Conformationally Restricted Analogues of Remoxipride as Potential Antipsychotic Agents

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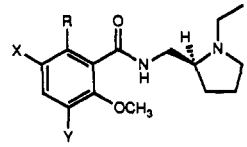
Several conformationally restricted derivatives of (*S*)-3-bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2,6-dimethoxybenzamide (remoxipride) were synthesized and evaluated *in vitro* for their ability to inhibit [^{3}H]raclopride binding at the dopamine D-2 receptor. The cyclic benzamides designed to mimic the intramolecular hydrogen bonding of desmethylremoxipride (**4**, FLA-797) included 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones, 2,3-dihydro-4*H*-1,3-benzthiazin-4-ones, phthalimides, 1-isoindolinones, 1,2-benzisothiazol-3(2*H*)-ones, and 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides. In this series, enhanced affinities to the dopamine D-2 receptor were not observed. The phthalimidine analogue **24b** ((*S*)-6-chloro-2-(1-ethylpyrrolidinyl)-1-isoindolinone) exhibited the highest affinity to the dopamine D-2 receptor with an IC_{50} of 1.3 μM, which was equipotent to remoxipride.

Introduction

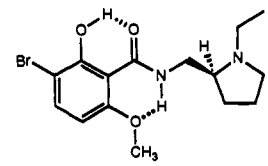
Schizophrenia is an often incapacitating mental disorder characterized by delusions, hallucinations, thought disorders, motoric symptoms, social withdrawal, apathy, and emotional withdrawal that affects an estimated 1.5–2 million Americans.[1,2] The causes of schizophrenia are unknown, and whether or not it is a discrete mental disorder remains controversial. Although no functional or structural changes in the brain have been unequivocally associated with the disease, it is generally accepted that the disorder is associated with hyperactivity of dopaminergic neurotransmission. Two dopamine receptors have been identified and characterized functionally: D-1 and D-2.[3] This classification is based on receptor binding studies and on the presence or absence of a positive coupling between the receptor and adenylate cyclase activity. Activation of the D-1 receptor is associated with stimulation of adenylate cyclase, while the D-2 receptor mediates dopaminergic effects that do not involve stimulation of this enzyme.[4] The distinct functions of the D-1 and D-2 receptors are not well defined; however, a strong correlation has been shown to exist between D-2 antagonism and antipsychotic activity.[5-7]

Researchers at Astra Lakemedel AB published a series of papers that reported the development of selective D-2 antagonists for the treatment of schizophrenia.[8-14] These compounds are 2-methoxybenzamides that contain an ethylpyrrolidine side chain and are exemplified by sulpiride (**1**), remoxipride (**2**), and eticlopride (**3**). Initial studies

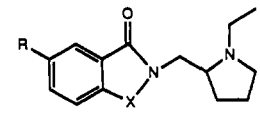


1: R = H; X = SO_2NH_2; Y = H (sulpiride)
2: R = OMe; X = Br; Y = H (remoxipride)
3: R = OH; X = Et; Y = Cl (eticlopride)

reporting the biological activities of remoxipride were particularly interesting.[9] It was found that the potent *in vivo* antagonism of apomorphine-induced hyperactivity by remoxipride was not accompanied by a corresponding affinity for the D-2 binding site *in vitro*. It was demonstrated that the enhanced *in vivo* activity could be attributed to the formation of an active metabolite, 5-bromo-6-methoxysalicyl amide **4**, which was an extremely potent inhibitor of [^{3}H]spiperone binding at the D-2 receptors *in vitro*.



4 (FLA-797)



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It was postulated that the high *in vitro* potency of desmethylremoxipride was due to the presence of a planar arrangement between the amide carbonyl and the aromatic ring. This planarity arises from intramolecular hydrogen bonding interactions as illustrated in structure **4**. In remoxipride, the presence of the methoxy groups in both ortho positions forces the amide group out of the plane and prevents this planar arrangement.

Working with this hypothesis, we investigated the use of conformationally restricted benzamides that contain a covalent connection between the amide nitrogen and the ortho position of the aromatic ring as illustrated with structure **5**. We postulated that the covalent bond would lock the amide into a planar arrangement relative to the aromatic ring and create compounds that contain a bicyclic ring system similar to the virtual ring formed by the hydrogen bonding in compound **4**. The synthesis and biological evaluation of these conformationally restricted analogues is discussed herein.[15]

Chemistry

For our investigation six different, constrained benzamide ring systems of general structure **5** were prepared: 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones (X = OCH_2), 2,3-dihydro-4*H*-1,3-benzthiazin-4-ones (X = SCH_2), phthalimides (X = (C=O)), 1-isoindolinones (X = CH_2), 1,2-benzisothiazol-3(2*H*)-ones (X = S), and 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides (X = SO_2) (Table I). The general route for the preparation of benzoxazinones **12** and **13** and benzthiazinone **14** is outlined in Scheme I. Salicyl and thiosalicyl amides **9-11** were prepared by heating the

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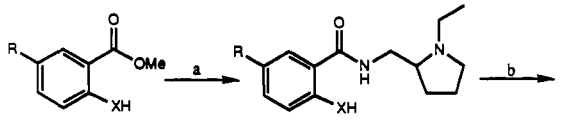
Table I. Dopamine D-2 Receptor Binding Affinities of Conformationally Restricted Benzamides 5 and Known 2-Methoxybenzamide Standards

compd no.[a]	X	R	absolute configuration	D-2 receptor binding[b,c] % inhibition at 10^{-5} M or (IC_{50} in μM)
12	OCH_2	H	R,S	26
13a	OCH_2	Br	R,S	9
13b	OCH_2	Br	S	67
14	SCH_2	H	R,S	26
22	CH_2	H	R,S	4
23	CH_2	Br	R,S	44
24a	CH_2	Cl	R,S	27
24b	CH_2	Cl	S	(1.3)
25	C=O	H	R,S	24
26	C=O	Br	S	1
33a	S	H	R,S	18
33b	S	H	S	37
34	S	Cl	S	70
35a	SO_2	H	R,S	0
35b	SO_2	H	S	0
1 (sulpiride)			S	(0.21)[d]
2a			R,S	62
2b (remoxipride)			S	(1.57)[d]
3 (eticlopride)			S	(0.00092)[d]
4 (FLA-797)			S	(0.012)[e]

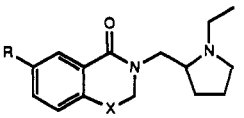
[a] a = racemic, b = (S)-isomer. [b] [^{3}H]Raclopride binding. [c] The parenthetical values are IC_{50} in μM. [d] Reference 9, [^{3}H]spiperone binding. [e] Reference 12, [^{3}H]spiperone binding.

