Cyclic Benzamides as Mixed Dopamine D_2/Serotonin 5-HT_2 Receptor Antagonists: Potential Atypical Antipsychotic Agents

Mark H. Norman,*,† Greg C. Rigdon,‡ Frank Navas III,† and Barrett R. Cooper‡

Divisions of Organic Chemistry and Pharmacology, Burroughs Wellcome Company, Research Triangle Park, North Carolina 27709

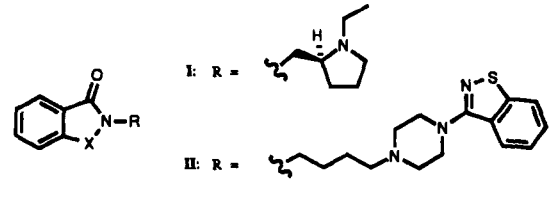
Received February 28, 1994®

A series of novel 4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl) cyclic amides was prepared and evaluated as potential antipsychotic agents. The target compounds were examined *in vitro* for their binding affinities to the dopamine D_2, serotonin 5-HT_2, and serotonin 5-HT_{1a} receptors and *in vivo* for their ability to antagonize the apomorphine-induced climbing response in mice. Derivatives that exhibited good D_2/5-HT_2 selectivity *in vitro* and good potency *in vivo* were selected for further evaluation in tests designed to assess their potential extrapyramidal side effect liability. Structural modifications discussed herein focus on the bicyclic amide subunit leading to the preparation of a variety of heterocyclic ring systems (i.e., phthalimide, isoindolinone, isoquinolinone, benzazepinone, indazolone, phthalazinone, 4-methyl phthalazinone, benzisothiazolone 1,1-dioxide, benzotriazinone, homophthalimide, benzisothiazolone, phthalazinedione, quinazolinone, and saturated phthalazinones). The potency and selectivity within this series was found to be dependent on ring size, nature of the covalent linking unit, relative position of the functional groups, degree of unsaturation, and relative stereochemistry. In general, the cyclic benzamides examined in this investigation exhibited receptor binding activities indicative of potential atypical antipsychotic agents. Several of these derivatives possessed *in vivo* activities that suggest they would be useful in the treatment of schizophrenia and would have a low propensity to induce extrapyramidal side effects. Two potent analogues were identified and selected for further evaluation: 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1-isoindolinone (**31**) and (±)-*cis*-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone hydrochloride (**52**).

Introduction

Schizophrenia has been referred to as the "cancer" of the mental illnesses.[1] The vast amount of research directed toward the treatment of schizophrenia in recent years attests to the inadequacy of current methods of treatment and the need for new and improved therapeutic agents.[2,3] Several neuroleptic drugs are clinically available to treat this devastating mental disorder; however, each of these agents has its shortcomings. Conventional or "typical" antipsychotic agents such as haloperidol and chlorpromazine relieve only the active or "positive" symptoms of schizophrenia such as delusions, hallucinations, and thought disorders, and leave the deficit or "negative" symptoms such as blunted affect, social isolation, and apathy unaffected.[3-6] More importantly, typical antipsychotics produce a high incidence of extrapyramidal side effects such as acute dystonia, Parkinsonism, and tardive dyskinesia. The only FDA-approved "atypical" antipsychotic agent to date is clozapine (Clozaril).[7,8] Clozapine is considered atypical because it is effective in treating both the positive and negative symptoms of schizophrenia without inducing extrapyramidal side effects.[9-11] Unfortunately, clozapine has severe side effects of its own, including the occurrence of agranulocytosis (which can be fatal) in 1–3% of patients and seizures in up to 5% of patients.[12] The pharmacology of clozapine has been extensively studied; however, the causes for its superior antipsychotic profile are not well understood. One theory, put forth by Meltzer *et al.*, is that clozapine's unusual clinical profile may result from the combination of potent serotonin 5-HT_2 antagonism with moderate dopamine D_2 antagonism.[13] Meltzer studied the biological profiles of a series of neuroleptic agents and suggested that compounds with D_2/5-HT_2 receptor binding ratios > 1 are likely to be atypical antipsychotics. For example, recent reports state that mixed dopamine and serotonin antagonists with D_2/5-HT_2 ratios >1, such as risperidone[14,15] and tiospirone,[16] have potential for the treatment of schizophrenia and lead to a low incidence of extrapyramidal side effects.

