(Aminoalkoxy)chromones. Selective σ Receptor Ligands

Ronald H. Erickson,* Kenneth J. Natalie, Jr., William Bock, Zhijian Lu, Farzaneh Farzin, Ronald G. Sherrill, David J. Meloni, Raymond J. Patch, Waclaw J. Rzesotarski, Jennifer Clifton, Michael J. Pontecorvo, Michael A. Bailey, Karen Naper, and William Karbon

Nova Pharmaceutical Corporation, 6200 Freeport Centre, Baltimore, Maryland 21224. *Received November 26, 1991*

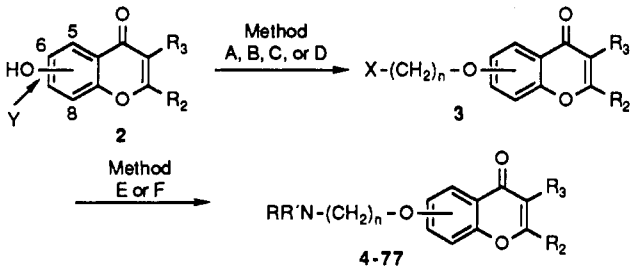
A series of (aminoalkoxy)chromones has been prepared, members of which bind potently (16–100 nM) at the σ binding site and bind weakly (>1000 nM) at the dopamine D_2 receptor and 33 other receptors, second messenger systems, and ion channels. At the σ receptor, the preferred position of attachment for the aminoalkoxy side chain to the chromone ring followed the rank order: 7-position > 5-position > 6-position. Chromones that contained a 2-substituent that was not coplanar with the chromone ring system showed improved binding over compounds with coplanar substituents. The most potent compound at the σ site, 7-[[7-(4-hydroxypiperidyl)heptyl]oxy]-2-phenylchromone (74), had receptor affinities (IC_{50}) of 16 nM at the [^{3}H]DTG site, 19 nM at the [^{3}H]-(+)-3-PPP site, and 4000 nM (K_i) at the dopamine D_2 receptor. The most selective compound examined, 6-[[6-(4-hydroxypiperidyl)hexyl]-oxy]-2-cyclopentylchromone (58), exhibited IC_{50}s of 51 nM at the [^{3}H]DTG site, 55 nM at the [^{3}H]-(+)-3-PPP site, and 21 000 nM (K_i) at the dopamine D_2 receptor. Compound 44 (6-[[6-(4-hydroxypiperidyl)hexyl]oxy]-3-methylflavone, NPC 16377) was systemically effective (ip and po) in two behavioral models predictive of antipsychotic compounds and systemically active in animal models of ischemia.

Introduction

The existence of a σ receptor was first postulated by Martin et al.[1] to account for the psychotomimetic effects of *N*-allylnormetazocine (SKF 10,047) in the chronic spinal dog. Although originally defined as an opioid receptor subtype, σ binding sites are distinguished by being insensitive to the opiate antagonist naloxone and by exhibiting a chemical enantioselectivity for the (+)-isomers of benzomorphan opiates (including SKF 10,047, pentazocine, and cyclazocine) rather than the (−)-isomers which are preferred by traditional opioid binding sites.[2-7] Later, σ binding sites were proposed to be identical to phencyclidine (PCP) binding sites;[8] however, substantial evidence now indicates that σ and PCP binding sites are distinct physical entities.[7,9]

The dopaminergic hypothesis, which postulates that dopaminergic activity is increased in the mesolimbic system of the brain, has been the dominate theory for the biological basis of schizophrenia for many years.[10-12] Neuroleptic drugs such as haloperidol and chlorpromazine are believed to elicit their therapeutic effect by blockade of dopamine D_2 receptors. The observation that many neuroleptic drugs bind to σ receptors with high affinity[4,13,14] led to the suggestion that the σ binding site may be responsible for some of the antipsychotic actions of these medications.[7,15] The subsequent discovery that potential antipsychotic agents such as rimcazole, remoxipride, and BMY 14802 were more potent at the σ binding site than the dopamine D_2 receptor has further supported this notion and stimulated research to develop agents which are more potent and selective for the σ binding site.

Scheme I[a]



[a] (Method A) Y = 6-8/Br-$(CH_2)_{3-6}$-Cl/K_2CO_3/acetone/Δ. (Method B) Y = 6-8/Br-$(CH_2)_{7-10}$-Br/K_2CO_3/acetone/Δ. (Method C) Y = 5/Br-$(CH_2)_{3-6}$-Cl/NaH/DMF/110 °C. (Method D) Y = 5/Br-$(CH_2)_{7-10}$-Br/DMF/110 °C. (Method E) NHRR′/NaI/K_2CO_3/DMF/110 °C. (Method F) 1. NaI/butanone/Δ. 2. NHRR′/EtOH/Δ.

(1) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The Effects of Morphine-like and Nalorphine-like Drugs in the Nondependent and Morphine Dependent Chronic Spinal Dog. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517–532.

(2) Brady, K. T.; Balster, R. T.; May, E. L. Stereoisomers of *N*-Allylnormetazocine: Phencyclidine-like Behavioral Effects in Squirrel Monkeys and Rats. *Science* **1982**, *215*, 178–180.

(3) Su, T. P. Evidence for sigma Opioid Receptor: Binding of Tritium Labeled SKF-10047 to Etorphine Inaccessible Sites in Guinea-pig Brain. *J. Pharmacol. Exp. Ther.* **1982**, *223*, 284–290.

(4) Tam, S. W.; Cook, L. sigma Opiates and Certain Antipsychotic Drugs Mutually Inhibit (+)-[^{3}H]SKF 10047 and [^{3}H]-Haloperidol Binding in Guinea Pig Brain Membranes. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 5618–21.

(5) Katz, J. L.; Spealman, R. D.; Clark, R. D. Stereoselective Behavioral Effects of *N*-Allylnormetazocine in Pigeons and Squirrel Monkeys. *J. Pharmacol. Exp. Ther.* **1985**, *232*, 452–461.

(6) Weber, E.; Sonders, M.; Quarum, M.; McLean, S.; Pou, S.; Keana, J. F. W. 1,3-Di(2-[5[^{3}H]tolyl)guanidine: A Selective Ligand That Labels sigma-type Receptors for Psychotomimetic Opiates and Antipsychotic Drugs. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8784–8788.

(7) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; de Costa, B.; Rice, K. Sigma Receptors: Biology and Function. *Pharmacol. Rev.* **1990**, *42*, 355–402.

(8) Shannon, H. E. Phencyclidine-like Discriminative Stimuli of (+)- and (−)-N-Allylnormetazocine in Rats. *Eur. J. Pharmacol.* **1982**, *84*, 225–8.

(9) Quirion, R.; Chicheportiche, R.; Contreras, P. C.; Johnson, K. M.; Lodge, D.; Tam, S. W.; Woods, J. H.; Zukin, S. R. Classification and Nomenclature of Phencyclidine and sigma Receptor Sites. *Trends Neurosci.* **1987**, *10*, 444–6.

(10) Snyder, S. H.; Banerjee, S. P.; Yamamura, H. I.; Greenberg, D. Drugs, Neurotransmitters and Schizophrenia. *Science* **1974**, *184*, 1243–1253.

(11) Losonczy, M. F.; Davidson, M.; Davis, K. L. The Dopamine Hypothesis of Schizophrenia. In *Psychopharmacology: The Third Generation of Progress*; Meltzer, H. Y., Ed.; Raven Press: New York, 1987; pp 715–726.

(12) McKenna, P. J. Pathology, Phenomenology and the Dopamine Hypothesis of Schizophrenia. *Br. J. Psychiatry* **1987**, *151*, 288–301.

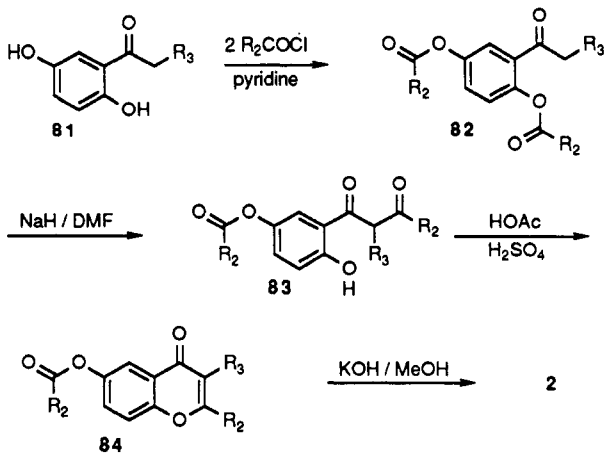
(13) Itzhak, Y. Pharmacological Specificity of Some Psychotomimetic and Antipsychotic Agents for the sigma and PCP Binding Sites. *Life Sci.* **1988**, *42*, 745–52.

(14) Largent, B. L.; Wikström, H.; Snowman, A. M.; Snyder, S. H. Novel Antipsychotic Drugs Share High Affinity for sigma Receptors. *Eur. J. Pharmacol.* **1988**, *155*, 345–347.

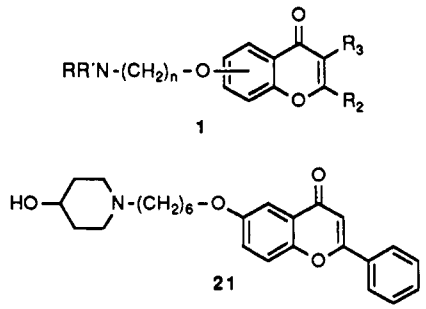
(15) Snyder, S. H.; Largent, B. L. Receptor Mechanisms in Antipsychotic Drug Action: Focus on Sigma Receptors. *J. Neuropsychiatry* **1989**, *1*, 7–15.

0022-2623/92/1835-1526$03.00/0

Scheme II. Method G



An examination of aminoalkyl ethers of chromones (1) showed that these compounds bind at the σ binding site with modest potency and are ca. 10-fold selective for the σ site versus the dopamine D_2 site. Further work led to the discovery that compound **21**, upon ip administration,



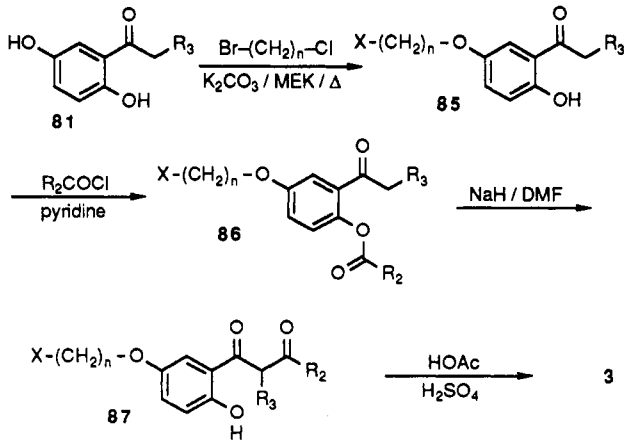
would reverse amphetamine-induced hyperlocomotion in mice, a behavioral model sensitive to antipsychotic compounds.[16] These discoveries led us to investigate the structure–activity relationships of **21** and the potential antipsychotic activity of structural analogues.