Scheme I[a]



6: X = O; R = H
7: X = O; R = Br
8: X = S; R = H

9: X = O; R = H
10: X = O; R = Br
11: X = S; R = H

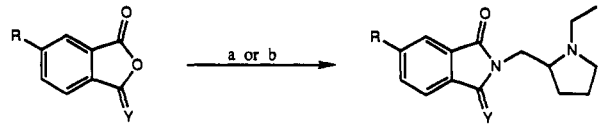


12: X = O; R = H
13: X = O; R = Br
14: X = S; R = H
15: X = O; R = CH_2Cl

[a] Reagents: (a) 2-(aminomethyl)-1-ethylpyrrolidine, 120–150 °C; (b) 1,3,5-trioxane, CH_2Cl_2 or $CHCl_3$, HOAc, HCl(g), 0 °C to room temperature.

corresponding methyl salicylates and methyl thiosalicylates 6-8 with either racemic 2-(aminomethyl)-1-ethylpyrrolidine or its (S)-enantiomer at 120–140 °C. The (S)-enantiomer of 2-(aminomethyl)-1-ethylpyrrolidine was obtained by fractional recrystallization of its ditartrate salt of D-(−)-tartaric acid, according to the method of Bulteau.[16] A number of methods were investigated to introduce the methylene bridge to form benzoxazinones 12 and 13. Although there are several reports of the synthesis of 2-substituted 1,3-benzoxazin-4-ones in the literature,[17,18] there are few examples of the preparation of the corresponding nonsubstituted analogues.[19] The reported cyclizations typically involve the acid-catalyzed condensations of salicylamides with aromatic or aliphatic aldehydes and ketones. When formaldehyde was used as the bridging aldehyde, however, polymerization[17,18] or general lack of reactivity was observed.[20] In our case, modification of the procedure reported by Finkelstein and Chiang provided the best results.[19] The salicyl or thiosalicyl amides were treated with 1,3,5-trioxane in anhydrous chloroform or dichloromethane and acetic acid. The mixture was cooled, and anhydrous hydrochloric acid was bubbled through to saturate the solution. The crude products were purified by flash chromatography to provide compounds 12-14. With unsubstituted salicyl amide 12, an interesting side product was identified as compound 15 (R = CH_2Cl). We postulate that this compound arises from an electrophilic addition of 12 to formaldehyde, followed by displacement of the resulting alcohol with chloride ion.

Scheme II[a]



Y = H, H
16: R = H } c
17: R = NO_2 } d
18: R = NH_2 } e
19: R = X

Y = O
20: R = H } f,g
21: R = Br

Y = H, H
22: R = H
23: R = Br
24: R = Cl

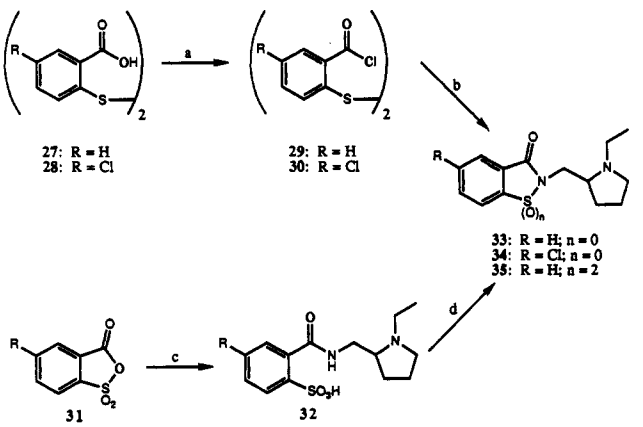
Y = O
25: R = H
26: R = Br

[a] Reagents: (a) 2-(aminomethyl)-1-ethylpyrrolidine, 205–215 °C; (b) 2-(aminomethyl)-1-ethylpyrrolidine, pyridine, reflux; (c) HNO_3, H_2SO_4, HOAc, room temperature; (d) $SnCl_2 \cdot 2H_2O$, $NaBH_4$, EtOAc, t-BuOH; (e) $NaNO_2$, HX, Cu_nX_n, H_2O; (f) Br_2, NaOH, H_2O, 90 °C; (g) $SOCl_2$, reflux.

The synthetic routes employed for the preparation of 1-isoindolines 22-24 and phthalimides 25 and 26 are outlined in Scheme II. Isoindolines 22-24 were prepared by condensing the appropriately substituted 1(3H)-isobenzofuranones with 2-(aminomethyl)-1-ethylpyrrolidine at 205–215 °C. The reaction equilibrium was shifted toward product formation by the removal of water through a Dean–Stark trap. The requisite 6-halo-1(3H)-isobenzofuranones were prepared by Sandmeyer reactions of the corresponding 6-amino derivative, which in turn was obtained by the reduction of 6-nitro-1(3H)-isobenzofuranone.[21] Phthalimides 25 and 26 were prepared in a similar manner by treatment of phthalic anhydrides 20 and 21, respectively, with 2-(amino)-1-ethylpyrrolidine in refluxing pyridine. Bromination of phthalic anhydride 20 in aqueous sodium hydroxide followed by dehydration of the resulting 5-bromophthalic acid monosodium salt with thionyl chloride provided 5-bromophthalic anhydride 21.

The general synthetic routes for the preparation of 1,2-benzisothiazol-3(2H)-ones 33-34 and saccharin derivative 35 are outlined in Scheme III. Dithiosalicylic acids 27 and 28 were treated with thionyl chloride and dimethylformamide in refluxing toluene to provide the corresponding 2,2′-dithiobisbenzoyl chlorides 29 and 30, respectively. The acid chlorides were converted to target compounds 33 and 34 by cleaving the disulfide bond with chlorine gas in dichloromethane and reacting the resulting dichlorides with 2-(aminomethyl)ethylpyrrolidine. The starting material, substituted 2,2′-dithiosalicylic acid 28, was obtained by the method of Katz et al.[22] Diazotization of commercially available 5-chloroanthranilic acid followed by treatment of the diazonium salt with potassium ethyl xanthate provided the corresponding xanthate intermediate. This intermediate was decomposed, and the resulting thiosalicylic acid was allowed to dimerize. Condensation of 2-(aminomethyl)-1-ethylpyrrolidine with o-sulfobenzoic acid anhydride provided o-sulfonic amide 32 in 97% yield. Dehydration of this intermediate with

Scheme III[a]



[a] Reagents: (a) $SOCl_2$, toluene, DMF, 75–80 °C; (b) $Cl_2(g)$, CH_2Cl_2, Et_3N, 2-(aminomethyl)-1-ethylpyrrolidine; (c) 2-(aminomethyl)-1-ethylpyrrolidine, benzene, 95 °C; (d) $SOCl_2$, PCl_5, reflux.

phosphorus pentachloride and thionyl chloride afforded 1,2-benzisothazol-3(2*H*)-one 1,1-dioxide **35**.

Results and Discussion

The conformationally constrained derivatives of the 2-methoxybenzamide antipsychotics prepared in this study were evaluated by their ability to inhibit [^{3}H]raclopride binding at the D-2 dopamine receptor *in vitro*. The pharmacological results of these cyclic benzamides are summarized in Table I. The letters **a** and **b** following the compound number denote the racemate and the (*S*)-isomer of the compound, respectively. Receptor binding affinities of known standards are included for comparison.

Remoxipride exhibits a moderate affinity for the dopamine D-2 receptor *in vitro* with an IC_{50} of 1.57 μM. The potency is increased 2 orders of magnitude for the corresponding 2-desmethyl metabolite in which intramolecular hydrogen bonding allows the aromatic ring and amide carbonyl to be coplanar (**4**; FLA-797 (IC_{50} = 0.012 μM)). Attempts to force this coplanarity and mimic the intramolecular hydrogen bonds found in FLA-797 by covalently constraining the amide provided compounds with reduced affinities for the D-2 receptor. For example, locking the amide into a six-membered ring while retaining the ortho oxygen yielded benzoxazinones (**12**, **13a,b**) that where appreciably less active than remoxipride. Removal of the ring oxygen increased affinity to the D-2 receptor to provide the most potent compound in our series, isoindolinone **24b**, which had an IC_{50} of 1.3 μM. This derivative is approximately equipotent to remoxipride.