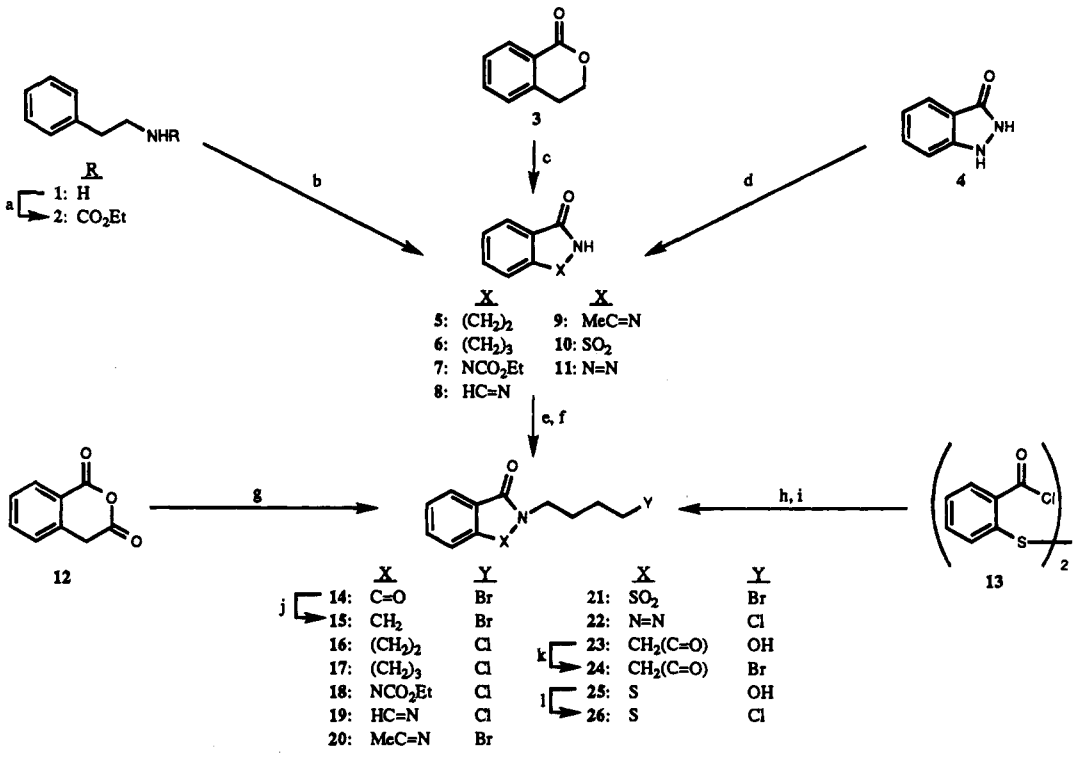
Previously we reported the preparation of several cyclic benzamides containing an ethyl pyrrolidine side chain as conformationally restricted derivatives of the dopamine D_2 antagonist remoxipride (structure I).[17] We have attempted to combine the potential dopamine activity of our cyclic benzamides with piperazinyl benzisothiazole, a pharmacophore known to possess serotonin activity.[16] Our investigations have resulted in the identification of a series of cyclic benzamides with dramatically increased potencies at the D_2 receptor (structure II). In addition, the structural modifications of the previously reported derivatives resulted in compounds that are serotonin 5-HT_2 antagonists and 5-HT_{1a} agonists. The preparation and preliminary pharmacology of this series of cyclic amides are described.



† Division of Organic Chemistry.
‡ Division of Pharmacology.
® Abstract published in *Advance ACS Abstracts*, June 15, 1994.

0022-2623/94/1837-2552$04.50/0

Scheme 1[a]



[a] Reagents: (a) $ClCO_2Et$, CH_2Cl_2, Et_3N; (b) polyphosphoric acid, 140–160 °C; (c) ref 19; (d) $ClCO_2Et$, pyridine, 0 °C-reflux; (e) NaH, DMF, 0 °C; (f) 1-bromo-4-chlorobutane or 1,4-dibromobutane; (g) 4-amino-1-butanol, pyridine, reflux; (h) Cl_2, CH_2Cl_2; (i) 4-amino-1-butanol, CH_2Cl_2, Et_3N; (j) Sn, HOAc, HBr, reflux; (k) PBr_3, 170 °C; (l) $SOCl_2$, toluene, room temperature.