Chemistry and Biology

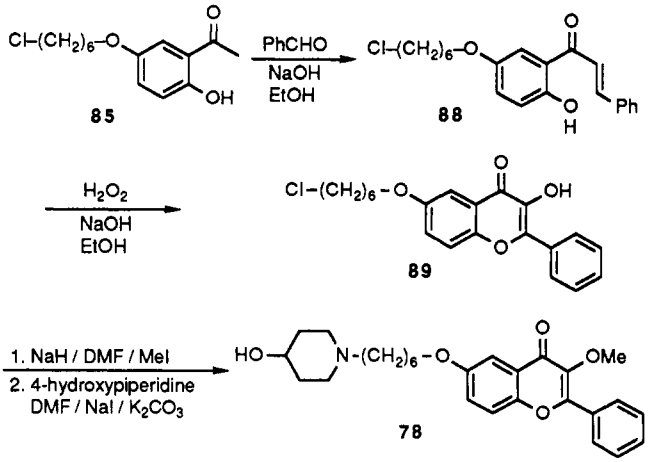
The compounds were synthesized as shown in Scheme I. The appropriately substituted hydroxychromone was treated with base and a dihaloalkane to form the (haloalkoxy)chromone **3**. The conditions used for this reaction depended upon the dihaloalkane used and the position of attachment of the hydroxyl group. When the hydroxyl was attached to carbon 6, 7, or 8 and the chain length was 3–6 methylene units, 2 equiv of the commercially available bromochloroalkane was used with potassium carbonate as the base in refluxing acetone or 2-butanone (method A). For chain lengths greater than six, 4 equiv of a dibromoalkane was used to minimize dimer formation (method B). When the hydroxyl group was attached to carbon 5 and the chain length was 3–6 methylene units, 2 equiv of bromochloroalkane was used with sodium hydride in DMF at 110 °C (method C) and for chain lengths greater than six, 4 equiv of a dibromoalkane was used (method D). The amino group was introduced by a Finkelstein reaction of the chloro compound **3** to give an (iodoalkoxy)chromone followed by reaction with the appropriate amine in either a one-step (method E) or a two-step (method F) procedure. The compounds' receptor binding potencies are listed in

(16) Segal, D. S.; Schuckit, M. A. Animal Models of Stimulant-Induced Psychosis. In *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives*; Creese, I., Ed.; Raven Press: New York, 1983; pp 131–167.

Scheme III. Method H



Scheme IV. Method I



Scheme V. Method J

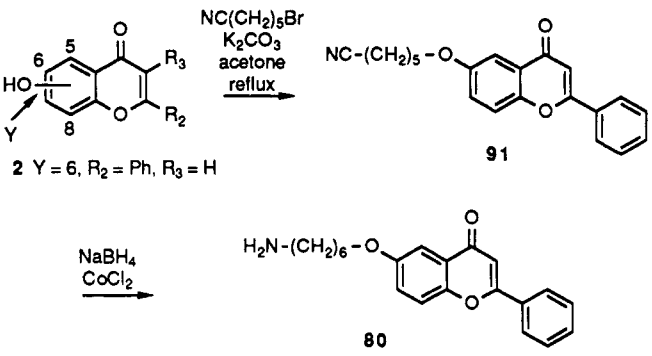


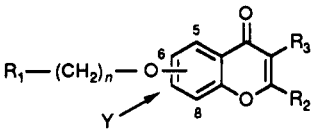
Table I and their method of synthesis and physical properties are in Table II.

In the cases where the appropriate chromone **2** was not commercially available, it was prepared as shown in Scheme II (method G). The acetophenone **81** was diacylated to give **82**, which, upon treatment with sodium hydride in DMF, underwent the Baker–Venkataraman rearrangement to give the diketone **83**. Then **83** was cyclized with a mixture of acetic and sulfuric acids to give **84**, which gave the desired **2** after hydrolysis using potassium hydroxide in methanol.

Alternatively, compound **3** could be made directly using the route shown in Scheme III (method H). Alkylation of the 2′,5′-acetophenone **81** gave acetophenone **85**. Acylation of **85** followed by the Baker–Venkataraman rearrangement and acid cyclization gave the desired **3**.

Compound **78** was prepared using a general procedure for the Algar–Flynn–Oyamada reaction reported by Smith

Table I. σ and Dopamine D_2 Binding of (Aminoalkoxy)chromones



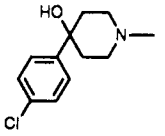
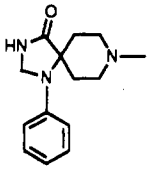
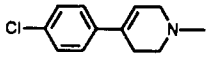
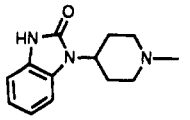
no.	n	Y[a]	R_1	R_2	R_3	DTG[b] IC_{50} (nM)	PPP[b] IC_{50} (nM)	D_2[c] K_i (nM)
4	3	5	4-hydroxypiperidyl	C_6H_5	H	125 ± 20	91 ± 9	8400
5	4	5	4-hydroxypiperidyl	C_6H_5	H	58 ± 12	177 ± 26	9500
6	5	5	4-hydroxypiperidyl	C_6H_5	H	54 ± 14	147 ± 6	5100
7	6	5	4-hydroxypiperidyl	C_6H_5	H	116 ± 69	195 ± 97	6100
8	7	5	4-hydroxypiperidyl	C_6H_5	H	36 ± 17	65 ± 8	2400
9	2	6	dimethylamino	C_6H_5	H	590 ± 32	40 ± 6	4500
10	3	6	dimethylamino	C_6H_5	H	408 ± 156	257 ± 62	3600
11	4	6	dimethylamino	C_6H_5	H	720 ± 199	400 ± 43	4200
12	5	6	dimethylamino	C_6H_5	H	529 ± 114	1800 ± 1000	8200
13	6	6	dimethylamino	C_6H_5	H	432 ± 177	335 ± 140[d]	5600
14	7	6	dimethylamino	C_6H_5	H	165 ± 58	188 ± 5	12000
15	8	6	dimethylamino	C_6H_5	H	227 ± 31	143 ± 5	2800
16	9	6	dimethylamino	C_6H_5	H	334 ± 116	202 ± 65	2200
17	10	6	dimethylamino	C_6H_5	H	297 ± 45	341 ± 139	2700
18	3	6	4-hydroxypiperidyl	C_6H_5	H	130 ± 14	123 ± 5	3400
19	4	6	4-hydroxypiperidyl	C_6H_5	H	337 ± 107	263 ± 62	6800
20	5	6	4-hydroxypiperidyl	C_6H_5	H	210 ± 78	270 ± 50	5100
21	6	6	4-hydroxypiperidyl	C_6H_5	H	100 ± 18	121 ± 26	3700
22	7	6	4-hydroxypiperidyl	C_6H_5	H	142 ± 92	118 ± 19	6500
23	8	6	4-hydroxypiperidyl	C_6H_5	H	79 ± 14	54 ± 24	8900
24	6	6	pyrrolidyl	C_6H_5	H	84 ± 24	88 ± 24	2300
25	6	6	piperidyl	C_6H_5	H	101 ± 49	54 ± 22	4500
26	6	6	$(CH_2)_6N$	C_6H_5	H	24 ± 3[d]	35 ± 21[d]	2300
27	6	6	(±)-3-hydroxypiperidyl	C_6H_5	H	86 ± 18	77 ± 10	5500
28	6	6	4-methylpiperidyl	C_6H_5	H	25 ± 14	23 ± 22[d]	570
29	6	6	*N*-benzylmethylamino	C_6H_5	H	52 ± 12	75 ± 13	1800
30	6	6	diethylamino	C_6H_5	H	91 ± 19[d]	100 ± 80[d]	3600
31	6	6	morpholino	C_6H_5	H	713 ± 197	237 ± 96	18000
32	6	6	4-(2-hydroxyethyl)piperazinyl	C_6H_5	H	63 ± 15	94 ± 18	8300
33	6	6	4-(2-hydroxyethyl)piperidyl	C_6H_5	H	16 ± 3[d]	68 ± 11[d]	2700
34	6	6	4-(2-pyrimidyl)piperazinyl	C_6H_5	H	1630 ± 460	14200 ± 5700	1300
35	6	6	4-(2-pyridyl)piperazinyl	C_6H_5	H	235 ± 69	928 ± 627	3000
36	6	6	4-(4-chlorophenyl)piperazinyl	C_6H_5	H	80 ± 13	93 ± 47	1300
37	6	6	(2-hydroxyethyl)methylamino	C_6H_5	H	242 ± 77	226 ± 47	4500
38	6	6	(±)-3-carbethoxypiperidyl	C_6H_5	H	155 ± 70	146 ± 72	700
39	6	6	4-carbethoxypiperidyl	C_6H_5	H	164 ± 100	102 ± 47	2800
40	6	6		C_6H_5	H	109 ± 6	53 ± 5	990
41	6	6		C_6H_5	H	1200 ± 330	1900 ± 400	180[e]
42	6	6		C_6H_5	H	49 ± 21	49 ± 31	1300
43	6	6		C_6H_5	H	369 ± 99	347 ± 62	220
44	6	6	4-hydroxypiperidyl	C_6H_5	Me	36 ± 4	43 ± 26[f]	2700[g]
45	6	6	4-hydroxypiperidyl	2-ClC_6H_5	H	47 ± 19	29 ± 10	4100
46	6	6	4-hydroxypiperidyl	2-thienyl	H	119 ± 43	232 ± 98	4000
47	6	6	4-hydroxypiperidyl	3-ClC_6H_5	H	156 ± 10	175 ± 37	6400[e]
48	6	6	4-hydroxypiperidyl	3-FC_6H_5	H	129 ± 29	259 ± 83	11000
49	5	6	4-hydroxypiperidyl	3-$MeOC_6H_5$	H	320 ± 102	327 ± 66	6200
50	6	6	4-hydroxypiperidyl	3-$MeOC_6H_5$	H	76 ± 38	111 ± 57	9500
51	6	6	4-hydroxypiperidyl	3-pyridyl	H	194 ± 115	210 ± 32	3800
52	6	6	4-hydroxypiperidyl	4-ClC_6H_5	H	195 ± 116[d]	164 ± 104	11000
53	6	6	4-hydroxypiperidyl	4-FC_6H_5	H	95 ± 9	132 ± 42	3800
54	5	6	4-hydroxypiperidyl	4-$MeOC_6H_5$	H	493 ± 107	600 ± 221	4200
55	6	6	4-hydroxypiperidyl	4-$MeOC_6H_5$	H	254 ± 203	332 ± 133	3700
56	6	6	4-hydroxypiperidyl	4-pyridyl	H	159 ± 45	308 ± 93	6900