As in the case of remoxipride, an increase in affinity to the receptor was observed when the ethylpyrrolidine side chain possessed the (*S*)-configuration as compared to the corresponding racemic compounds (**13b**, **24b**, and **33b** vs **13a**, **24a**, and **33a**, respectively). This increase in activity, however, was not observed in the benzisothiazolone 1,1-dioxide series, **35a** and **35b**. The effects of substitution of bromine or chlorine in the position meta to the carbonyl were inconsistent within the series. In the isoindolinone and benzisothiazolone series, an increase in binding was observed (**22** vs **23** and **33b** vs **34**, respectively), while analogous substitutions in the benzoxazinone and phthalimide series were detrimental to activity (**12** vs **13a** and **25** vs **26**, respectively).

The lack of activity in this series may be due to unfavorable conformations of these constrained derivatives. The conformation of each cyclic benzamide in our study was examined with molecular modeling techniques. Each benzamide ring system was created and minimized in MacroModel employing the MM2 force field. The minimized ring systems were superimposed on the X-ray crystal structure of eticlopride (obtained from the Cambridge Data Base), and conformational differences were observed. The results indicated that these conformationally restricted derivatives may not adequately mimic the hydrogen bonding system found in the 2-methoxy-6-hydroxybenzamides. For example, while the amide carbonyl of the benzoxazinone system overlapped well with eticlopride, the longer C–S bond in the benzthiazinone system distorted the ring and pushed the carbonyl out of a planar arrangement. The benzisothiazole, isoindolinone, and phthalimide systems were planar; however, the carbonyl groups in these 5-membered rings were at different angles with respect to the aromatic ring system relative to eticlopride. Another possible explanation for the lack of activity is suggested from the initial SAR studies with remoxipride.[11] In these studies it was found that alkylation of the amide nitrogen was detrimental to activity. This observation is consistent with the results for our cyclic benzamides. A critical interaction therefore may be lost upon alkylation of the amide nitrogen to form the covalent linkages of compound **5**.

Summary

A number of conformationally restricted derivatives of (*S*)-3-bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2,6-dimethoxybenzamide (remoxipride) were prepared. In general the restraints imposed resulted in a significant decrease in the ability of these analogues to inhibit [^{3}H]-raclopride binding at the D-2 receptor. Of the cyclic benzamides studied, isoindolinone **24b** maintained the highest affinity to the dopamine D-2 receptor with an IC_{50} comparable to remoxipride. We postulate that the decrease in activity of these analogues may be due to unfavorable conformations of the locked amides or the loss of a critical receptor interaction upon cyclization to form the tertiary amides.

Experimental Section

General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dichloromethane (CH_2Cl_2), pyridine, and dimethylformamide (DMF) were obtained from Aldrich Chemical Co. in Sure/Seal bottles. Triethylamine (TEA) was distilled from CaH_2 prior to use. Flash chromatography was performed using EM Science silica gel 60 (230–400-mesh ASTM). Thin-layer chromatography (TLC) was performed with Analtech silica gel GF TLC plates (250 mm). ^{1}H NMR and ^{13}C NMR were determined with superconducting FT-NMR spectrometers operating at 200 and 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in hertz. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. The letters **a** and **b** following the compound number denote the racemate and the (*S*)-isomer of the compound, respectively.

5-Bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2-hydroxybenzamide Fumarate (10a). To a 100-mL round-bottomed flask were added methyl 5-bromosalicylate (24.5 g, 0.106 mol) and 2-(aminomethyl)-1-ethylpyrrolidine (20.4 g, 0.159 mol, 1.5 equiv). The reaction mixture was placed under N_2 and heated in an oil bath at 120 °C with stirring for 2 h. The solution was

allowed to cool to room temperature, and the MeOH was removed with a rotary evaporator to give 44.5 g of a viscous orange oil. A portion of this crude material (8.98 g, 27.5 mmol) was taken up in acetone, and fumaric acid (3.20 g, 27.5 mmol, 1.0 equiv) was added. The solution was heated briefly on a steam bath to dissolve the fumaric acid. The resulting orange mixture was cooled in an ice–water bath, and ether was added that induced sticky solids to come out of solution. The solvent was decanted, and the remaining crude salt was triturated in hot EtOH. The mixture was allowed to cool, and the solids were filtered, washed with cold EtOH, and dried in a vacuum oven to give 6.52 g of a light orange-tan powder. This material was recrystallized from 95% EtOH to give 4.92 g of **10a** as an off-white powder. The fumarate of the remaining crude free base was prepared in the same manner to give an additional 20.71 g (55% total) of **10a**. Mp: 177–178.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 (t, 3, J = 7.2), 1.75 (m, 3), 2.00 (m, 1), 2.76 (m, 2), 3.07–3.65 (m, 5), 6.53 (s, 2), 6.90 (d, 1, J = 8.8), 7.48 (dd, 1, J = 8.8, 2.6), 8.00 (d, 1, J = 2.6), 9.48 (br s, 1), 11.20 (br s, 3). ^{13}C NMR (DMSO-d_6): δ 11.45, 21.94, 27.60, 40.26, 48.41, 52.79, 64.15, 109.23, 118.14, 119.82, 130.80, 134.73, 135.72, 158.86, 167.16, 167.42. Anal. ($C_{14}H_{19}N_2O_2Br\cdot C_4H_4O_4$) C, H, N.

(*S*)-5-Bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2-hydroxybenzamide Fumarate (10b). This material was prepared according to the method described for **10a**. From methyl 5-bromosalicylate (8.35 g, 0.036 mol) and (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[16] (5.10 g, 0.040 mol, 1.1 equiv) was obtained 7.43 g (46%) of **10b** as white crystals. $[\alpha]^{20}_D$: −5.8° (c = 1.02, DMF). Mp: 155–157 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 (t, 3, J = 7.2), 1.76 (m, 3), 1.99 (m, 1), 2.70 (m, 2), 3.15 (m, 2), 3.35 (m, 1), 3.71 (m, 2), 6.54 (s, 2), 6.90 (d, 1, J = 8.8), 7.49 (dd, 1, J = 8.8, 2.5), 8.01 (d, 1, J = 2.5), 9.40 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 11.72, 21.97, 27.72, 40.37, 48.36, 52.84, 63.95, 109.30, 118.13, 119.79, 130.78, 134.66, 135.74, 158.76, 167.10, 167.27. Anal. ($C_{14}H_{19}N_2O_2Br\cdot C_4H_4O_4$) C, H, N.