Chemistry

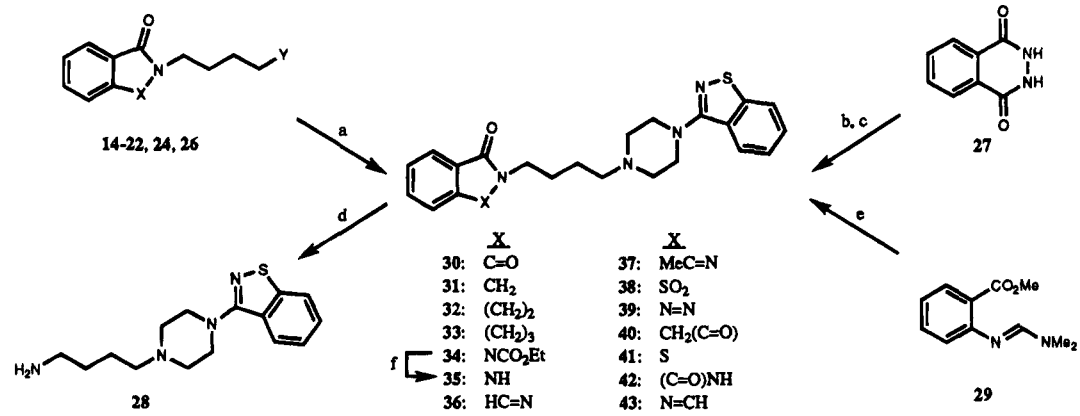
Fourteen cyclic benzamides (**30**–**43**) as well as two saturated phthalazinones (**52** and **53**) containing the butyl piperazinyl benzisothiazole side chain were prepared. Due to the structural diversity of this series, several synthetic approaches were necessary to prepare these targets. The methods employed to synthesize these cyclic amides are summarized in Schemes 1–3. Where possible, the synthetic sequences have been grouped into generalized methods.

The most general approach employed to prepare the target compounds involved displacement of an appropriate halide with 3-(1-piperazinyl)-1,2-benzisothiazole. The required intermediate alkylating agents **14**–**22**, **24**, and **26** were synthesized as outlined in Scheme 1. The majority of these compounds could be obtained directly by alkylation of cyclic amides **5**–**11** with an appropriate alkyl halide. Isoquinolinone **5** was prepared by a modification of the procedure reported by Davies *et al.*[18] Treatment of phenethylamine (**1**) with ethyl chloroformate followed by cyclization of the resulting ethyl carbamate **2** in polyphosphoric acid provided 3,4-dihydro-1(2*H*)-isoquinolinone (**5**). The homologous analogue, benzazepinone **6**, was obtained in four steps from isochroman-1-one (**3**) by the method of Gilman.[19] The anilino-nitrogen of indazolone **4** was protected by treatment with ethyl chloroformate in pyridine to give compound **7** in 51% yield.[20] Phthalazinones **8** and **9**, sulfimide **10**, and benzotriazinone **11** were available from commercial suppliers.[21] Alkylation of cyclic benzamides **5**–**11** with either 1-bromo-4-chlorobutane or 1,2-dibromobutane provided the requisite intermediate halides **16**–**22**, respectively. In some cases where 1-bromo-4-chlorobutane was used as the alkylating agent the product was obtained as a mixture of the bromide and chloride. Reaction of protected indazolone **7** with 1-bromo-4-chlorobutane also gave the corresponding O-alkylated product.

The remaining intermediate alkylating agents (**14**, **15**, **24**, and **26**) shown in Scheme 1 were obtained by a variety of alternative methods. For example, phthalimidine **15** was obtained by the monoreduction of commercially available *N*-(4-bromobutyl)phthalimide (**14**) with tin and acetic acid. Homophthalimide and benzisothiazolone intermediates **24** and **26** were prepared from their corresponding primary alcohols **23** and **25**, respectively, as follows. Treatment of homophthalic anhydride **12** with 4-amino-1-butanol in refluxing pyridine gave alcohol **23**. The crude alcohol was converted to bromide **24** with phosphorus tribromide at 170 °C. Alternatively, the corresponding mesylate could be prepared by treatment of alcohol **23** with mesyl chloride in dichloromethane. The disulfide bond of 2,2′-dithiobenzoyl chloride (**13**)[16] was cleaved with chlorine gas, and reaction of the resulting dichloride intermediate with 1-amino-4-butanol provided benzisothiazolone alcohol **25** in good yield. The corresponding benzisothiazolone chloride **26** was prepared by the treatment of alcohol **25** with thionyl chloride in toluene.