Table I (Continued)

no.	n	Y[a]	R_1	R_2	R_3	DTG[b] IC_{50} (nM)	PPP[b] IC_{50} (nM)	D_2[c] K_i (nM)
57	6	6	4-hydroxypiperidyl	cyclobutyl	H	61 ± 17	50 ± 6	14000[e]
58	6	6	4-hydroxypiperidyl	cyclopentyl	H	51 ± 16	55 ± 34	21000[e]
59	5	6	4-hydroxypiperidyl	cyclohexyl	H	217 ± 54	190 ± 57	12000
60	6	6	4-hydroxypiperidyl	cyclohexyl	H	88 ± 6	46 ± 22	25000
61	6	6	4-hydroxypiperidyl	cyclohexyl	Me	84 ± 28	125 ● 83	4700
62	5	6	4-hydroxypiperidyl	isobutyl	H	139 ± 58	261 ± 52	13000
63	6	6	morpholino	cyclohexyl	H	239 ● 40	95 ± 30	14000[e]
64	6	6	piperidyl	cyclobutyl	H	51 ● 23	34 ± 21	5500
65	6	6	piperidyl	cyclopentyl	H	26 ± 2	38 ± 21	3200
66	6	6	piperidyl	cyclohexyl	H	55 ● 13	32 ● 13	7700
67	6	6	piperidyl	2-ClC_6H_5	H	60 ± 8	63 ± 32	2200
68	6	6	piperidyl	2-thienyl	H	72 ± 33	73 ● 30	1400
69	6	6	piperidyl	3-pyridyl	H	119 ± 44	192 ± 37	2300
70	6	6	piperidyl	4-pyridyl	H	67 ± 2	92 ± 15	1800
71	4	7	4-hydroxypiperidyl	C_6H_5	H	33 ± 3	73 ± 24	1000
72	5	7	4-hydroxypiperidyl	C_6H_5	H	55 ● 27	92 ± 25	5900
73	6	7	4-hydroxypiperidyl	C_6H_5	H	45 ± 17[f]	70 ± 38[f]	6000[d]
74	7	7	4-hydroxypiperidyl	C_6H_5	H	16 ± 3	19 ± 6	4000
75	8	7	4-hydroxypiperidyl	C_6H_5	H	22 ± 2	23 ± 9	2800
76	2	7	dimethylamino	C_6H_5	H	605 ● 331	362 ● 204	13000
77	6	8	4-hydroxypiperidyl	C_6H_5	H	36 ± 5	215 ● 27	940
78	6	6	4-hydroxypiperidyl	C_6H_5	MeO	93 ± 25	106 ● 52	2600
79	6[h]	6	4-hydroxypiperidyl	C_6H_5	Me	99 ± 13	127 ± 45	2700
80	6	6	NH_2	C_6H_5	H	2100 ± 1100	3700 ± 2200	8200

[a] Y = position of attachment side chain. [b] All values are the mean (±SEM) for triplicate determinations unless noted. [d] $N = 4$. [e] $N = 3$. [f] $N = 6$. [g] $N = 7$. [h] Side chain is [6-(4-hydroxypiperidyl)-4(Z)-hexenyl]oxy.

et al.[17] (Scheme IV). Reaction of acetophenone **85** (prepared as in Scheme III) with benzaldehyde using sodium hydroxide in ethanol gave the chalcone **88**, which was treated with hydrogen peroxide to give the flavone **89**. Alkylation of **89** with methyl iodide followed by reaction with 4-hydroxypiperidine gave the desired **78** (method I).

Scheme V shows the synthesis of compound **80**. Alkylation of 6-hydroxyflavone gave the nitrile **91**. Reduction of the nitrile to the primary amine **80** was accomplished using sodium borohydride/cobalt(II) chloride.[18]

Potency of the compounds at the σ binding site was determined in guinea pig brain by competition studies using [^{3}H]DTG or [^{3}H]-(+)-3-PPP, which are known to label pharmacologically distinct σ binding sites.[19] In this study, only two compounds (**9** and **77**; vide infra) demonstrated any selectivity for one ligand versus the other. Affinity for the dopamine D_2 site was determined by competition studies using [^{3}H]sulpiride in rat striatum according to the method of Imafuku.[20]

Results and Discussion

The examination of a number of parameters for compound **21** and its analogues showed some general trends that gave modest increases in potency and/or selectivity and these are discussed below.

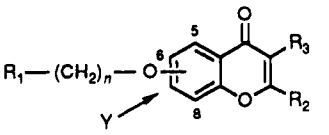
Chain Length. The length of the aminoalkoxy side chain had only modest effect upon potency at the σ binding site although longer chain lengths (n = 6–8) were slightly more potent. With the side chain attached to the 5-position (**4–8**) or the 7-position (**71–75**), a length of $n = 7$ gave the most potent compounds versus [^{3}H]DTG or [^{3}H]-(+)-3-PPP. On the 6-position, $n = 8$ gave the most potent compound when 4-hydroxypiperidine was the amine (**18–23**) and $n = 7$ when dimethylamine (**9–17**) was the amine. The DTG/(+)-3-PPP selectivity of compound **9** was unique in the dimethylamine series. This compound was weak at the DTG σ site (590 nM) but was almost 15 times more potent at the (+)-3-PPP site (40 nM). This does not appear to be simply a function of chain length, since the 7-positional analogue (**76**) failed to discriminate between the two σ ligands. Chain length had no significant effect upon potency at the dopamine D_2 receptor.

Position of Attachment. Of the parameters examined, the position of side-chain attachment was the most critical in terms of σ receptor affinity. The most potent compounds were found when the side chain was attached to the 7-position (**71–75**). These compounds were from 2 to 10-fold more potent than the 6-position analogues (**18–23**) and all exhibited IC_{50}'s < 100 nM. Compound **74** has the highest potency of all the compounds examined versus both [^{3}H]DTG or [^{3}H]-(+)-3-PPP. Attachment of the side chain to carbon 5 (**4–8**) gave increases (relative to the 6-position) in potency at the DTG site but had little effect upon potency at the (+)-3-PPP site. The 8-position analogue of **21** (**77**) exhibited a 6-fold selectivity for the DTG site (36 nM) versus the (+)-3-PPP site (215 nM). Position of attachment had little effect upon potency at the dopamine D_2 receptor.

These results suggest that the 4-position carbonyl is important for binding at the σ site. It is known that the γ-pyrone ring has basic properties and that this basicity has also been observed in flavones.[21,22] Further, it has been reported that flavone will form a crystalline, unstable

(17) Smith, M. A.; Neumann, R. M.; Webb, R. A. A Modification of the Algar-Flynn-Oyamada Preparation of Flavonols. *J. Heterocycl. Chem.* **1968**, *5*, 425–426.
(18) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. Reduction of Organic Compounds with Sodium Borohydride-Transition Metal Salt Systems (1). Reduction of Organic Nitrile, Nitro and Amide Compounds to Primary Amines. *Tetrahedron Lett.* **1969**, 4555–4558.
(19) Karbon, E. W.; Naper, K.; Pontecorvo, M. J. [^{3}H]DTG and [^{3}H](+)-3-PPP Label Pharmacologically Distinct σ Binding Sites in Guinea Pig Brain Membranes. *Eur. J. Pharmacol.* **1991**, *193*, 21–27.
(20) Imafuku, J. The Characterization of [^{3}H]-Sulpiride Binding Sites in Rat Striatal Membranes. *Brain Res.* **1987**, *402*, 331–338.
(21) Gripenberg, J. Flavones. In *The Chemistry of Flavonoid Compounds*; Geissman, T. A., Ed.; MacMillan: New York, 1962; pp 406–440.
(22) Davis, C. T.; Geissman, T. A. Basic Dissociation Constants of Some Substituted Flavones. *J. Am. Chem. Soc.* **1954**, *76*, 3507–3511.