***N*-((1-Ethyl-2-pyrrolidinyl)methyl)-2-mercaptobenzamide (11).** To a 100-mL round-bottomed flask were added methyl thiosalicylate (20.0 g, 0.119 mol) and 2-(aminomethyl)-1-ethylpyrrolidine (22.9 g, 0.178 mol, 1.5 equiv). The light orange solution was placed under N_2 and allowed to heat at reflux for 18 h. The MeOH and excess 2-(aminomethyl)-1-ethylpyrrolidine were removed by bulb-to-bulb distillation under reduced pressure (0.2–0.5 mm). A small quantity of crystals that formed in the distillation pot upon standing at room temperature was removed. The remaining residue was dissolved in MeOH and cooled in a freezer. Crystallization was induced by adding a small amount of the seed crystals. The resulting precipitate was filtered, washed with EtOAc, and dried in a vacuum oven to give 4.47 g of a light yellow powder. An analytically pure sample was obtained by recrystallizing this material twice from acetonitrile to give 1.08 g (3%) of **11** as an off-white powder. The solvent was removed from the recrystallization filtrates by rotary evaporation to give an additional 24.4 g (81% total) of the title compound. Mp: 145–146 °C. ^{1}H NMR ($CDCl_3$): δ 1.10 (t, 3, J = 7.2), 1.73 (m, 3), 2.25 (m, 2), 1.92 (m, 1), 2.68 (m, 1), 3.18 (m,1), 3.30 (m, 1), 3.71 (dd, 1, J = 7.7, 2.4), 3.78 (dd, 1, J = 7.5, 2.4), 6.75 (m, 1), 7.29 (m, 2), 7.52 (m, 1), 7.77 (dd, 1, J = 8.0, 1.1). ^{13}C NMR ($CDCl_3$): δ 13.80, 22.96, 28.20, 40.77, 48.26, 53.55, 62.52, 126.01, 126.93, 127.34, 131.14, 133.87, 168.06. Anal. ($C_{14}H_{20}N_2OS$) C, H, N.

2,3-Dihydro-3-((1-ethyl-2-pyrrolidinyl)methyl)-4*H*-1,3-benzoxazin-4-one (12). To a 100-mL round-bottomed flask were added methyl salicylate (25.0 g, 0.164 mol) and 2-(aminomethyl)-1-ethylpyrrolidine (31.6 g, 0.246 mol, 1.5 equiv). The light orange solution was heated at reflux for 2 h. The reaction mixture was transferred to a 250-mL round-bottomed flask with the aid of toluene. The majority of toluene and excess amine were removed with a rotary evaporator. The crude material was purified by bulb-to-bulb distillation under reduced pressure at 100–140 °C (0.50–0.35 mm), to give 49.0 g (>100%) of **9** as a viscous oil. A portion (14.7 g, 0.059 mol) of this orange oil was dissolved in $CHCl_3$ (100 mL). Acetic acid (15 mL) and 1,3,5-trioxane (5.33 g, 0.059 mol, 1.0 equiv) were added to the stirring solution. The reaction mixture was cooled in an ice–water bath, and HCl(g) was bubbled through the solution for 0.75 h. The cold bath was removed, the flask was stoppered, and the reaction mixture was allowed to stir at room temperature for 5 h. The solution was cooled in an ice–water bath, and saturated aqueous K_2CO_3 was slowly added to quench the reaction. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 18.8 g of a dark orange viscous oil. This crude material was purified by flash chromatography with EtOAc–0.1% TEA as eluant to give 5.0 g of the title compound contaminated with 6-(chloromethyl)-3-((1-ethyl-2-pyrrolidinyl)-methyl)-2,3-dihydro-4*H*-1,3-benzoxazin-4-one (**15**). A portion (1.69 g) of this mixture was dissolved in acetonitrile (10 mL), and diethylamine (1 mL) was added. The solution was warmed on a steam bath for 0.25 h and allowed to stir at room temperature overnight. The acetonitrile and excess diethylamine were removed by a rotary evaporator to give 1.62 g of a viscous orange oil. The remainder of the material was reacted in a similar manner, and the products were combined. The crude material was purified by flash chromatography with EtOAc–0.1% TEA as eluant to give 3.12 g (24% based on **6**) of **12** as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.10 (t, 3, J = 7.2), 1.73 (m, 3), 1.89 (m, 1), 2.04–2.38 (m, 2), 2.68–2.96 (m, 2), 3.13 (m, 1), 3.31 (dd, 1, J = 14.0, 5.3), 3.83 (dd, 1, J = 14.0, 4.3), 5.22 (d, 1, J = 8.5), 5.35 (d, 1, J = 8.5), 6.95 (dd, 1, J = 8.2, 0.64), 7.10 (dt, 1, J = 7.7, 1.0), 7.42 (ddd, 1, J = 8.2, 7.4, 1.7), 7.95 (dd, 1, J = 7.8, 1.7). ^{13}C NMR ($CDCl_3$): δ 14.12, 23.22, 28.47, 48.02, 49.13, 53.60, 63.42, 79.55, 116.22, 119.10, 122.46, 128.39, 133.79, 157.89, 162.44. Anal. ($C_{15}H_{20}N_2O_2$) C, H, N.

6-Bromo-3-((1-ethyl-2-pyrrolidinyl)methyl)-2,3-dihydro-4*H*-1,3-benzoxazin-4-one Fumarate (13a). Chloroform (60 mL), acetic acid (10 mL), and 1,3,5-trioxane (2.84 g, 0.032 mol, 1.0 equiv) were added to hydroxybenzamide **10a** (10.3 g, 0.032 mol). The resulting light orange solution was cooled in an ice–water bath, and anhydrous HCl(g) was bubbled through the solution for 0.5 h. The flask was stoppered, the cold bath was removed, and the reaction mixture was allowed to stir at room temperature for 20 h. Additional portions of 1,3,5-trioxane (2.84 g) and acetic acid (5.0 mL) were added, and stirring was continued for 2 h. The solution was cooled in an ice–water bath, and the reaction was quenched by the slow addition of saturated aqueous K_2CO_3. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The organic extracts were combined, dried over $MgSO_4$, filtered, and reduced in volume to give 11.7 g of an orange oil. This crude material was purified by flash chromatography on silica gel with EtOAc–0.1% TEA as eluant to give 3.47 g of the free base. This oil was dissolved in acetone, and fumaric acid (1.19 g, 0.010 mol, 1.0 equiv) was added. The solution was heated and filtered hot. Ether was added until the solution became cloudy. Upon cooling, the salt came out of solution as a sticky oil. The solvent was decanted, the residual oil was dissolved in hot EtOH, and ether was added until the solution became cloudy. The solids that formed upon cooling were filtered, washed with ether, and dried in a vacuum oven to give 2.58 g (18%) of **13a** as tan plates. Mp: 151–153 °C. ^{1}H NMR (DMSO-d_6): δ 1.06 (t, 3, J = 7.2), 1.52–1.91 (m, 4), 2.38 (m, 2), 2.94 (m, 2), 3.17 (m, 1), 3.43 (dd, 1, J = 14.0, 6.2), 3.68 (dd, 1, J = 14.0, 4.5), 5.36 (dd, 2, J = 12.4, 8.7), 6.56 (s, 2), 7.05 (d, 1, J = 8.6), 7.68 (dd, 1, J = 8.6, 2.5), 7.84 (d, 1, J = 2.5). ^{13}C NMR (DMSO-d_6): δ 12.44, 22.09, 27.81, 45.84, 48.15, 52.69, 62.99, 78.82, 113.95, 118.98, 120.41, 129.81, 134.41, 136.64, 156.74, 160.48, 166.79. Anal. ($C_{15}H_{19}N_2O_2Br\cdot C_4H_4O_4$) C, H, N.