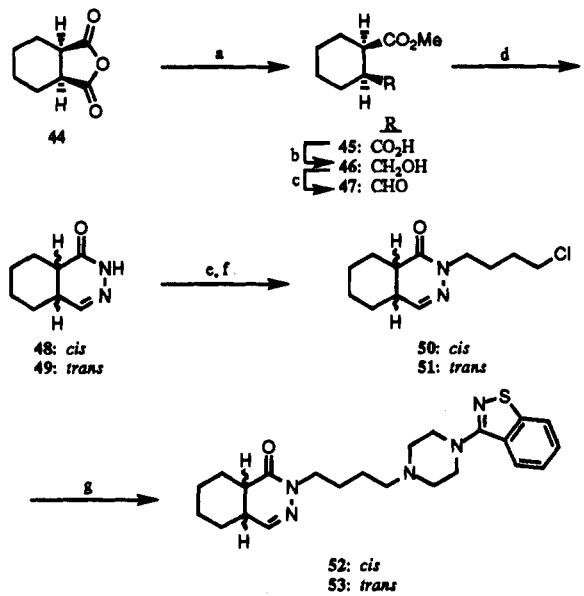
The syntheses of the final cyclic benzamide targets are illustrated in Scheme 2. All of the compounds were treated with ethereal hydrochloric acid and isolated as their hydrochloride salts. Intermediate halides **14**–**22**, **24**, and **26** were reacted with 3-(1-piperazinyl)-1,2-benzisothiazole[16] in refluxing acetonitrile to provide phthalimide **30**, isoindolinone **31**, isoquinolinone **32**, benzazepinone **33**, indazolone-1-carboxylate **34**, phthalazinone **36**, 4-methyl phthalazinone **37**, benzisothiazolone 1,1-dioxide **38**, benzotriazinone **39**, homophthalimide **40**, and benzisothiazolone **41**. Basic hydrolysis of ethyl carbamate **34** provided unsubstituted indazolone derivative **35**. Due to the two adjacent nitrogens

Scheme 2[a]



[a] Reagents: (a) 3-(1-piperazinyl)-1,2-benzisothiazole,[16] CH_3CN, Et_3N, reflux; (b) NaH, DMF, 0 °C; (c) 8-(1,2-benzisothiazol-3-yl)-8-aza-5-azoniaspiro[4.5]decane bromide,[16] reflux; (d) $H_2NNH_2 \cdot H_2O$, MeOH, reflux; (e) 1,4-dioxane, *p*-TsOH, **28**, reflux; (f) EtOH, KOH, reflux.

Scheme 3[a]



[a] Reagents: (a) MeOH, reflux; (b) THF, $BH_3 \cdot THF$, −7 °C−room temperature; (c) SO_3−pyridine, DMSO, CH_2Cl_2, Et_3N, 0 °C; (d) $H_2NNH_2 \cdot H_2O$, EtOH, reflux; (e) NaH, DMF, 0 °C; (f) 1-bromo-4-chlorobutane; (g) 3-(1-piperazinyl)-1,2-benzisothiazole,[16] CH_3CN, Et_3N, reflux.

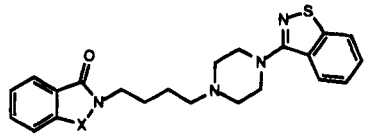
in phthalhydrazide (**27**), it was not possible to achieve monoalkylation with 1-chloro-4-bromobutane. Therefore, to prepare phthalazinedione **42**, it was necessary to employ 8-(1,2-benzisothiazol-3-yl)-8-aza-5-azoniaspiro-[4.5]decane bromide[16] as the alkylating agent. Deprotonation of phthalhydrazide (**27**) with sodium hydride in dimethylformamide followed by treatment of the resulting anion with this spirocyclic quaternary ammonium salt provided phthalazinedione derivative **42** directly. The final target outlined in Scheme 2 required the use of primary amine **28**. Compound **28** was easily obtained by the deprotection of phthalimide **30** with hydrazine hydrate in refluxing methanol. Condensation of this primary amine with methyl 2-(*N*,*N*-dimethyl-*N*′-formamidinyl)benzoate (**29**)[22] provided quinazolinone **43** in good yield.

To investigate different geometric, lipophilic, and steric requirements within this series, two isomeric saturated phthalazinones **52** and **53** were prepared (Scheme 3). Reaction of *cis*-1,2-cyclohexanedicarboxylic anhydride (**44**) with methanol provided the mixed acid ester **45**. Aldehyde **47** was prepared by the reduction of the carboxylic acid group of compound **45** with diborane followed by oxidation of the resulting alcohol **46** with sulfur trioxide−pyridine complex. Cyclization of ester aldehyde **47** with hydrazine provided a *cis/trans* mixture of saturated phthalazinones **48** and **49** in a 3 to 1 ratio as determined by integration of the corresponding imine ^1H NMR signals at 7.00 and 6.96 ppm, respectively. Alternatively, **45** could be converted directly to phthalazinones **48** and **49** by reduction with thexylchloroborane−dimethyl sulfide by the method of Brown *et al.*[23] followed by treatment of the resulting crude aldehyde with hydrazine hydrate. The extent of epimerization could be reduced to <10% by running the reaction at a lower temperature with fewer equivalents of hydrazine hydrate. It was possible to separate isomers **48** and **49** by column chromatography; however, due to further epimerization in the subsequent alkylation step, this purification was not practical. Deprotonation of the *cis/trans* saturated phthalazinone mixture followed by alkylation with 1-bromo-4-chlorobutane provided the corresponding chlorides **50** and **51**, which were separable by flash chromatography. Chlorides **50** and **51** were independently treated with 3-(1-piperazinyl)-1,2-benzisothiazole[16] to give the required phthalazinones **52** and **53**.