Table II. Physical Properties of (Aminoalkoxy)chromones



no.	M[a]	cryst solv	yield[b]	mp, °C	formula	anal.[c]
4	C, E	ethanol	33	213–215	$C_{23}H_{25}NO_4 \cdot HCl$	C, H, N, Cl
5	C, E	ethanol	32	161–163	$C_{24}H_{27}NO_4 \cdot HCl$	C, H, N, Cl
6	C, E	ethanol	33	184–185	$C_{25}H_{29}NO_4 \cdot HCl$	C, H, N, Cl
7	C, E	ethanol	40	210–211	$C_{26}H_{31}NO_4 \cdot HCl \cdot 0.25H_2O$	C, H, N, Cl
8	D, E	ethanol	35	190–193	$C_{27}H_{33}NO_4 \cdot HCl \cdot 0.25H_2O$	C, H, N, Cl
9	*d*		34	221–223[e]	$C_{19}H_{19}NO_3 \cdot HCl$	C, H, N, Cl
10	A, F	diethyl ether	49	46–48	$C_{20}H_{21}NO_3$	C, H, N
11	A, F	ethanol	26	215–219	$C_{21}H_{23}NO_3 \cdot HCl$	C, H, N, Cl
12	A, F		44	224–226	$C_{22}H_{25}NO_3 \cdot HCl$	C, H, N, Cl
13	A, F		16	182–187	$C_{23}H_{27}NO_3 \cdot HCl$	C, H, N, Cl
14	B, F	ethanol	57	90–91	$C_{24}H_{29}NO_3$	C, H, N
15	B, F	diethyl ether	24	73–75	$C_{25}H_{31}NO_3$	C, H, N
16	B, F	diethyl ether	34	52–53	$C_{26}H_{33}NO_3$	C, H, N
17	B, F	ethanol	18	158–160	$C_{27}H_{35}NO_3 \cdot HCl \cdot 0.75H_2O$	C, H, N, Cl
18	A, E	ethanol	70	117–118	$C_{23}H_{25}NO_4$	C, H, N
19	A, E	ethanol	66	124–125	$C_{24}H_{27}NO_4$	C, H, N
20	A, E	ethanol	73	128–129	$C_{25}H_{29}NO_4$	C, H, N
21	A, E	ethanol	71	208–210	$C_{26}H_{31}NO_4 \cdot HCl$	C, H, N, Cl
22	B, E	ethanol	57	135–136	$C_{27}H_{33}NO_4$	C, H, N
23	B, E	ethyl acetate/hexanes	42	57–58	$C_{28}H_{35}NO_4$	C, H, N
24	A, E		63	179–181	$C_{25}H_{29}NO_3 \cdot HCl$	C, H, N, Cl
25	A, E	diethyl ether	58	167–170	$C_{26}H_{31}NO_3 \cdot HCl$	C, H, N
26	A, E	ethanol	52	173–175	$C_{27}H_{33}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
27	A, E		77	197–202	$C_{26}H_{31}NO_4 \cdot HCl \cdot 0.25H_2O$	C, H, N, Cl
28	A, E		72	209–214	$C_{27}H_{33}NO_3 \cdot HCl$	C, H, N, Cl
29	A, E	diethyl ether	76	178–179	$C_{29}H_{31}NO_3 \cdot HCl$	C, H, N, Cl
30	A, E	ethanol	78	159–161	$C_{25}H_{31}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H, C, Cl
31	A, E	ethanol	52	176–178	$C_{25}H_{29}NO_4 \cdot HCl$	C, H, N
32	A, E	ethanol	60	239–241	$C_{27}H_{34}N_2O_4 \cdot 2HCl \cdot H_2O$	C, H, N, Cl
33	A, E	methanol	76	204–206	$C_{28}H_{35}NO_4 \cdot HCl$	C, H, N, Cl
34	A, E	ethanol	65	218–221	$C_{29}H_{32}N_4O_3 \cdot HCl \cdot H_2O$	C, H, N, Cl
35	A, E	ethanol	65	215–217	$C_{30}H_{33}N_3O_3 \cdot HCl$	C, H, N, Cl
36	A, E	ethanol	73	227–229	$C_{31}H_{33}ClN_2O_3 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
37	A, E	ethanol	27	134–137	$C_{24}H_{29}NO_4 \cdot HCl$	C, H, N, Cl
38	A, E		62	164–165	$C_{29}H_{35}NO_5 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
39	A, E	ethanol	47	88–90	$C_{29}H_{35}NO_5$	C, H, N
40	A, E	ethanol	69	219–222	$C_{32}H_{34}ClNO_4 \cdot HCl$	C, H, N, Cl
41	A, E	2-propanol	59	246–250[e]	$C_{34}H_{37}N_3O_4 \cdot HCl$	C, H, N, Cl
42	A, E	ethyl acetate	42	213–216	$C_{32}H_{32}ClNO_3 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
43	A, E	ethanol	66	225–227	$C_{33}H_{35}N_3O_4 \cdot HCl \cdot H_2O$	C, H, N, Cl
44	E, G	ethanol	45	175–177	$C_{27}H_{33}NO_4 \cdot HCl$	C, H, N, Cl
45	E, G		34	176–177	$C_{26}H_{30}ClNO_4 \cdot HCl$	C, H, N, Cl
46	E, G		37	211–212	$C_{24}H_{29}NSO_4 \cdot HCl$	C, H, N, S, Cl
47	E, G	ethyl acetate/hexanes	41	120–121	$C_{26}H_{30}ClNO_4$	C, H, N, Cl
48	E, G	ethyl acetate	35	136–137	$C_{26}H_{30}FNO_4$	C, H, N
49	E, G	ethyl acetate	51	115–116	$C_{26}H_{31}NO_5$	C, H, N
50	E, G	ethyl acetate	42	119–120	$C_{27}H_{33}NO_5$	C, H, N
51	E, G	2-propanol	33	161–162	$C_{25}H_{30}N_2O_4 \cdot HCl$	C, H, N, Cl
52	E, G	ethyl acetate/hexanes	39	127–128	$C_{26}H_{30}ClNO_4$	C, H, N, Cl
53	E, G	ethyl acetate	26	130–131	$C_{26}H_{30}FNO_4$	C, H, N
54	E, G	ethyl acetate	34	138–139	$C_{26}H_{31}NO_5$	C, H, N
55	E, G	ethyl acetate/hexanes	26	134–135	$C_{27}H_{33}NO_5$	C, H, N
56	E, G	2-propanol	38	165–166	$C_{25}H_{30}N_2O_4 \cdot HCl$	C, H, N, Cl
57	E, G		33	111–113	$C_{24}H_{33}NO_4 \cdot HCl$	C, H, N, Cl
58	E, G	2-propanol	27	125–126	$C_{25}H_{35}NO_4 \cdot HCl \cdot 0.25H_2O$	C, H, N, Cl
59	E, G	ethyl acetate	23	85–86	$C_{25}H_{35}NO_4$	C, H, N
60	E, G		32	155–156	$C_{26}H_{37}NO_4 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
61	E, G		27	109–110	$C_{27}H_{39}NO_4 \cdot HCl$	C, H, N, Cl
62	E, G	ethyl acetate	30	98–99	$C_{23}H_{33}NO_4$	C, H, N
63	E, G		43	167–168	$C_{25}H_{35}NO_4 \cdot HCl$	C, H, N, Cl
64	E, G		45	165–166	$C_{24}H_{34}ClNO_3 \cdot HCl$	C, H, N, Cl
65	E, G		43	138–139	$C_{25}H_{35}NO_3 \cdot HCl$	C, H, N, Cl
66	E, G		46	164–165	$C_{26}H_{37}NO_3 \cdot HCl$	C, H, N, Cl
67	E, G		46	192–193	$C_{26}H_{30}ClNO_3 \cdot HCl \cdot H_2O$	C, H, N, Cl
68	E, G		41	184–185	$C_{24}H_{29}NSO_3 \cdot HCl \cdot 0.25H_2O$	C, H, N, S, Cl
69	E, G	2-propanol	48	192–193	$C_{25}H_{30}N_2O_3 \cdot HCl$	C, H, N, Cl
70	E, G	2-propanol	48	186–187	$C_{25}H_{30}N_2O_3 \cdot HCl$	C, H, N, Cl
71	A, E	ethanol	56	207–209	$C_{24}H_{27}NO_4 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
72	A, E	ethyl acetate	51	94–95	$C_{25}H_{29}NO_4 \cdot H_2O$	C, H, N
73	A, E		68	169–170	$C_{26}H_{31}NO_4 \cdot HCl$	C, H, N, Cl

Table II (Continued)

no.	M[a]	cryst solv	yield[b]	mp, °C	formula	anal.[c]
74	B, E		57	143–144	$C_{27}H_{33}NO_4$·HCl	C, H, N, Cl
75	B, E	ethanol	45	153–154	$C_{28}H_{35}NO_4$·HCl	C, H, N, Cl
76	d	diethyl ether	48	118–119[f]	$C_{19}H_{19}NO_3$	C, H, N
77	A, E	diethyl ether	12		$C_{26}H_{31}NO_4$·HCl	C, H, N, Cl
78	H		10	124–125	$C_{27}H_{33}NO_5$·HCl·0.5H_2O	C, H, N
79	g			83–84	$C_{27}H_{31}NO_4$	C, H, N
80	I	ethanol	40	218–221[e]	$C_{21}H_{23}NO_3$·HCl	C, H, N, Cl[h]

[a] M = method of synthesis (described in text and Experimental Section). [b] Yield is the overall percent yield of analytically pure product from commercially available materials. [c] All analyses were ±0.4% unless noted. [d] Prepared by the general method of ref 32. [e] Compound melted with decomposition. [f] Lit. mp 115–117 °C (ref 32). [g] Prepared as described in ref 33. [h] Cl: calcd, 9.48; found, 8.89.

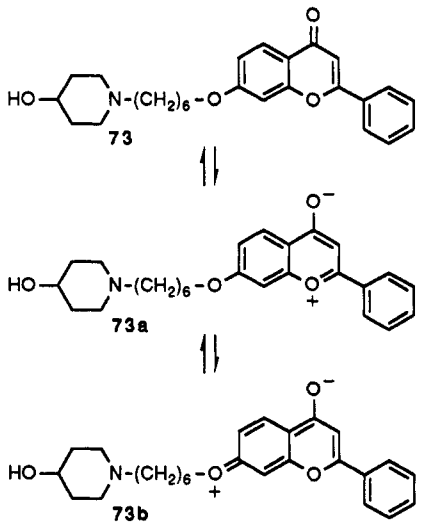


Figure 1.

hydrochloride salt.[23] The addition of the electron-donating alkoxy group to the 7-position of the flavone ring will make the 4-carbonyl group even more basic through the addition of another resonance form as shown for compound **73** in Figure 1. In fact, a dihydrochloride salt of compound **73** was isolated.[24] Attachment of the alkoxy chain to the 5-position would have the same electronic effect as attachment to the 7-position but would introduce some steric hindrance to the 4-carbonyl group. This may explain why the 5-position compounds were more potent than the 6-position analogues but less potent than the 7-position analogues at the σ binding site.

Substitution in 2-Phenyl Ring. Introduction of an ortho chloro group onto the 2-phenyl group of compound **21** (**45**) gave a 2-fold and 4-fold increase at the DTG and (+)-3-PPP sites, respectively. A similar substitution on compound **25** gave a ca. 2-fold increase versus the DTG site but no change at the (+)-3-PPP site. Introduction of a chloro group into the 3- or 4-position of the 2-phenyl group led to a decrease in potency. A 4-fluoro substituent (**21** vs **53**) had no effect upon σ potency, while a 3-fluoro substituent (**21** vs **48**) had no effect versus DTG but caused a small decrease versus (+)-3-PPP. A 4-methoxy substituent (**21** vs **55**; **20** vs **54**) gave a 2.5–3-fold decrease in potency at the σ site while a 3-methoxy substituent had no effect upon potency in one case (**21** vs **50**) and only a small effect in another (**20** vs **49**). At the dopamine D_2 receptor, compounds with 4-methoxy or 4-fluoro substituents showed no change in potency while all other substituents gave 2–3-fold decreases in potency.

Replacement of 2-Phenyl Ring. When the 2-phenyl ring of **21** was replaced with cycloalkyl groups (**57**, **58**, **60**), this led to small increases in potency at the σ site but a 4–6-fold reduction in potency at the dopamine D_2 receptor. The 2-cyclopentyl compound (**58**) with IC_{50}s of 51 and 55 nM versus [^{3}H]DTG and [^{3}H]-3-PPP, respectively, and a K_i of 21 μM at the D_2 receptor was the most selective compound of all those examined in this report. Replacement of the 2-phenyl group with thiophene (**21** vs **46**) or pyridine (**21** vs **51** or **56**) gave a decrease in potency versus [^{3}H]DTG or [^{3}H]-3-PPP. At the dopamine D_2 site, replacement of the 2-phenyl group of **21** with 2-thienyl or 3-pyridyl had no effect upon potency while replacement with 4-pyridyl gave a 2-fold decrease in potency. The same changes on compound **25** gave 2–3-fold increases in D_2 potency.