(*S*)-6-Bromo-3-((1-ethyl-2-pyrrolidinyl)methyl)-2,3-dihydro-4*H*-1,3-benzoxazin-4-one Fumarate Hydrate (13b). This compound was prepared according to the method described for compound **13a**. From hydroxybenzamide **10b** (3.89 g, 0.119 mol), acetic acid (4 mL), and 1,3,5-trioxane (1.07 g, 0.119 mol, 1.0 equiv) in $CHCl_3$ (25 mL) was obtained 4.45 g of a crude orange oil. The crude material was purified by flash chromatography on silica gel with 2:1 EtOAc–hexanes with 0.1% TEA as eluant to give 1.63 g of **13b** as its free base. This material was dissolved in acetone, and fumaric acid (0.56 g, 48 mmol, 1.0 equiv) was added. The solution was heated, and small amounts of EtOH were added until the solids dissolved. The mixture was filtered hot. The solids that formed upon cooling were filtered, washed with cold acetone, and dried in a vacuum oven to give 1.78 g (32%) of **13b** as white crystals. Mp: 145–148 °C. $[\alpha]^{20}_D$: −31.43° (c = 1.05, DMF). ^{1}H NMR (DMSO-d_6): δ 1.10 (t, 3, J = 7.2), 1.69 (m, 3), 1.92 (m, 1), 2.55 (m, 2), 3.06 (m, 2), 3.28 (dt, 1, J = 10.0, 5.3), 3.53 (dd, 1, J = 14.0, 6.8), 3.73 (dd, 1, J = 14.0, 4.7), 5.37 (s, 2), 6.54

(s, 2), 7.05 (d, 1, J = 8.7), 7.67 (dd, 1, J = 8.7, 2.5), 7.72 (br s, 2), 7.84 (d, 1, J = 2.5). ^{13}C NMR (DMSO-d_6): δ 12.13, 21.98, 27.82, 45.59, 48.15, 52.63, 63.10, 78.79, 113.98, 118.99, 120.37, 129.82, 134.54, 136.67, 156.75, 160.55, 167.04. Anal. ($C_{15}H_{19}N_2O_2$-Br·$C_4H_4O_4$·0.75 H_2O) C, H, N, H_2O.

3-((1-Ethyl-2-pyrrolidinyl)methyl)-2,3-dihydro-4*H*-1,3-benzothiazin-4-one Fumarate (14). This material was prepared according to the method as described for compound **13a**. Crude mercaptobenzamide 11 (24.4 g, 0.092 mol) was treated with 1,3,5-trioxane (8.32 g, 0.092 mol, 1.0 equiv), acetic acid (15 mL), and anhydrous HCl(g) in $CHCl_3$ (90 mL). The crude product was purified by flash chromatography on silica gel with EtOAc–0.05% TEA as eluant to give 2.06 g of a side product, 2-((1-ethyl-2-pyrrolidinyl)methyl)-1,2-benzisothiazole-3(2*H*)-one (**33a**), as a light oil and 3.79 g of the target compound, **14**, as its free base. Benzisothiazinone **14** was dissolved in ether, and fumaric acid (1.57 g, 13.5 mmol, 1.0 equiv) was added. The mixture was heated, and EtOH was slowly added until all of the solids were dissolved. The solids that formed upon cooling were filtered, washed with cold ether, and dried in a vacuum oven to give 3.48 g (8.4%) of **14** as an off-white powder. Mp: 134–136 °C. ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 3, J = 7.2), 1.78 (m, 3), 2.02 (m, 1), 2.70 (m, 2), 3.23 (m, 2), 3.39 (m, 1), 3.69 (dd, 1, J = 13.8, 7.4), 3.83 (dd, 1, J = 13.8, 4.8), 4.86 (d, 1, J = 12.9), 4.91 (d, 1, J = 12.9), 6.58 (s, 3), 7.32 (dt, 1, J = 7.8, 1.6), 7.45 (m, 2), 7.96 (dd, 1, J = 7.9, 1.1), 11.45 (br s, 2). ^{13}C NMR (DMSO-d_6): δ 11.72, 21.82, 28.08, 48.27, 48.88, 52.64, 63.26, 125.89, 127.18, 128.88, 130.04, 131.81, 134.47, 137.22, 163.45, 166.88. Anal. ($C_{15}H_{20}N_2$-OS·1.5$C_4H_4O_4$) C, H, N.

6-Amino-1-(3*H*)-isobenzofuranone (18). To a 1-L round-bottomed flask were added 6-nitro-1(3*H*)-isobenzofuranone[21] (20.0 g, 0.112 mol), $SnCl_2$·$2H_2O$ (125 g, 0.558 mol, 5.0 equiv), and 400 mL of a 9:1 solution of EtOAc and tert-butyl alcohol. The reaction mixture was heated at 60–78 °C for 1 h. Sodium borohydride (2.11 g, 0.558 mol, 0.5 equiv) was slowly added via a solid addition funnel to the 60 °C solution, which produced an evolution of gas. The reaction mixture was allowed to heat at 60–75 °C for an additional 1 h following the addition of the sodium borohydride. The solution was allowed to cool to room temperature and concentrated to half its volume with a rotary evaporator. The resulting creamy white solution was poured into cold distilled water (300 mL) with stirring. The pH was slowly adjusted to 7–8 (pH paper) by the addition of cold, saturated aqueous K_2CO_3. The mixture was extracted with EtOAc (5 × 250 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 16.0 g of **18** as a light yellow powder. This material was used without further purification. ^{1}H NMR ($CDCl_3$): δ 3.94 (br s, 2), 5.21 (s, 2), 6.97 (dd, 1, J = 8.2, 2.3), 7.13 (d, 1, J = 2.3), 7.23 (d, 1, J = 8.2).

5-Bromo-1,3-isobenzofurandione (21). To a 1-L round-bottomed flask were added sodium hydroxide (54.0 g, 1.35 mol) and distilled water (450 mL). Phthalic anhydride (100 g, 0.675 mol) was added to the aqueous sodium hydroxide solution with stirring. Bromine (112 g, 0.700 mol) was added via an addition funnel over a 0.5-h period, and the resulting solution was heated at 90 °C for 6 h. As the reaction proceeded, a yellow precipitate formed. The solution was allowed to cool to room temperature and cooled further in a refrigerator. The light yellow solids were filtered and washed with cold water. The crude material was purified by recrystallization twice from hot water to provide 60.0 g (33%) of the monosodium 4-bromophthalic acid salt as an off-white solid. A portion of this salt (30.0 g, 0.112 mol) was placed in a 250-mL round-bottomed flask, and thionyl chloride (60.0 mL) was added in portions. The mixture was placed under N_2 and heated at reflux for 2.5 h. As the mixture was heated, it became a homogeneous light yellow solution. The reflux condenser was replaced with a distillation head, and the excess thionyl chloride was removed by distillation under aspirator pressure. As the thionyl chloride was removed, the pot residue became clear and it solidified. The solids were triturated with hot EtOAc and filtered hot. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from EtOAc to give 3.56 g of **21** as white crystals. An additional 18.8 g (88% total from monosodium 4-bromophthalic acid) was obtained as a second crop. Mp: 106–108 °C. ^{1}H NMR ($CDCl_3$): δ 7.88 (dd, 1, J = 8.1, 0.6), 8.04 (dd, 1, J = 8.1, 1.6), 8.15 (dd, 1, J = 1.6, 0.6). ^{13}C NMR ($CDCl_3$): δ 126.85, 128.89, 129.79, 131.47, 132.89, 139.29, 161.34, 161.84. Anal. ($C_8H_3O_3Br$) C, H.