Results and Discussion

The target compounds were examined *in vitro* for their binding affinities to dopamine D_2, serotonin 5-HT_{1a}, and serotonin 5-HT_2 receptors (Table 1). Affinities for the dopamine site were measured by the ability of the compounds to displace [^3H]raclopride from the D_2 receptor isolated from the striata of male Sprague−Dawley rats.[24] Serotonergic 5-HT_{1a} and 5-HT_2 binding affinities were determined by displacement of [^3H]-8-hydroxy-2-(di-*n*-propylamino)tetralin and [^3H]ketanserin, respectively.[25,26] The ratios of D_2 (IC_{50}) to 5-HT_2 (IC_{50}) receptor binding were calculated as a measure of the compound's potential selectivity.[13] As a primary screen the compounds were also evaluated *in vivo* for their ability to antagonize the apomorphine-induced climbing response in mice.[27] Antagonism of this response indicates dopamine antagonism in the mesolimbic dopamine system, which is believed to be dysfunctional in schizophrenic patients. Results of this *in vivo* assay are shown in Table 1. The corresponding biological data for the typical antipsychotic haloperidol and the atypical antipsychotic clozapine are included for comparison.

Table 1. Biological Activities of Cyclic Benzamide Derivatives and Reference Standards in Receptor Binding (*in vitro*) and Primary CNS Screens (*in vivo*)



compd no.[a]	X	receptor binding[b] (IC_{50} nM)				antagonism of apomorphine-induced mouse climbing ED_{50} (mg/kg, po)
		D_2	5-HT_{1a}	5-HT_2	D_2/5-HT_2	
30	C=O	49	0.19	7.6	6.4	6.2
31	CH_2	43	7.0	5.1	8.4	6.3
32	$(CH_2)_2$	5.8	0.64	1.9	3.0	16.4
33	$(CH_2)_3$	5.2	4.1	4.2	1.2	>25
34	$N(CO_2Et)$	23	33	7.9	2.9	>25
35	NH	500	350	150	3.3	>25
36	HC=N	32	10	1.8	17.8	9.5
37	MeC=N	5.0	3.4	0.84	6.0	30.4
38	SO_2	11	0.4	1.1	10	48.7
39	N=N	27	1.7	2.9	9.3	19.1
40	CH_2(C=O)	94	1.8	4.7	20	12.2
41	S	600	120	140	4.3	>25
42	(C=O)NH	220	2.6	76	2.9	>25
43	N=CH	17	0.59	2.3	7.4	6.2
52[c]	HC=N	1.6	0.82	0.76	2.1	16.2
53[c]	HC=N	10	0.021	0.38	26.3	25
haloperidol		40	7000	360	0.01	0.5
clozapine		290	2000	28	10.4	22.5

[a] Hydrochloride salts. [b] D_2: [^{3}H]raclopride binding; 5-HT_{1a}: [^{3}H]-8-OH-DPAT binding; 5-HT_2: [^{3}H]ketanserin binding. [c] Hexahydro-1(2*H*)-phthalazinone.