Amino Group. A variety of amino groups were examined (**13**, **21**, **24–43**, **80**) but no clear conclusion can be reached other than primary amines (**80**) do not bind potently to the σ receptor. The most potent and selective amino groups examined were hexamethylenimine (**26**, 24 nM vs DTG and 35 nM vs (+)-3-PPP) and 4-(2-hydroxyethyl)piperidine (**33**, 16 nM vs DTG and 68 nM vs (+)-3-PPP). Although 4-methylpiperidine (**28**) was also potent at the σ receptor (25 nM vs DTG and 24 nM vs (+)-3-PPP), it gave a 20-fold increase at the dopamine D_2 receptor compared to **21**.

3-Position Substitution. The substitution of a methyl group (**44**) for the 3-position hydrogen of **21** resulted in a 3-fold increase in potency at both the DTG and the (+)-3-PPP site. This change did not result in an increase in potency when it was incorporated on the 2-cyclohexyl compound (**60** vs **61**). The introduction of an MeO group (**78**) to position 3 of **21** had no effect upon potency at the two σ sites or the dopamine D_2 receptor.

It is possible that the increase in potency of **44** relative to **21** may be due to a preference by the σ receptor for a 2-substituent that is not coplanar with the chromone ring system. The placement of a methyl group on the 3-position results in steric interaction with the ortho hydrogens of the 2-phenyl ring. The ring must then rotate out of the plane of the chromone ring to relieve this crowding (Figure 2). Evidence for this rotation is found in the ^{1}H NMR

(23) Blasdale, W. C. The Composition of the Solid Secretion Produced by *Primula Denticulata J. Am. Chem. Soc.* **1945**, *67*, 491.

(24) **73**·2HCl: mp 130–135 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 2 H), 1.54 (m, 2 H), 1.89 (m, 4 H), 2.47 (m, 2 H), 2.92 (m, 2 H), 3.1–3.5 (m, 6 H), 3.58 (m, 0.5 H), 4.08 (t, J = 6.3 Hz, 2 H), 4.23 (s, 0.5 H), 7.08 (s, 1 H), 7.08 (m, 1 H), 7.55 (m, 3 H), 7.95 (m, 2 H), 8.14 (m, 2 H). Anal. Calcd for $C_{26}H_{31}NO_4$·2HCl: C, 63.16; H, 6.73; N, 2.83; Cl, 14.34. Found: C, 62.86; H, 6.72; N, 2.80; Cl, 12.94. The dihydrochloride salt could be manipulated without special precautions; however, it was unstable, and drying of the compound in an abderhalden at high vacuum and 100 °C resulted in the loss of the HCl complexed with the flavone ring to give **73**·HCl: mp 169.5–170.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 2 H), 1.54 (m, 2 H), 1.89 (m, 4 H), 2.47 (m, 2 H), 2.92 (m, 2 H), 3.1–3.5 (m, 6 H), 3.58 (m, 0.5 H), 4.08 (t, J = 6.3 Hz, 2 H), 4.23 (s, 0.5 H), 6.74 (s, 1 H), 6.96 (m, 1 H), 7.55 (m, 3 H), 7.89 (m, 2 H), 8.09 (m, 2 H). Anal. Calcd for $C_{26}H_{31}NO_4$·HCl: C, 68.19; H, 7.04; N, 3.06; Cl, 7.74. Found: C, 67.85; H, 7.20; N, 3.11; Cl, 7.44.

spectra of 21 and 44.[25] The two ortho protons of 21 appear at δ 8.09, indicating that the α,β-unsaturated carbonyl system of the pyrone ring is having an electronic effect upon them—a situation requiring coplanarity. In contrast, the two ortho protons of 44 appear at δ 7.70—a situation indicating the phenyl ring is rotated out of plane with the pyrone ring. The introduction of the 3-MeO may have had no effect upon σ potency since the 2-phenyl group did not rotate out of plane (ortho protons at 8.03).

This may also explain why an ortho chloro substituent (45 and 67 discussed above)[26] in the 2-phenyl group caused an increase in potency at the σ receptor. In both compounds the ortho proton appeared at δ 7.80. Since a chloro group is predicted to have a negligible electronic effect on a proton in a meta relationship to it,[27] the spectra of 45 and 67 can only be explained by rotation of the 2-phenyl ring out of the plane of the pyrone ring.

As mentioned above, most of these compounds have substantial selectivity for the σ receptor versus the dopamine D_2 receptor. In addition, these compounds are also quite selective versus other receptor, second messenger, and ion channel systems when they were tested in the 35 assays of the Profile screening system.[28] For example, when tested at a concentration of 10^{-7} M, compounds 25, 44, and 66 inhibited binding <50% in all of the assays except that for the σ receptor. Compound 21 showed weak activity at the serotonin $5HT_2$ receptor where at 10^{-7} M it gave 56% displacement of the radioligand. Compound 44 (NPC 16377) was selected for further evaluation as an antipsychotic not only because of its potency at the σ receptor and its selectivity for the σ receptor versus the dopamine D_2 receptor and other receptors but also for its ability to reverse amphetamine-induced hyperlocomotion

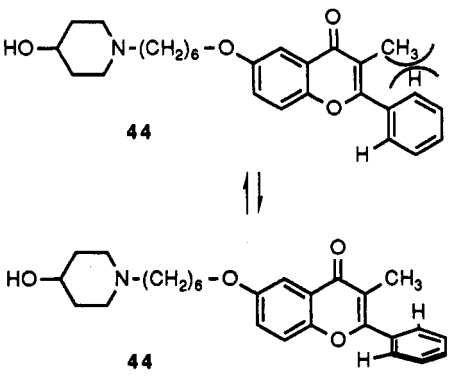


Figure 2.

(ip and po) in mice and its ability to reduce avoidance (ip and po) and increase escape behavior in the conditioned avoidance paradigm.[29,30]

In summary, a series of (aminoalkoxy)chromones has been prepared, members of which bind potently (16–100 nM) at the σ binding site and bind weakly (>1000 nM) at the dopamine D_2 receptor and 33 other receptors, second messenger systems, and ion channels. At the σ receptor, the preferred position of attachment for the aminoalkoxy side chain to the chromone ring followed the rank order: 7-position > 5-position > 6-position. Chromones that contained a 2-substituent that was not coplanar with the chromone ring system showed improved binding over compounds with coplanar substituents. The most potent compound at the sigma site, 7-[[7-(4-hydroxypiperidyl)-heptyl]oxy]-2-phenylchromone (74), had receptor affinities (IC_{50}) of 16 nM at the [^{3}H]DTG site, 19 nM at the [^{3}H]-3-PPP site, and 4000 nM (K_i) at the dopamine D_2 receptor. The most selective compound examined, 6-[[6-(4-hydroxypiperidyl)hexyl]oxy]-2-cyclopentylchromone (58), exhibited IC_{50}s of 51 nM at the [^{3}H]DTG site, 55 nM at the [^{3}H]-3-PPP site, and 21 000 nM (K_i) at the dopamine D_2 receptor. Compound 44 (6-[[6-(4-hydroxypiperidyl)-hexyl]oxy]-3-methylflavone, NPC 16377) was systemically effective (ip and po) in two behavioral models predictive of antipsychotic compounds and systemically active in animal models of ischemia.[30]

Experimental Section

All melting points were obtained on a Bristoline hot-stage microscope or a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Beckman FT 1300 spectrophotometer. NMR spectra were obtained on a General Electric QE300 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. 5-Hydroxyflavone was purchased from Indofine Chemical Co., 6-hydroxyflavone from Penta Manufacturing, and 7-hydroxyflavone from Aldrich Chemical Co. 8-Hydroxyflavone was synthesized by the method of Awad et al.[31]

(25) 21: ^{1}H NMR (DMSO-d_6) δ 1.36 (m, 2 H), 1.47 (m, 2 H), 1.75 (m, 6 H), 1.90–2.10 (m, 2 H), 2.98 (m, 4 H), 3.23 (m, 2 H), 3.63 (br s, 0.5 H), 3.93 (br s, 0.5 H), 4.07 (t, J = 6.5 Hz, 2 H), 5.04 (br s, 0.5 H), 5.12 (br s, 0.5 H), 7.03 (s, 1 H), 7.41 (m, 2 H), 7.61 (m, 3 H), 7.76 (m, 1 H), 8.09 (m, 2 H). 44: ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 2 H), 1.47 (m, 2 H), 1.6–1.8 (m, 6 H), 1.90 (m, 2 H), 2.02 (s, 3 H), 2.8–3.0 (m, 6 H), 3.60 (br s, 0.5 H), 3.90 (br s, 0.5 H), 4.06 (t, J = 6.2 Hz, 3 H), 7.35–7.45 (m, 2 H), 7.58 (m, 4 H), 7.70 (m, 2 H).

(26) 45: ^{1}H NMR (DMSO-d_6) δ 1.34–1.39 (m, 2 H), 1.42–1.48 (m, 2 H), 1.70–1.81 (m, 7 H), 1.89–1.99 (m, 2 H), 2.87–3.12 (m, 4 H), 3.32–3.38 (m, 2 H), 3.59 (m, 1 H), 4.10 (t, J = 6.5 Hz, 2 H), 4.98–5.02 (m, 1 H), 6.62 (s, 1 H), 7.43 (m, 1 H), 7.55–7.71 (m, 5 H), 7.79–7.82 (m, 1 H). 67: ^{1}H NMR (DMSO-d_6) δ 1.35–1.51 (m, 4 H), 1.66–1.81 (m, 10 H), 2.78–2.83 (m, 2 H), 2.95–3.00 (m, 2 H), 3.30–3.41 (m, 3 H), 4.11 (t, J = 6.5 Hz, 2 H), 6.62 (s, 1 H), 7.42–7.46 (m, 1 H), 7.56–7.71 (m, 5 H), 7.79–7.82 (m, 1 H).

(27) Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. In *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: New York, 1983; p H255.

(28) Profile screening is by NovaScreen, a division of Nova Pharmaceutical Corp. and includes the following receptor/second messenger/channel systems (radioligand displaced): adenosine A_1 ([^{3}H]CPX); adenosine S_2 ([^{3}H]NECA); α_1-adrenergic ([^{3}H]Prazosin); α_2-adrenergic ([^{3}H]RX 781094); β-adrenergic ([^{3}H]iodopindolol); (EAA ([^{3}H]glycine); EAA ([^{3}H]AMPA); EAA ([^{3}H]kainic acid); EAA ([^{3}H]CGS 19755); EAA ([^{3}H]TCP); IAA-glycine ([^{3}H]strychnine); IAA-$GABA_A$ ([^{3}H]GABA); IAA-$GABA_B$ ([^{3}H]GABA + isoguvacine); IAA-benzodiaepine ([^{3}H]flunitrazepam); dopamine D_1 ([^{3}H]SCH 23390); dopamine D_2 ([^{3}H]sulpiride); serotonin-1 ([^{3}H]-5HT); serotonin-2 ([^{3}H]-ketanserin); histamine-1 ([^{3}H]pyrilamine); calcium channel ([^{3}H]nitrendipine); calcium channel ([^{3}H]omegaconotoxin); potassium channel ([^{3}H]apamin); chloride channel ([^{3}H]TBOB); muscarinic-1 ([^{3}H]pirenzepine); muscarinic-2 ([^{3}H]QNB); nicotinic ([^{3}H]NMCI); μ-opiate ([^{3}H]DAGO); δ-opiate ([^{3}H]-DADLE); κ-opiate ([^{3}H]U69593); σ receptor ([^{3}H]DTG); leukotriene B_4 ([^{3}H]LTB_4); leukotriene D_4 ([^{3}H]LTD_4); thromboxane A_2 ([^{3}H]SQ 29548); adenylate cyclase ([^{3}H]forskolin); protein kinase C ([^{3}H]PDBU).