2-((1-Ethyl-2-pyrrolidinyl)methyl)-1-isoindolinone Hydrochloride (22). To a 50-mL round-bottomed flask were added phthalide (10.0 g, 74.6 mmol) and 2-(aminomethyl)-1-ethylpyrrolidine (9.56 g, 74.6 mmol, 1.0 equiv). The resulting slurry was placed under N_2 and heated at 205 °C for 20 h. Water was collected in a Dean–Stark trap. An additional portion of the amine (0.95 g, 7.4 mmol, 0.1 equiv) was added, and heating was continued for 6 h. Another portion of the amine was added (0.95 g, 7.4 mmol, 0.1 equiv), and heating was continued for an additional 16 h. The crude oil was purified by flash chromatography on silica gel with EtOAc as eluant to give 10.7 g (59%) of the free amine as a light orange oil. A portion of this material (7.95 g) was dissolved in EtOAc, and HCl (1.0 equiv of a 1 N solution in ether) was added. The crude hydrochloride salt was recrystallized from EtOH to give 2.33 g of **22** as an off-white powder. An additional 1.80 g (45% total) of **12** was obtained as a second crop. Mp: 173–175 °C. ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 1, J = 7.2), 1.88 (m, 3), 2.15 (m, 1), 3.07 (m, 2), 3.37 (m, 1), 3.55 (sextet, 1, J = 5.7), 4.00 (m, 2), 4.53 (d, 1, J = 17.6), 4.67 (d, 1, J = 17.6), 7.50 (m, 1), 7.60 (d, 2, J = 3.8), 7.69 (d, 1, J = 7.4), 11.15 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 10.17, 21.28, 28.16, 42.40, 48.25, 50.57, 52.48, 64.49, 122.81, 123.38, 127.84, 131.51, 131.59, 142.14, 168.15. Anal. ($C_{15}H_{20}N_2O$·HCl) C, H, N.

6-Bromo-2-((1-ethyl-2-pyrrolidinyl)methyl)-1-isoindolinone Hydrochloride (23). To a 250-mL round-bottomed flask equipped with a Dean–Stark trap and a reflux condenser were added 6-bromo-1(3*H*)-isobenzofuranone[21] (**19**, X = Br; 7.83 g, 36.7 mmol) and 2-(aminomethyl)-1-ethylpyrrolidine (9.42 g, 73.5 mmol, 2.0 equiv). The solution was placed under N_2 and heated at 205–215 °C for 22 h. The crude dark orange oil was purified by flash chromatography with EtOAc–0.1% TEA as eluant to give 9.78 g (82%) of the free base as an orange oil. A portion of this material (6.24 g) was dissolve in EtOAc and treated with HCl (19.3 mL of a 1 N solution in ether). The crude hydrochloride salt was recrystallized from EtOH to give 2.82 g of an off-white powder. This material was recrystallized from acetonitrile to provide 1.76 g (56% based on recovered starting material) of **23** as white crystals. Mp: 191–192 °C. ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 3, J = 7.2), 1.89 (m, 3), 2.14 (m, 1), 3.07 (m, 2), 3.34 (m, 1), 3.55 (m, 1), 3.74 (m, 1), 3.97 (m, 2), 4.61 (d, 1, J = 18.0), 4.65 (d, 1, J = 18.0), 7.59 (d, 1, J = 8.8), 7.79 (dd, 2, J = 7.2, 1.8), 11.05 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 10.17, 21.24, 28.13, 42.46, 48.25, 50.48, 52.49, 64.42, 120.94, 125.43, 125.72, 133.84, 134.28, 141.27, 166.76. Anal. ($C_{15}H_{18}N_2OBr$·HCl) C, H, N.

6-Chloro-2-((1-ethyl-2-pyrrolidinyl)methyl)-1-isoindolinone Hydrochloride (24a). This compound was obtained from 6-chloro-1(3*H*)-isobenzofuranone[21] (**19**, X = Cl) and 2-(aminomethyl)-1-ethylpyrrolidine by an analogous method to that described for compound **23**. Mp: 167–169 °C. ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 3, J = 7.2), 1.84 (m, 3), 2.12 (m, 1), 3.06 (m, 2), 3.37 (m, 1), 3.58 (m, 1), 3.74 (m, 1), 4.00 (m, 2), 4.53 (d, 1, J = 17.9), 4.67 (d, 1, J = 17.9), 7.66 (m, 3), 11.08 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 10.19, 21.25, 28.14, 42.45, 48.24, 50.41, 52.47, 64.40, 122.41, 125.41, 131.52, 132.76, 133.54, 140.87, 166.87. Anal. ($C_{15}H_{19}N_2OCl$·HCl) C, H, N.

(*S*)-6-Chloro-2-((1-ethyl-2-pyrrolidinyl)methyl)-1-isoindolinone Hydrochloride (24b). This compound was obtained from 6-chloro-1(3*H*)-isobenzofuranone[21] (**19**, X = Cl; 2.05 g, 14.8 mmol) and (*S*)-2-(aminomethyl)-1-ethylpyrrolidine (2.85 g, 22.2 mmol, 1.5 equiv) by an analogous method to that described for compound **23**. The title compound was obtained as a tan powder [1.72 g (37%)]. Mp: 158–161 °C. ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 3, J = 7.2), 1.90 (m, 3), 2.14 (m, 1), 3.06 (m, 2), 3.36 (m, 1), 3.57 (m, 1), 3.74 (m, 1), 3.98 (m, 2), 4.53 (d, 1, J = 17.9), 4.67 (d, 1, J = 17.9), 7.67 (m, 3), 10.97 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 10.21, 21.24, 28.14, 42.45, 48.24, 50.41, 52.47, 64.40, 122.41, 125.41, 131.52, 132.76, 133.54, 140.87, 166.87. Anal. ($C_{15}H_{19}N_2OCl$·HCl) C, H, N.

***N*-((1-Ethyl-2-pyrrolidinyl)methyl)phthalimide Hydrochloride (25).** Phthalic anhydride (2.53 g, 17.1 mmol), 2-(aminomethyl)-1-ethylpyrrolidine (1.99 g, 15.5 mol), pyridinium *p*-toluenesulfonate (4.29 g , 17.1 mmol), and anhydrous dimethylformamide were placed in a round-bottomed flask under N_2 and heated at reflux overnight. The solution was concentrated

in vacuo, and the residue was dissolved in CH_2Cl_2. The solution was washed with saturated aqueous K_2CO_3 followed by saturated NaCl. The organic layers were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator. The crude material was purified by flash chromatography with a gradient eluant (2:1, 1:1, 0:1 hexanes–EtOAc) to give 6.1 g (76%) of phthalimide **25** as its free base. This material was dissolved in EtOAc, and HCl (23.6 mL, 1.0 equiv of a 1 N solution in ether) was added. The hydrochloride salt was recrystallized from 95% EtOH to give 4.51 g (56%) of **25** as off-white crystals after drying in a vacuum oven. Mp: 259–263 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (t, 3, J = 7.2), 1.87 (m, 3), 2.13 (m, 1), 3.08 (m, 2), 3.53 (m, 3), 4.01 (m, 2), 7.98 (m, 4), 10.94 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 10.15, 20.69, 28.00, 36.77, 47.73, 52.38, 64.29, 123.16, 131.62, 134.45, 167.92. Anal. ($C_{15}H_{18}N_2O_2$·HCl) C, H, N.