Although each of the compounds studied exhibited somewhat different pharmacological profiles, a few generalizations can be made. For example, most of the compounds exhibited moderate to potent affinities for the dopamine D_2 receptor; IC_{50}'s ranged from 1.6 to 600 nM. In a study of several clinical neuroleptics, Seeman showed that a strong correlation exists between dopamine D_2 antagonism and antipsychotic activity.[28a] Derivatives with lower affinities to the D_2 receptor (i.e., indazolone **35**, benzisothiazolone **41**, and phthalazinedione **42**) were also weaker in the *in vivo* assay. In addition, the compounds exhibited more potent affinities to both serotonin 5-HT_{1a} and serotonin 5-HT_2 receptors than to the dopamine D_2 receptor. In electrophysiology studies a number of the compounds inhibited dorsal raphe neuronal firing rates, indicating that they were agonists at the 5-HT_{1a} receptor.[28b] For example, isoindolinone **31** inhibited dorsal raphe neuronal firing rates *in vitro* with an IC_{50} of 0.02 μM. Anxiolytic agents that are serotonin 5-HT_{1a} partial agonists, such as gepirone, have been shown to effectively reverse the catalepsy induced by the typical antipsychotic haloperidol.[29a] We postulate that this activity should help to relieve the anxiety that can often trigger psychotic episodes and may also reduce the occurrence of extrapyramidal side effects. In addition to being serotonin 5-HT_{1a} agonists, the compounds potently inhibited the 5-methoxy-*N*,*N*-dimethyltryptamine-induced head twitch response in mice, demonstrating *in vivo* antagonism of 5-HT_2 receptors (e.g., isoindolinone **31**; ED_{50} = 5.2 mg/kg, po).[29b] Serotonin 5-HT_2 antagonists such as ritanserin have been shown to be effective in the treatment of the negative symptoms of schizophrenia and are beneficial in reducing extrapyramidal side effects.[30]

The diverse types of cyclic amides (**30**–**43**, **52**, and **53**) were chosen to examine the effects of several structural variables on biological activity and to develop an understanding of the structure–activity relationship within this series. The factors that were explored included varied ring sizes (five-, six-, and seven-membered rings), different functionalities within the amide ring system (hydrocarbon-, carbonyl-, and heteroatom-linking units), relative positions of the functional groups or atoms (e.g., N=CH vs HC=N), degree of unsaturation (phenyl vs cyclohexyl), and relative stereochemistries (*cis* vs *trans*).

The homologous series of isoindolinone **31**, isoquinolinone **32**, and benzazepinone **33** clearly demonstrates the effect of ring size. As the size of the ring was increased from 5 to 6 and 6 to 7, the ratio of *in vitro* binding between dopamine D_2 and serotonin 5-HT_2 became less favorable, and the *in vivo* inhibition of apomorphine-induced mouse climbing was diminished. This reduction in oral activity may be the result of the increased lipophilicity obtained with increasing ring size. In another homologous series (phthalimide **30** vs homophthalimide **40**), a slight decrease in *in vivo* activity was also observed. In this case, however, the D_2/5-HT_2 ratio was more favorable for the six-membered anhydride **40**.

In addition to ring size, the nature and relative position of the functional groups that composed the ring system were important factors. For example, in the five-membered ring series, phthalimide **30** and isoindolinone **31** showed good selectivity and potency, while rings containing heteroatom linking units were significantly less active (i.e., indazolone-1-carboxylate **34**, indazolone **35**, and benzisothiazolone **41**). The relative placement of the functional groups and heteroatoms was critical in six-membered ring amides. Phthalazinone **36** was more selective (D_2/5-HT_2 ratio) but slightly less potent *in vivo* than the corresponding derivative for which the nitrogen and carbon were inverted (i.e., quinazolinone **43**). In this case the placement of the nitrogen on the aromatic ring may contribute to the enhanced activity. Alternatively, the heteroatom attached to the amide nitrogen may be viewed as being detrimental to *in vivo* activity, as was observed in the

Table 2. Secondary Pharmacological Activities of Cyclic Benzamide Derivatives and Reference Standards in Assays Indicating EPS Liability Potential

compd no.[a]	antagonism of apomorphine-induced stereotypy (mouse) ED_{50} (mg/kg, po)	induction of catalepsy (mouse) ED_{50} (mg/kg, po)	stereotype[b] climbing	catalepsy[c] climbing
31	24.7	>360	3.9	>50
36	29.8	70.4	2.5	5.9
39	57.8	252.0	3.0	13.2
40	40.3	132.9	3.3	10.9
haloperidol	0.9	3.0	1.8	6.0
clozapine	78.8	161.2	3.5	7.2

[a] Hydrochloride salts. [b] Ratio of ED_{50} for antagonism of apomorphine-induced stereotypy to ED_{50} for antagonism of apomorphine-induced climbing. [c] Ratio of ED_{50} for induction of catalepsy to ED_{50} for antagonism of apomorphine-induced climbing.

cases of indazolone **35**, benzisothiazolone **41**, and phthalazinedione **42**.