(29) Karbon, E. W.; Abreu, M. E.; Erickson, R. H.; Kaiser, C.; Natalie, K.; Clissold, D.; Borosky, S.; Bailey, M.; Martin, L. A.; Pontecorvo, M. J.; Enna, S. J.; Ferkany, J. W. Receptor Binding, Neurochemical and Neuroendocrine Profile of NPC 16377, a Potent and Selective sigma Receptor Ligand. *J. Pharmacol. Exp. Ther.* **1991**, submitted.

(30) Clissold, D.; Pontecorvo, M. J.; Jones, B. E.; Abreu, M. E.; Karbon, E. W.; Erickson, R. H.; Kaiser, C.; Natalie, K.; Borosky, S.; Hartmann, T.; Mansbach, R. S.; Ferkany, J. W.; Enna, S. J. Behavioral and Neuroprotective Properties of NPC 16377, a Potent and Selective sigma Receptor Ligand. *J. Pharmacol. Exp. Ther.* **1991**, submitted.

(31) Awad, W. I.; El-Neweihy, M. F.; Selim, S. F. Studies on 3-Acylcatechols. II. A New Synthesis of 8-Hydroxyflavone. *J. Org. Chem.* **1960**, *25*, 1333–1336.

Method A. Illustrated by the Synthesis of 6-[(6-Chlorohexyl)oxy]flavone. A mixture of 6-hydroxyflavone (8.8 g, 37 mmol), 1-bromo-6-chlorohexane (11 g, 55 mmol), and potassium carbonate (10 g, 74 mmol) was suspended in 225 mL of acetone and refluxed for 16 h. The solvent was removed in vacuo and the residue was stirred with 150 mL of methylene chloride. After filtration, the solvent was removed in vacuo and the residue was triturated with ether (100 mL) and filtered to give 12 g (87%) of 6-[(6-chlorohexyl)oxy]flavone (3), which was used directly in the next step: mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 4 H), 1.83 (m, 4 H), 3.57 (t, J = 6.7 Hz, 2 H), 4.08 (t, J = 6.7 Hz, 2 H), 6.83 (s, 3 H), 7.29 (m, 1 H), 7.55 (m, 5 H), 7.93 (m, 2 H).

Method B. Illustrated by the Synthesis of 6-[(8-Bromooctyl)oxy]flavone. A mixture of 6-hydroxyflavone (5.0 g, 21 mmol), 1,8-dibromooctane (23 g, 84 mmol), and potassium carbonate (12 g, 84 mmol) was suspended in 250 mL of acetone and the mixture was refluxed for 24 h. The reaction was filtered, and the mother liquors were concentrated to ca. 100 mL on a rotary evaporator. After cooling, the product was collected (two crops) by filtration to give 6.7 g (70%) of 6-[(8-bromooctyl)oxy]flavone (3, Y = 6, n = 8, R_2 = Ph, R_3 = H), which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.30–1.60 (m, 8 H), 1.85 (m, 4 H), 3.41 (t, J = 6.5 Hz, 2 H), 4.08 (t, J = 6.5 Hz, 2 H), 6.82 (s, 1 H), 7.29 (dd, J = 3.7, 12.8 Hz, 1 H), 7.54 (m, 5 H), 7.93 (m, 2 H).

Method C. Illustrated by the Synthesis of 5-[(6-Halohexyl)oxy]flavone. 5-Hydroxyflavone (5.24 g, 22 mmol) was dissolved in 100 mL of anhydrous DMF. Then 0.73 g (24 mmol) of sodium hydride (80% oil dispersion) was added. After the evolution of hydrogen ceased, 8.79 g (44 mmol) of 1-bromo-6-chlorohexane was added. The mixture was stirred at 90–100 °C for 16 h. The reaction was cooled to room temperature, 300 mL of water was added, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried over sodium sulfate. The solvent was removed in vacuo to give a solid which was recrystallized from ether to give 4.34 g (50%) of a 50:50 (by ^{1}H NMR) mixture of 5-[(6-chlorohexyl)oxy]flavone and 5-[(6-bromohexyl)oxy]flavone (3, Y = 5, n = 6, R_2 = Ph, R_3 = H), which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2 H), 1.95 (m, 2 H), 3.45 (t, J = 6.8 Hz, $BrCH_2$), 3.57 (t, J = 6.8 Hz, $ClCH_2$), 4.12 (t, J = 6.5 Hz, 2 H), 6.69 (s, 1 H), 6.80 (d, J = 8.3 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 7.52 (m, 4 H), 7.89 (m, 2 H).

Method D. Illustrated by the Synthesis of 5-[(7-Bromoheptyl)oxy]flavone. Sodium hydride (0.14 g of 80% oil dispersion, 4.6 mmol) was added to a solution of 7-hydroxyflavone (1.00 g, 4.2 mmol) in 20 mL of anhydrous DMF at room temperature. After the evolution of hydrogen ceased, a solution of 1,7-dibromoheptane (4.76 g, 18 mmol) in 40 mL of anhydrous DMF was added and the mixture was heated at 110 °C for 16 h. The mixture was cooled to room temperature and 100 mL of water was added. The mixture was extracted with ether (3 × 50 mL) and ethyl acetate (50 mL). The combined organic layers were washed with brine (50 mL) and dried over sodium sulfate. The solvent was removed in vacuo and the residue purified by flash chromatography (silica gel; hexane/ethyl acetate, 70:30) to give 0.75 g (46%) of 5-[(7-bromoheptyl)oxy]flavone, which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.30–1.70 (m, 6 H), 1.80–2.00 (m, 4 H), 3.43 (t, J = 6.7 Hz, 2 H), 4.08 (t, J = 6.7 Hz, 2 H), 6.70 (s, 1 H), 6.81 (d, J = 8.4 Hz, 1 H), 7.15 (d, J = 8.4 Hz, 1 H), 7.52 (m, 4 H), 7.91 (m, 2 H).

Method E. Illustrated by the Synthesis of 6-[[6-[4-(2-Hydroxyethyl)piperidyl]hexyl]oxy]flavone Hydrochloride (33). A mixture of 6-[(6-chlorohexyl)oxy]flavone (method A) (2.00 g, 5.6 mmol), 4-(2-hydroxyethyl)piperidine (1.09 g, 8.4 mmol), sodium iodide (0.92 g, 6.1 mmol), and potassium carbonate (1.16 g, 8.4 mmol) in 10 mL of anhydrous DMF was stirred at 80–90 °C for 24 h. The reaction was cooled to room temperature and water (300 mL) was added to the flask. The resulting precipitate was collected by filtration and dissolved in methylene chloride (350 mL). This solution was washed with water (2 × 150 mL) and brine (2 × 150 mL) and then the solution was dried over sodium sulfate. Removal of the solvent gave 2.32 g of the free base, which was dissolved in hot EtOAc and filtered. Then 1 equiv of a 1 M anhydrous solution of HCl in ether (Aldrich Chemical Co.) was added. The mixture was cooled in the freezer for 1 h and the resulting solid was collected by vacuum filtration and recrystallized from methyl alcohol to give 6-[[6-[4-(2-hydroxyethyl)piperidyl]hexyl]oxy]flavone hydrochloride (33), which was dried over P_2O_5 in high vacuum at 100 °C (yield = 2.29 g, 76%): mp 204–206 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 8 H), 1.76 (m, 7 H), 2.79–2.95 (m, 6 H), 3.41 (m, 2 H), 4.07 (t, J = 6.2 Hz, 2 H), 4.42 (t, J = 4.9 Hz, 1 H), 7.01 (s, 1 H), 7.40 (m, 2 H), 7.59 (d, 3 H), 7.73 (d, 1 H), 8.08 (m, 2 H), 9.92 (br s, 1 H); IR (KBr) 3379, 2939, 2659, 2546, 1627, 1602 cm^{-1}; TLC (EtOAc/MeOH/NEt_3, 40:2:1, silica gel; UV visualization, R_f = 0.17. Anal. Calcd for $C_{28}H_{35}NO_4$·HCl: C, 69.18; H, 7.48; N, 2.88; Cl, 7.29. Found: C, 68.93; H, 7.52; N, 2.84; Cl, 7.20.

Method F. Illustrated by the Synthesis of 6-[[5-(*N*,*N*-dimethylamino)pentyl]oxy]flavone Hydrochloride (12). A mixture of 6-[(5-chloropentyl)oxy]flavone (method A) (2.00 g, 5.8 mmol) and sodium iodide (3.5 g, 23 mmol) in 100 mL of 2-butanone was refluxed for 48 h. The solvent was removed in vacuo and the residue was stirred with 120 mL of methylene chloride and filtered. Removal of the solvent in vacuo from the mother liquors gave 1.85 g (73%) of 6-[(5-iodopentyl)oxy]flavone, which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 2 H), 1.85 (m, 4 H), 3.19 (t, J = 6.6 Hz, 2 H), 4.02 (t, J = 6.6 Hz, 2 H), 6.79 (s, 1 H), 7.25 (m, 2 H), 7.48 (m, 4 H), 7.85 (m, 2 H).

6-[(5-Iodopentyl)oxy]flavone (1.70 g, 3.9 mmol) and dimethylamine (16 mmol, 1.8 g of 40% aqueous solution) were added to 100 mL of EtOH, and the mixture was refluxed for 16 h. The solvent was removed in vacuo and 100 mL of 5% aqueous KOH was added to the residue. This mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with water (2 × 100 mL) and brine (200 mL). After drying over sodium sulfate, the solvent was removed in vacuo to give 1.11 g of the free base. The free base (1.00 g, 2.9 mmol) was dissolved in hot EtOAc and the solution filtered. Then 2.9 mL of a 1.0 M anhydrous solution of HCl in ether (Aldrich Chemical Co.) was added. The mixture was cooled in the freezer for 1 h and the resulting precipitate was collected by vacuum filtration and dried over P_2O_5 in high vacuum at 100 °C to give 0.92 g (60%) of 6-[[5-(*N*,*N*-dimethylamino)pentyl]oxy]flavone hydrochloride (12): mp 224–226 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2 H), 1.86 (m, 2 H), 2.00 (m, 2 H), 2.83 (s, 3 H), 2.85 (s, 3 H), 3.05 (m, 2 H), 4.10 (t, J = 6.1 Hz, 2 H), 7.27 (s, 1 H), 7.40 (dd, J = 9.2, 3.0 Hz, 1 H), 7.57 (m, 5 H), 7.99 (m, 2 H), 12.50 (br s, 1 H); IR (KBr) 3442, 2960, 2867, 2610, 2468, 1730, 1648, 1622 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_3$·HCl: C, 68.12; H, 6.76; N, 3.61; Cl, 9.14. Found: C, 67.98; H, 6.77; N, 3.54; Cl, 9.21.