(*S*)-4-Bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)phthalimide Hydrochloride (26). To a 100-mL round-bottomed flask were added 5-bromo-1,3-isobenzofurandione (**21**, 2.50 g, 11.0 mmol), (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[16] (1.48 g, 11.5 mmol, 1.05 equiv), and anhydrous pyridine (30.0 mL). The light orange reaction mixture was placed under N_2 and heated at reflux for 18 h. The resulting dark orange solution was allowed to cool to room temperature, and the pyridine was removed with a rotary evaporator. The residue was taken up in CH_2Cl_2 and washed with saturated aqueous K_2CO_3. The organic extract was dried over $MgSO_4$, filtered, and concentrated to give 3.30 g of an orange oil. This crude material was adsorbed onto silica gel and purified by flash chromatography with 9:1 CH_2Cl_2–MeOH with 0.1% TEA as eluant to provide 1.46 g of a viscous orange oil. This free amine was dissolved in EtOAc, and HCl (4.30 mL, 1.0 equiv of a 1 N solution in ether) was added. EtOH (95%) was added to the hydrochloride solution, and the solution was heated and filtered hot. The solids that formed upon cooling were filtered, washed with ether and dried in a vacuum oven to give 0.98 g (24%) of **26** as an off-white powder. Mp: 258–260 °C. $[\alpha]^{20}_D$: −19.3° (c = 0.26, EtOH). ^{1}H NMR (DMSO-d_6): δ 1.32 (t, 3, J = 7.2), 1.78 (m, 1), 1.91 (q, 2, J = 7.1), 2.16 (sextet, 1, J = 3.8), 3.09 (m, 2), 3.58 (m, 3), 4.03 (m, 2), 7.84 (d, 1, J = 7.9), 8.06 (dd, 1, J = 7.9, 1.5), 8.11 (d, 1, J = 1.5), 10.84 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 10.24, 20.67, 27.98, 36.86, 47.76, 52.43, 64.38, 125.07, 126.10, 128.03, 130.70, 133.77, 137.14, 166.78, 167.33. Anal. ($C_{15}H_{17}N_2O_2Br$·HCl) C, H, N.

2-((1-Ethyl-2-pyrrolidinyl)methyl)-1,2-benzisothiazol-3(2*H*)-one Fumarate (33a). The title compound (2.06 g, 7.85 mmol), obtained as a side product in the preparation of benzisothiazinone **14**, was dissolved in acetone, and fumaric acid (0.91 g, 7.85 mmol, 1.0 equiv) was added. The mixture was heated, EtOH was added to dissolve the solids, and the solution was filtered hot. The solids that formed upon cooling were filtered, washed with cold EtOH and ether, and dried in a vacuum oven to give **33a** as a light yellow solid. Mp: 114–115 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 (t, 3, J = 7.2), 1.64 (m, 3), 1.88 (m, 1), 2.40 (m, 2), 3.00 (m, 2), 3.20 (m, 1), 3.68 (dd, 1, J = 14.4, 5.1), 4.17 (dd, 1, J = 14.4, 3.8), 6.58 (s, 2), 7.40 (dt, 1, J = 7.9, 1.0), 7.65 (dt, 1, J = 7.1, 1.3), 7.85 (dd, 1, J = 8.5, 1.3), 7.93 (dd, 1, J = 8.1, 0.84), 9.85 (br s, 2). ^{13}C NMR (DMSO-d_6): δ 13.02, 22.49, 27.36, 45.04, 47.93, 52.70, 62.60, 121.48, 123.48, 125.19, 125.47, 131.71, 134.21, 141.97, 165.14, 166.40. Anal. ($C_{14}H_{18}NB_2OS$·$C_4H_4O_4$) C, H, N.

(*S*)-2-(1-Ethyl-2-pyrrolidinyl)-1,2-benzisothiazol-3(2*H*)-one (33b). To a 250-mL beaker equipped with a magnetic stirring bar were added 2,2′-dithiobis(benzoyl chloride)[23] (**29**, 20.0 g, 58.3 mmol) and CH_2Cl_2 (50 mL). Chlorine gas was bubbled through the mixture until the solution became clear orange. The solution was slowly poured into a mixture of (*S*)-2-(aminomethyl)-1-ethylpyrrolidine (8.22 g, 64.1 mmol, 1.1 equiv), CH_2Cl_2 (50 mL) and TEA (11.8 g, 116.5 mmol, 2.0 equiv). The reaction mixture bubbled and smoke was evolved upon this addition. Saturated aqueous K_2CO_3 was added to the dark orange solution, and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 24.3 g of a dark orange, viscous oil. This material was purified by flash chromatography with 1:1 CH_2Cl_2–EtOAc as eluant to give 9.36 g (56%) of **33b** as an orange oil. An analytically pure sample was obtained by further purification of a portion (4.49 g) of this material by flash chromatography on silica gel with 1:1 CH_2Cl_2–EtOAc as eluant to give 3.25 g of a light orange oil. This material crystallized upon standing and was recrystallized from ether to give 1.25 g of **33b** as a green-yellow solid. Mp: 60.5–82 °C. $[\alpha]^{20}_D$: −40.4° (c = 0.5, EtOH). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3, J = 7.2), 1.67 (m, 3), 1.69 (m, 1), 2.21 (m, 1), 2.35 (m, 1), 2.84 (m, 1), 2.94 (m, 1), 3.20 (ddd, 1, J = 9.1, 4.5, 4.5), 3.56 (dd, 1, J = 14.0, 4.7), 4.33 (dd, 1, J = 14.0, 3.4), 7.35 (dt, 1, J = 7.9, 1.0), 7.55 (m ,2), 8.02 (d, 1, J = 7.9). ^{13}C NMR ($CDCl_3$): δ 13.98, 23.35, 28.04, 46.56, 48.74, 53.36, 62.74, 119.96, 124.23, 125.01, 126.44, 131.50, 142.47, 166.28. Anal. ($C_{14}H_{18}N_2OS$) C, H, N.

