by filtration, washed with additional CH_2Cl_2, and dried to give the desired product in 80–90% yield; mp 197–200 °C.

3-Hexyl-1,3-dihydro-1-phenyl-3-(4-pyridinylmethyl)-2H-indol-2-one Hydrochloride (28). By substituting n-bromohexane in Method A, the desired product was obtained in 84% yield after recrystallization from EtOAc: mp 127–128 °C; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 0.81 (t, 3H, CH_3), [0.89, 1.05 (2m, 2H), 1.17 (m, 6H), 2.06 (m, 2H), $(CH_2)_5$], [3.43 (d, J = 12.4 Hz, 1H), 3.61 (d, J = 12.4 Hz, 1H) CH_2-Pyr], [6.53 (m, 1H), 7.18 (m, 2H), 7.5 (m, 6H), 7.65 (m, 1H) Ph], [7.09 (d, J = 6.3 Hz, 2H), 8.69 (d, J = 6.3 Hz, 2H) Pyr]; IR (Nujol) 1716 (C=O) cm^{-1}; UV–vis (c = 0.0255, MeOH) λ_{max} 246 (13 785) nm; MS (NH_3-CI) *m/e* 385 (M + 1). Anal. Calcd for $C_{26}H_{28}N_2O$·HCl, MW 420.98: C, 74.18; H, 6.94; N, 6.65. Found: C, 74.12; H, 6.87; N, 6.52.

Biological Assays. Acetylcholine Release Assay (AcCh Rel). Tissue preparation and release assays were performed as described previously Nickolson et al.[13] Male Wistar rats (Charles River, 200–300 g) were euthanized by decapitation and the striatum was immediately dissected. The tissues were then chopped into 0.25 × 0.25 cm^2 squares using a McIlwain tissue chopper. Approximately 100 mg of the tissue slices were transferred to 10 mL of of Krebs–Ringer solution, made up of 116 mmol of NaCl, 3 mmol of KCl, 1.3 mmol $CaCl_2$, 1.2 mmol KH_2PO_4, 1.2 mmol Na_2SO_4, 25 mmol of $NaHCO_3$, and 11 mM glucose and containing radiolabeled neurotransmitter precursor, 10 nmol of choline chloride containing 20 μL of [^{3}H]choline chloride (80 Ci/mmol) for acetylcholine release; the preparation was allowed to incubate for 30 min under an atmosphere of O_2:CO_2 (95:5). After the incubation period, the slices were washed (3×) with fresh Krebs–Ringer buffer and aliquots of the slices (approx. 5 mg) were transferred to perfusion chambers of Brandel SF-20 superfusion apparatus. The slices were superfused (washed) with oxygenated Krebs–Ringer solution at a rate of 0.25 mL/min for 20 min before fractions of the effluent were taken. Ten millimole of hemicholinium-3 was added to the superfusion medium to inhibit reuptake of [^{3}H]choline during the release assay. After the 20-min washout period, fractions were collected in 4 min intervals (1.0-mL of fractions) and were collected directly into scintillation vials; at the end of the experiment, the chambers were emptied into scintillation vials and residual radioactivity is extracted from the slices in 100 mL of of 1.0 N HCl. Scintillation cocktail is subsequently added to the vials that were then assessed for radioactivity in a scintillation counter.

A total of 15 fractions were collected from each chamber during an experiment. Stimulated release is elicited by raising the KCl concentration to 20 mmol (NaCl concentration adjusted to 100.2 mmol) for a period of 4 min immediately before fraction 4 (S1), fraction 8 (S2), and fraction 13 (S3). The screening compound is introduced during fraction 5 (lowest dose) and fraction 10 (high dose), with a 4-min washout in between.

Fractional releases were calculated by dividing the radioactivity (dpm) found in each fraction by the total radioactivity in the tissue at the start of the experiment and is expressed as a percentage. Stimulated release is defined as the fractional release found during K^+ stimulation minus the amount of fractional release found before and after stimulation.

Behavioral Test Procedure. Rat Passive Avoidance Hypoxia Induced Amnesia[12,14] (PA). Unfasted male CD rats, weighing between 165 and 210 g were trained in a PA apparatus using the following procedure: rats were placed in the clear side of the two compartment chamber and allowed 90 s to enter the dark compartment. Ten seconds after entering the dark chamber, a 3 s footshock (1.0 mA) was applied to the grid floor followed by an additional 10-s delay and another 3-s footshock was applied. Retentions were tested 4 h later. The rats were allowed 300 s to enter the dark compartment; time was taken. Memory disruption was induced by exposing the rats to a gas mixture containing 6.5% oxygen supplemented with nitrogen for 30 min prior to passive avoidance training. Doses of the test compound were administered (0.1 mL/100 g sc) relative to time of PA training. Typical results are shown in Table V for compound 8.

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(30) Compounds **2**, **6-8**, and **10-15** were energy minimized and the distance (D, in Å) for the energy-minimized conformer was measured from the oxindole 3-carbon to the ester carbonyl oxygen (Y = O=COR') or the nitrile nitrogen (Y = CN). These distances (D) were compared with the number of methylenes (m), for [R = $(CH_2)_mY$], to produce the following:

$$D, \text{ in Å} = 1.345m + 1.750$$

$$n = 10, r^2 = 0.984, \text{SE} = 0.303, F = 492.206.$$

These results suggested that the simpler m could be used in place of the more complicated D.
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