Method G. Illustrated by the Synthesis of 6-Hydroxy-3-methylflavone. To a solution of 30 g (180 mmol) of 2,5-dihydroxypropiophenone in 180 mL of pyridine under argon was added 44 mL of benzoyl chloride over 5 min. The exothermic reaction brought the solution to near reflux. The hot mixture was stirred for an additional 10 min and then an aliquot was quenched into ether/15% v/v HCl and an examination of the organic layer by TLC (silica gel, 75:25 hexanes/EtOAc) indicated complete reaction. The reaction was stirred for an additional 20 min and then was quenched into a mixture of ether/15% v/v aqueous HCl prechilled to 0–5 °C. An additional 500 mL of ethyl acetate was added to dissolve the product which precipitated during the quench. The organic layer was separated, washed with aqueous Na_2CO_3 (11 g in 250 mL of H_2O), dried over $MgSO_4$, and concentrated in vacuo to give a solid residue which was dissolved in 100 mL of EtOAc at reflux. Hexanes (400 mL) was added to the hot solution, which was cooled to room temperature at which point a precipitate formed. The resulting slurry was cooled to 0–5 °C in an ice water bath and filtered. The filter cake was washed with hexanes (200 mL) and dried overnight under vacuum at 72 °C to provide 62.85 g (93%) of 82 (R_2 = Ph, R_3 = Me): mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3 H), 2.92 (q, J = 7.2 Hz, 2 H), 7.30 (d, J = 8.7 Hz, 1 H), 7.45 (dd, J = 3.0,

(32) Klosa, V. J. Synthese von Aithern des 7-Hydroxyflavon. *J. Prakt. Chem.* **1963**, *22*, 259–266.

(33) Subramanian, V.; Lu, Z.; Erickson, R. H. Synthesis of Tritium Labeled Aminoalkoxychromones, NPC16377 and NPC13839, as Probes of sigma Receptors. *J. Labeled Radiopharm*, submitted.

8.7 Hz, 1 H), 7.54 (m, 4 H), 7.67 (m, 3 H), 8.21 (m, 4 H).

To a suspension of 5.05 g (168 mmol) of sodium hydride (80% dispersion in mineral oil) in 200 mL of anhydrous DMF at 0–5 °C under argon was added a solution of 60.0 g (160 mmol) of dibenzoylpropiophenone (82, R_2 = Ph, R_3 = Me) in 175 mL of anhydrous DMF over 30 min. After 1.5 h at 0–5 °C, the reaction was quenched by the addition of 11 mL of acetic acid. This slurry was diluted with 225 mL of ethyl ether and 50:50 saturated aqueous NaCl/H_2O (500 mL). The layers were separated, and the aqueous layer was extracted with 250 mL of ethyl ether. The combined organic layers were washed with 50:50 saturated aqueous NaCl/H_2O (250 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to a solid residue. The solid was crystallized from 125 mL of refluxing EtOAc under argon by slow addition of 375 mL of hexanes and subsequent cooling to room temperature and then to 0–5 °C. The solid was collected by filtration and dried overnight under high vacuum at 56 °C to provide 41.8 g (70%) of 83 (R_2 = Ph, R_3 = Me) (mp 129–131 °C), which was used directly in the next step.

The diketone 83 (R_2 = Ph, R_3 = Me) (40.0 g) was suspended in 200 mL of acetic acid and 2.0 mL of sulfuric acid. After a 1-h reflux under argon, the reaction was cooled to room temperature, diluted with 400 mL of hexanes, and filtered. The filter cake was washed with hexanes and then dried overnight under vacuum to provide 39.6 g (104%) of 84 (R_2 = Ph, R_3 = Me): mp 122–125 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 7.53 (m, 7 H), 7.67 (m, 3 H), 8.07 (m, 1 H), 8.21 (m, 2 H).

To a slurry of 84 (R_2 = Ph, R_3 = Me) (35 g) in 400 mL of methanol and 100 mL of CH_2Cl_2 cooled to 0–5 °C under argon was added 9.7 g (1.5 equiv) of KOH in 75 mL of methanol. An additional 100 mL of CH_2Cl_2 was then added. After 1 h at 0–5 °C, an additional 0.1 g of KOH in 5 mL of methanol was added. The reaction was quenched after 2 h with acetic acid until the pH reached 7.0 (by pH paper). This mixture was concentrated by heating until the pot temperature reached 65 °C at which point 400 mL of H_2O water was added. Then, the mixture was cooled to 50 °C and then diluted with an additional 200 mL of H_2O. The resulting slurry was cooled to 0–5 °C and filtered. The filter cake was washed with H_2O and then dried overnight under vacuum at 56 °C to afford 20.2 g (80%) of 6-hydroxy-3-methylflavone: mp 208–209 °C; ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3 H), 7.21 (m, 2 H), 7.33 (m, 1 H), 7.52 (m, 4 H), 7.68 (m, 2 H).

Method H. Illustrated by the Synthesis of 6-[(6-Chlorohexyl)oxy]-3-methylflavone. A mixture of 2′,5′-dihydroxypropiophenone (10.0 g, 60 mmol), 1-bromo-6-chlorohexane (12.4 g, 62 mmol), and potassium carbonate (12.4 g, 90 mmol) in 175 mL of 2-butanone was refluxed for 16 h. The solvent was removed in vacuo and the residue was stirred with 200 mL of methylene chloride. After filtration, the filtrate was washed with 10% KOH (100 mL), water (100 mL), and brine (100 mL). The solution was dried over magnesium sulfate and the solvent was removed to give an oil which solidified on standing and was used without further purification: yield, 14.2 g (83%) of 5′-[(6-chlorohexyl)oxy]-2′-hydroxypropiophenone as a yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.52 (m, 4 H), 1.80 (m, 4 H), 3.01 (q, J = 7.2 Hz, 2 H), 3.56 (t, J = 6.6 Hz, 2 H), 3.93 (t, J = 6.3 Hz, 2 H), 6.91 (d, J = 9.0 Hz, 1 H), 7.08 (dd, J = 3.0, 9.0 Hz, 1 H), 7.21 (d, J = 3.0 Hz, 1 H), 11.93 (s, 1 H).

To a solution of 5′-[(6-chlorohexyl)oxy]-2′-hydroxypropiophenone (10.0 g, 35 mmol) in 25 mL of pyridine was added 4.1 mL (35 mmol) of benzoyl chloride. The solution was stirred at 80 °C for 3 h. After cooling to room temperature, the solution was poured into ice-cold 3 M HCl (300 mL) and the mixture was extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with 3 M HCl and dried over $MgSO_4$. Removal of the solvent gave 13.1 g of 86 (n = 6, R_2 = Ph, R_3 = Me) as an oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3 H), 1.51 (m, 4 H), 1.82 (m, 4 H), 2.88 (q, J = 7.2 Hz, 2 H), 3.56 (t, J = 6.7 Hz, 2 H), 4.00 (t, J = 6.4 Hz, 2 H), 7.11 (m, 2 H), 7.30 (d, J = 3.0 Hz, 1 H), 7.52 (m, 2 H), 7.65 (m, 1 H), 8.20 (dd, J = 1.5, 8.7 Hz, 2 H).

A solution of compound 86 (n = 6, R_2 = Ph, R_3 = Me) (13.1 g, 34 mmol) in 40 mL of anhydrous THF was added slowly to a stirred slurry of sodium hydride (1.1 g, 35 mmol) in 60 mL of anhydrous THF. This mixture was warmed to 80 °C where an evolution of gas was observed. The reaction was stirred for an additional 2 h at 80 °C and cooled to room temperature, and the solvent was removed in vacuo. Cold 3 M HCl (200 mL) was added to the residue and the mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulfate. Removal of the solvent in vacuo gave 12.5 g of material, which was dissolved in 30 mL of acetic acid. To this solution was added 1.0 mL of sulfuric acid. This mixture was refluxed for 3 h and then cooled to room temperature. The solution was neutralized with saturated aqueous sodium carbonate and extracted with ethyl acetate (2 × 100 mL). After the combined organic layers were dried over sodium sulfate, the solvent was removed in vacuo to give an oil which was purified by flash chromatography (hexanes/EtOAc, 4:1) to give 4.1 g of 6-[(6-chlorohexyl)oxy]-3-methylflavone as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 4 H), 1.83 (m, 4 H), 2.17 (s, 3 H), 3.56 (t, J = 6.7 Hz, 2 H), 4.08 (t, J = 6.4 Hz, 2 H), 7.21 (dd, J = 3.0, 11.5 Hz, 1 H), 7.38 (d, J = 11.5 Hz, 1 H), 7.53 (m, 3 H), 7.63 (m, 3 H); IR (KBr) 2946, 1630, 1609 cm^{-1}.

Method I. Illustrated by the Synthesis of 6-[[6-(4-Hydroxypiperidyl)hexyl]oxy]-3-methoxyflavone (78). Benzaldehyde (12.4 g, 11.9 mL, 120 mmol) and 5′-[(6-chlorohexyl)oxy]-2′-hydroxyacetophenone (method G) (31.6 g, 120 mmol) were dissolved in 250 mL of 95% EtOH. A solution of 24 g of NaOH in 40 mL of water was added. The deep red solution was stirred briefly with a glass rod and allowed to sit at room temperature for 6 h at which time it had become a gelatinous solid. An additional 1000 mL of 95% EtOH and a solution of 8 g of NaOH in 40 mL of water were added, and the solid was broken up. This mixture was cooled to ca. 17 °C and magnetically stirred. Then 20 mL of a 30% solution of hydrogen peroxide was added in ca. 2-mL portions. (There was still undissolved material.) The solution thickened briefly after each addition and was stirred with a glass rod until the magnetic stirring again became effective. Then the reaction was removed from the ice bath and allowed to warm to room temperature and stirred for 16 h. A yellow precipitate was visible. The solution's pH was adjusted to 3 using hydrochloric acid. The precipitate was collected by vacuum filtration and washed with water (4 × 20 mL), EtOH (3 × 5 mL), and ether (3 × 20 mL) to give 16.1 g (37%) of 6-[(6-chlorohexyl)oxy]-3-hydroxyflavone (89): ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 4 H), 1.67 (m, 4 H), 3.66 (t, J = 6.6 Hz, 2 H), 4.09 (t, J = 6.6 Hz, 2 H), 7.43 (m, 2 H), 7.58 (m, 3 H), 7.73 (d, J = 8.9 Hz, 1 H), 8.21 (d, J = 8.5 Hz, 2 H).