The final two variables that were investigated (i.e., degrees of unsaturation and relative stereochemistry) can be analyzed upon examination of phthalazinone **36** and saturated phthalazinones **52** and **53**. As can be seen from Table 1 each of these derivatives exhibited a unique biological profile. Phthalazinone **36** showed the better *in vivo* potency while the corresponding saturated analogues exhibited higher affinities in the receptor binding assays (especially to the serotonergic receptors). In addition, the results from epimeric phthalazinones **52** and **53** illustrated how a relatively minor structural change can significantly affect activity. The *cis*-isomer **52** was more potent at the dopamine D_2 receptor and retained good *in vivo* activity, while the *trans*-isomer **53** was extremely potent at the serotonin 5-HT_2 receptor but had reduced oral activity in the mouse climbing assay.

On the basis of their D_2/5-HT_2 receptor binding ratios and their potencies in the mouse climbing assay, four compounds were chosen for further investigation (compounds **31**, **36**, **39**, and **40**). These derivatives showed good oral potencies (ED_{50}'s = 6.3–19.1 mg/kg) and exhibited D_2/5-HT_2 receptor binding ratios comparable or superior to clozapine. Two behavioral tests were performed in mice to assess potential extrapyramidal side effect liability: antagonism of apomorphine-induced stereotypy and induction of catalepsy (Table 2).[31,32] The ratios of side-effect (ED_{50}) to desired-effect (ED_{50}) were calculated and are reported in Table 2. All of the derivatives were superior to haloperidol in their side-effect to desired-effect ratios (stereotypy/climb and catalepsy/climb). Isoindolinone **31**, benzotriazinone **39**, and homophthalimide **40** demonstrated a level of selectivity comparable to clozapine when antagonism of apomorphine-induced stereotypy was used as a measure of potential extrapyramidal side effects. Furthermore, these compounds were superior to clozapine when the catalepsy/climb ratios were compared. In fact, isoindolinone **31** induced catalepsy in mice only at extremely high doses. Phthalazinone **36** induced catalepsy at low doses and its catalepsy/climb ratio was no better than haloperidol.

Because they demonstrated extremely potent activities at the serotonergic receptors, saturated phthalazinones **52** and **53** were also examined further. These compounds were evaluated for their ability to inhibit the conditioned avoidance response in rats, an alternative behavioral screen commonly used to identify potential neuroleptic agents.[33] Phthalazinone **52** was very potent in this assay with an ED_{50} = 0.78 mg/kg (po), while the corresponding *trans*-isomer **53** was inactive at 4 times this dose. These results suggest that the conformation of the saturated bicyclic ring system is critical for activity and that these isomeric compounds are not being epimerized *in vivo*. The pharmacology of *cis*-saturated phthalazinone **52** is currently being evaluated in detail and the results of these investigations will be reported elsewhere.

Conclusion

Several cyclic amides containing the 4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl side chain were synthesized and their *in vitro* potencies at dopamine D_2, serotonin 5-HT_{1a}, and serotonin 5-HT_2 receptors were evaluated. The compounds were also tested in behavioral screens predictive of antipsychotic activity and extrapyramidal side effects. The cyclic benzamides possessed receptor binding activities indicative of potential atypical antipsychotic activity (i.e., moderate D_2 antagonism, potent serotonin 5-HT_2 antagonism, and serotonin 5-HT_{1a} agonism). In addition to having desirable receptor binding profiles, several of these derivatives demonstrated *in vivo* activities that suggest they would be useful in the treatment of schizophrenia and would have a low propensity to induce extrapyramidal side effects. For example, isoindolinone **31** possessed a good receptor binding profile and exhibited excellent *in vivo* selectivities. In addition to this cyclic benzamide, saturated phthalazinone **52** potently inhibited conditioned avoidance responding in rat. These two compounds were selected for further pharmacological studies.

Experimental Section

Chemistry. General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane, toluene, pyridine, and dimethyl sulfoxide (DMSO) were obtained from Aldrich Chemical Co. in Sure/Seal bottles. Triethylamine was distilled from CaH_2 prior to use. All reactions involving air- or moisture-sensitive compounds were performed under a N_2 atmosphere. Flash chromatography [34] and flush chromatography were performed using EM Science silica gel 60 (230–400-mesh ASTM). The term flush chromatography refers to column chromatography when suction is applied to the bottom of the column to increase the flow rate of the eluant. Thin-layer chromatography (TLC) was performed with Analtech silica gel FG TLC plates (250 μm). ^1H NMR and ^{13}C NMR were determined with superconducting, FT NMR spectrometers operating at 200, 300, and 500 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^1H 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 either Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. 3-(1-Piperazinyl)-1,2-benzisothiazole and 8-(1,2-benzisothiazol-3-yl)-5,8-diazaspiro[4.5]decane bromide were prepared according to the methods described by Yevich *et al.*[16]