(*S*)-5-Chloro-2-((2*S*)-1-ethyl-2-pyrrolidinyl)-1,2-benzisothiazol-3(2*H*)-one (34). To a 1-L round-bottomed flask were added 5-chloro-2,2′-dithiosalicylic acid[22] (**28**, 21.2 g, 56.5 mmol), toluene (100 mL), dimethylformamide (0.5 mL), and thionyl chloride (8.25 mL, 13.4 g, 11.3 mmol, 2.2 equiv). The reaction mixture was heated under N_2 at 65–70 °C for 20 h. The solution was cooled with an ice–water bath, and the solids were filtered and washed with cold petroleum ether. Additional amounts of solid precipitated out of solution in the filtrate. These solids were filtered and combined with the first crop to give a total of 10.7 g of 5-chloro-2,2′-dithio(bisbenzoyl) chloride **30** (46%) as a light brown solid. This crude acid chloride was placed in a 100-mL round-bottomed flask with CH_2Cl_2 (50 mL). Chlorine gas was bubbled through the light brown slurry. A solution of CH_2Cl_2 (50 mL) and (*S*)-2-(aminomethyl)-1-ethylpyrrolidine (7.32 g, 57.1 mol, 2.2 equiv) was slowly added. The reaction mixture was transferred to a separatory funnel and washed with saturated aqueous K_2CO_3. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 5.92 g of a crude orange oil. This material was purified by flash chromatography on silica gel with EtOAc as eluant and again with 2:1 EtOAc–CH_2Cl_2 with 0.1% TEA as eluant to give 0.62 g (4%) of **34** as a light orange oil. $[\alpha]^{20}_D$: −35.5° (c = 0.617, EtOH). ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3, J = 7.2), 1.65 (m, 3), 1.90 (m, 1), 2.22 (m, 1), 2.40 (m, 1), 2.86 (m, 2), 3.18 (m, 1), 3.53 (dd, 1, J = 14.1, 4.3), 4.34 (dd, 1, J = 14.1, 3.3), 7.43 (dd, 1, J = 8.5, 0.63), 7.52 (dd, 1, J = 8.5, 2.0), 7.99 (d, 1, J = 2.0). ^{13}C NMR ($CDCl_3$): δ 13.92, 23.43, 27.89, 46.53, 48.64, 53.24, 62.52, 121.18, 125.64, 126.12, 131.33, 131.91, 140.95, 165.24. Anal. ($C_{14}H_{17}N_2OS$) C, H, N.

2-((1-Ethyl-2-pyrrolidinyl)methyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide Fumarate (35a). To a 500-mL round-bottomed flask equipped with a Dean–Stark trap was added o-sulfobenzoic acid cyclic anhydride (**31**; 10.0 g, 5.43 mmol), 2-(aminomethyl)-1-ethylpyrrolidine (8.35 g, 6.51 mmol, 1.2 equiv), and benzene (200 mL). The light yellow reaction mixture was heated at reflux overnight and cooled in an ice bath. The solids that formed were filtered, washed with toluene, and air dried to give 21.56 g of **32a** as a light brown powder. Phosphorus pentachloride (7.50 g) and thionyl chloride (85.0 mL) were added to this material. The resulting dark orange solution was heated at reflux for 0.75 h. The excess thionyl chloride was removed by distillation through an inverted Hopkins condenser. The pot residue was dissolved in CH_2Cl_2 and washed with distilled water. The aqueous wash was neutralized to pH 7 (pH paper) by the addition of saturated aqueous K_2CO_3 and extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to give a dark brown powder. This material was dissolved in hot EtOAc, and hexanes were added. The solution was filtered hot and allowed to cool. The crystals were filtered, washed with hexanes, and dried in a vacuum oven to give 3.91 g (25% overall) of the title compound as its free base. The solids were dissolved in acetone, and fumaric acid (1.5 g) was added. The solution was heated, and EtOH was added to dissolve the solids. The solids that formed upon cooling were filtered, washed with cold ether, and dried in a vacuum oven to give 2.03 g of **35a** as a white powder. Mp: 140–142 °C. ^{1}H NMR (DMSO-d_6): δ 1.09 (t, 3, J = 7.1), 1.70 (m, 3), 1.89 (m, 1), 2.34 (q, 1, J = 8.7), 2.50 (m, 1), 3.96 (m, 2), 3.15 (m, 1), 3.61 (dd, 1, J = 14.6, 8.5), 3.74 (dd, 1, J = 14.6, 4.2), 6.60 (s, 2), 8.07 (m ,3), 8.32 (dd, 1, J = 6.9, 0.92). ^{13}C NMR (DMSO-d_6): δ 13.27, 22.19, 28.71, 42.53, 48.28, 53.06, 61.46, 121.48, 125.03, 126.11, 134.06, 135.19, 135.77, 136.61, 158.99, 166.19. Anal. ($C_{14}H_{18}N_2O_3S$·$C_4H_4O_4$) C, H, N.

(*S*)-2-((1-Ethyl-2-pyrrolidinyl)methyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide (35b). This compound was prepared according to the method described for compound **35a**. From o-sulfobenzoic acid cyclic anhydride (10.0 g, 5.43 mmol) and (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[16] (8.35 g, 6.51 mmol, 1.2

equiv) was obtained 16.4 g (97%) of **32b** as a tan powder. Dehydration of this material with phosphorus pentachloride (7.50 g) and thionyl chloride (85.0 mL) provided 2.55 g (16%) of **35b** as light brown crystals after recrystallization of the crude material from EtOAc–hexanes. Mp: 106–108 °C. $[\alpha]^{20}_D$: −43.7° (c = 0.524, EtOAc). ^{1}H NMR (DMSO-d_6): δ 1.05 (t, 3, J = 7.2), 1.66 (m, 3), 1.84 (m, 1), 2.19 (m, 1), 2.36 (m, 1), 2.85 (m, 2), 3.07 (m, 1), 3.58 (dd, 1, J = 14.4, 8.7), 3.66 (dd, 1, J = 14.4, 4.2), 8.05 (m, 3), 8.30 (dd, 1, J = 8.1, 0.53). ^{13}C NMR (DMSO-d_6): δ 13.77, 22.42, 28.82, 43.30, 48.33, 53.15, 61.12, 121.44, 124.99, 126.10, 135.14, 135.73, 136.65, 158.94. Anal. ($C_{14}H_{18}N_2O_3S$) C, H, N.

Pharmacology: Radioligand Binding Assay. The radioligand binding assay of Dewar *et al.*[24] was employed with modifications. Male Sprague–Dawley rats (150–175 g) (Harlan Laboratories, Indianapolis, IN) were decapitated. The brains were removed rapidly and placed on ice. The striata were dissected, placed in cold 50 mM Tris Buffer pH 7.4 (5–10 mg wet weight/mL) and homogenized. The homogenate was centrifuged at 20000g for 10 min at 4 °C. The supernatant was discarded, and the pellet was resuspended (10 mg wet weight/mL) in cold Incubation Buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, pH 7.4).

The binding assay was performed using the D-2 antagonist [^{3}H]raclopride (DuPont, Boston, MA) at a final assay concentration of 10^{-9} M. Specific binding was defined as the total binding minus the nonspecific binding obtained in the presence of (±)-sulpiride (3×10^{-4} M). Compounds were screened at 10^{-5} M final assay concentration. The concentration that inhibited specific binding by 50 % (IC_{50}) was determined for those compounds that had a strong affinity to the D-2 receptor. Using Incubation Buffer for all assay additions, the total assay volume was 0.5 mL with a protein concentration of 0.3 mg/mL. After a 30 min incubation at 25 °C the assay was stopped by rapid filtration onto Brandel GFG filter followed by washing three times with cold 50 mM Tris. Radioactivity was determined using liquid scintillation spectrometry in a Packard counter.

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