6-[(6-Chlorohexyl)oxy]-3-hydroxyflavone (89) (10.0 g, 27 mmol) was dissolved in 100 mL of anhydrous THF. Then 800 mg of an 80% oil dispersion of NaH (27 mmol) was added. After the evolution of hydrogen had ceased, 8.3 mL (134 mmol) of methyl iodide was added and the reaction was stirred under argon at room temperature for 48 h. Then the reaction was poured into 400 mL of water. The solution was extracted by EtOAc (3 × 150 mL), and the combined organic layers were washed with water (3 × 100 mL) and brine (100 mL). After drying over sodium sulfate, the solvent was removed in vacuo to give a solid which was recrystallized from EtOAc to give 7.5 g (72%) of 6-[(6-chlorohexyl)oxy]-3-methoxyflavone, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 4 H), 1.64 (m, 4 H), 3.68 (t, J = 6.6 Hz, 2 H), 3.91 (s, 3 H), 4.12 (t, J = 6.6 Hz, 2 H), 7.42 (m, 2 H), 7.4–7.6 (m, 4 H), 8.21 (m, 2 H).

6-[(6-Chlorohexyl)oxy]-3-methoxyflavone (3.4 g, 8.9 mmol), sodium iodide (1.3 g, 18 mmol), potassium carbonate (2.9 g, 21 mmol), and 4-hydroxypiperidine (1.8 g, 18 mmol) were added to 50 mL of 2-butanone, and the mixture was refluxed for 96 h. The solvent was removed in vacuo and the residue was stirred with EtOAc (150 mL). This solution was washed with water (2 × 30 mL) and brine (30 mL). After drying over sodium sulfate, the solvent was removed in vacuo to give an oil which was purified by flash chromatography (silica gel; EtOAc/MeOH/NEt_3, 40:2:1) to give the free base (2.0 g). The free base was dissolved in hot EtOAc and the solution filtered. Then 1 equiv of a 1.0 M anhydrous solution of HCl in ether (Aldrich Chemical Co.) was added. The solution was cooled in the freezer and the resulting precipitate was collected by vacuum filtration and dried over P_2O_5 in high vacuum at 100 °C to give 1.9 g (43%) of 6-[[6-(4-hydroxypiperidyl)hexyl]oxy]-3-methoxyflavone hydrochloride (78): mp 124–125 °C; ^{1}H NMR (DMSO-d_6) δ 1.32–1.36 (m, 3 H), 1.43–1.46 (m, 3 H), 1.66–1.87 (m, 6 H), 2.93–2.97 (m, 5 H), 3.25–3.31

(m, 2 H), 3.79 (s, 3 H), 4.05-4.07 (t, J = 6.5 Hz, 2 H), 4.97-5.02 (d, 1 H), 7.37-7.43 (m, 2 H), 7.56-7.57 (m, 3 H), 7.68-7.71 (d, J = 9 Hz, 1 H), 8.01-8.04 (m, 2 H), 10.01 (s, 1 H); IR (KBr) 3400, 2940, 1620 cm^{-1}. Anal. Calcd for $C_{27}H_{33}NO_5$·HCl·0.5H_2O: C, 65.25; H, 7.09; N, 2.81. Found: C, 65.20; H, 7.02; N, 2.81.

Method J. Illustrated by the Synthesis of 6-[(6-Aminohexyl)oxy]flavone (80). A mixture of 6-hydroxyflavone (5.00 g, 21 mmol), 6-bromocapronitrile (7.7 g, 44 mmol), and potassium carbonate (12 g, 88 mmol) in 200 mL of acetone was refluxed for 16 h. The reaction was cooled to room temperature and filtered. The mother liquors were concentrated in vacuo to give an off-white solid which was triturated with 25 mL of ether and filtered to give 6.32 g (90%) of 6-[(5-cyanopentyl)oxy]flavone (91), which was pure by ^{1}H NMR: ($CDCl_3$) δ 1.70 (m, 2 H), 1.75 (m, 2 H), 1.88 (m, 2 H), 2.41 (t, J = 6.7 Hz, 2 H), 4.09 (t, J = 6.2 Hz, 2 H), 6.82 (s, 1 H), 7.30 (m, 1 H), 7.54 (m, 5 H), 7.92 (m, 2 H).

6-[(5-Cyanopentyl)oxy]flavone (1.73 g, 4.4 mmol) and cobalt(II) chloride hexahydrate (2.09 g, 8.8 mmol) were dissolved in 50 mL of EtOH. Sodium borohydride (0.84 g, 22 mmol) was added in portions over 5 min at room temperature. The addition was accompanied by the evolution of gas and the solution turned black. After stirring at room temperature for 1 h, TLC (silica gel; ether; UV visualization) indicated complete reaction. The reaction was poured into 100 mL of 3 N HCl and the resulting solution was stirred at room temperature for 1.5 h. The solution was filtered and concentrated in vacuo to ca. 100 mL. Then ammonium hydroxide was added to adjust the pH to 8. A yellow precipitate was collected by filtration and dried to give 1.03 g (2.6 mmol) of the amine. The amine was dissolved in 300 mL of EtOH and 2.6 mL of a 1 M anhydrous solution of HCl in ether was added. The solution was concentrated in vacuo to ca. 150 mL and cooled in the freezer. The resulting orange precipitate was collected by vacuum filtration to give 0.72 g (44%) of 6-[(6-aminohexyl)-oxy]flavone hydrochloride (80): mp 218-221 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.43 (m, 4 H), 1.58 (m, 2 H), 1.76 (m, 2 H), 2.77 (m, 2 H), 4.08 (t, J = 6.4 Hz, 2 H), 7.00 (s, 1 H), 7.43 (m, 2 H), 7.60 (m, 3 H), 7.75 (m, 1 H), 7.8 (br, 2 H), 8.09 (m, 2 H); IR (KBr) 3428, 2934, 2875, 1630 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_3$·HCl: C, 67.46; H, 6.47; N, 3.75; Cl, 9.48. Found: C, 67.09; H, 6.67; N, 3.50; Cl, 8.89.

Substitution on the Phe^3 Aromatic Ring in Cyclic δ Opioid Receptor-Selective Dermorphin/Deltorphin Tetrapeptide Analogues: Electronic and Lipophilic Requirements for Receptor Affinity†

Deborah L. Heyl and Henry I. Mosberg*

College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109. *Received October 7, 1991*

In an effort to explore structural features affecting receptor recognition in a series of conformationally restricted tetrapeptides related to the cyclic, δ opioid receptor-selective analogue, Tyr-D-Cys-Phe-D-PenOH, electronic, lipophilic, and steric effects at the Phe^3 residue were assessed by substitution at different positions of the side-chain aromatic ring by halogens, alkyl, hydroxyl, and nitro groups. Effects on opioid receptor binding affinity and selectivity were determined. The results, which are generally consistent with reports of analogous modifications in linear and cyclic pentapeptide enkephalins, indicate that steric, lipophilic, and electronic properties are all important determinants of δ opioid receptor recognition. Specifically, modifications which increase lipophilicity or exert electron-withdrawing effects on the aromatic ring enhance binding affinity, while hydrophilic, bulky, or electron-releasing modifications are detrimental. These observations are in excellent agreement with quantitative structure-activity relationship (QSAR) results reported for Phe^4 modifications in linear opioid pentapeptide enkephalin analogues, suggesting that the Phe^3 tetrapeptide side chain and the Phe^4 pentapeptide side chain interact with the same δ receptor binding subsite.

Introduction

While convincing in vivo and in vitro pharmacological evidence of opioid receptor heterogeneity has long been available[1-4] and the existence of at least μ, δ, and κ classes of opioid receptors is widely accepted, the elucidation of the specific structural and conformational requirements for ligand interaction with these different receptor types remains elusive. Since it is conceivable that the μ, δ, and κ receptor types may mediate different pharmacological events, such knowledge may lead to the eventual design of selective enkephalin analogues or other analgesic compounds which exhibit desired pharmacological actions, yet are devoid of negative side effects. In our efforts to uncover both the structural and conformational features required of the ligand for δ and μ receptor recognition and to develop potent ligands with high selectivity for a single receptor type, we have employed the approach of designing enkephalin analogues into which conformational restrictions have been incorporated. Since this reduces the number of spatial orientations a large molecule may assume, peptide analogues designed with the appropriate conformational constraints may display selectivity resulting from the ability to adopt the required binding conforma-

* Author to whom correspondence should be addressed.

† Abbreviations recommended by IUPAC-IUB Commission of Biochemical Nomenclature have been used. Other abbreviations: ACN, acetonitrile; N^α-Boc, N^α-*tert*-butyloxycarbonyl; COSY, correlation spectroscopy; DAMGO, Tyr-D-Ala-Gly-*N*-MePhe-Gly-ol; DCC, dicyclohexylcarbodiimide; DMF, dimethylformamide; DPDPE, Tyr-D-Pen-Gly-Phe-D-PenOH; DPM, disintegrations per minute; FAB-MS, fast atom bombardment mass spectrometry; HOAc, acetic acid; HOBt, 1-hydroxybenzotriazole; metkephamide, Tyr-D-Ala-Gly-Phe-*N*-MeMetNH$_2$; NMR, nuclear magnetic resonance; NOE, nuclear Overhauser effect; NOESY, nuclear Overhauser effect spectroscopy; RP-HPLC, reverse-phase high performance liquid chromatography; TFA, trifluoroacetic acid; TLC, thin-layer chromatography; TSP, 3-(trimethylsilyl)-propionic acid; Tris, tris(hydroxymethyl)aminomethane; U69,593, 5α,7α,8β-(-)-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide.

(1) Portoghese, P. S. A New Concept on the Model of Interaction of Narcotic Analgesics with Receptors. *J. Med. Chem.* **1965**, *8*, 609-616.
(2) Martin, W. R. Opioid Antagonists. *Pharmacol. Rev.* **1967**, *19*, 463-521.
(3) Gilbert, P. E.; Martin, W. R. The Effects of Morphine and Nalorphine-Like Drugs in the Nondependent, Morphine-Dependent, and Cyclazocine-Dependent Chronic Spinal Dog. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 66-82.
(4) Lord, J. A. H.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W. Endogenous Opioid Peptides: Multiple Agonists and Receptors. *Nature* **1977**, *267*, 495-499.

0022-2623/92/1835-1535$03.00/0