3,4-Dihydro-1(2*H*)-isoquinolinone (5).[18] Phenethylamine (31.1 mL, 30.0 g, 0.248 mol), triethylamine (34.6 mL, 25.1 g, 0.248 mol, 1.0 equiv), and anhydrous CH_2Cl_2 (300 mL) were added to a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and a N_2 inlet. The solution was cooled with an ice–water bath, and a solution

of ethyl chloroformate (23.7 mL, 26.9 g, 0.248 mol, 1.0 equiv) in CH_2Cl_2 (25 mL) was added dropwise. The reaction mixture was stirred for 0.5 h and Et_2O (150 mL) was added. The resulting suspension was filtered and the filtrate was concentrated to give 46.0 g (96%) of ethyl *N*-(2-phenethyl)carbamate as an oil, which solidified to a white solid upon standing. The crude ethyl *N*-(2-phenethyl)carbamate (46.0 g, 0.238 mol) and polyphosphoric acid (475.0 g) were added to a 1-L, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser. The mixture was heated in an oil bath at 140–160 °C for 2 h. The reaction mixture was allowed to cool to room temperature and poured into distilled H_2O (2.4 L). The organic layers were extracted with EtOAc, washed with saturated NaCl, dried over $MgSO_4$, filtered, and concentrated to give 4.36 g of an orange oil. The crude material was purified by flash chromatography with EtOAc as eluant to give 1.85 g (5.1% based on phenethylamine) of 3,4-dihydro-1(2*H*)-isoquinolinone (**5**)[18] as a light orange oil: ^{1}H NMR ($CDCl_3$) δ 3.01 (t, 2, J = 6.6), 3.58 (dt, 2, J = 2.9, 6.6), 6.20 (br s, 1), 7.22 (dd, 1, J = 0.7, 7.4), 7.36 (ddd, 1, J = 1.3, 7.6, 8.3), 7.46 (ddd, 1, J = 1.6, 7.5, 9.0), 8.07 (dd, 1, J = 1.1, 7.7).

Ethyl 2,3-Dihydro-3-oxo-1*H*-indazole-1-carboxylate (7). This compound was prepared according to the method described by Wyrick *et al.*[20] from 3-indazolinone (20.0 g, 0.149 mol) and ethyl chloroformate (28.5 mL, 32.4 g, 0.299 mol, 2.0 equiv): yield 15.6 g (51%); mp 193–195 °C [lit.[20] mp 198–201 °C]; ^{1}H NMR (DMSO-d_6) δ 1.37 (t, 3, J = 7.1), 4.41 (q, 2, J = 7.1), 7.34 (ddd, 1, J = 0.8, 7.1, 8.0), 7.61 (ddd, 1, J = 1.2, 7.2, 8.4), 7.75 (dt, 1, J = 7.8, 1.0), 8.04 (d, 1, J = 8.4), 12.13 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 14.14, 62.84, 114.09, 117.16, 120.43, 123.36, 130.00, 140.28, 150.04, 158.50. Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

2-(4-Bromobutyl)-1-isoindolinone (15). *N*-(4-Bromobutyl)phthalimide (**14**) (15.6 g, 0.056 mol), glacial acetic acid (100 mL), tin metal (15.83, 0.133 mol, 2.4 equiv), and hydrobromic acid (20 mL) were added to a 250-mL, round-bottomed flask. The resulting light yellow reaction mixture was placed under N_2 and heated at reflux for 6 h. The solution was filtered and the tin was washed with acetic acid. Most of the acetic acid was removed with a rotary evaporator and the resulting creamy residue was taken up in CH_2Cl_2 and washed with H_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 9.37 g of a light orange oil. This material was purified by flash chromatography with 3:1 hexanes–EtOAc as eluant to give 0.89 g (6%) of 2-(4-bromobutyl)-1-isoindolinone (**15**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.86 (m, 4), 3.47 (t, 2, J = 6.2), 3.66 (t, 2, J = 6.7), 4.39 (s, 2), 7.46 (t, 2, J = 6.4), 7.53 (m, 1), 7.84 (dd, 1, J = 6.8, 0.38); ^{13}C NMR ($CDCl_3$) δ 26.84, 29.64, 33.44, 41.25, 49.80, 122.70, 123.71, 128.08, 131.30, 132.75, 141.03, 179.05. Note: Higher yields resulted when hydrochloric acid was used instead of hydrobromic acid in the above method; however, the resulting product was a mixture of the chloride and bromide. Anal. ($C_{12}H_{14}NOBr$) C, H, N.

2-(4-Chlorobutyl)-3,4-dihydro-1(2*H*)-isoquinolinone (16). Sodium hydride as an 80% oil dispersion (0.945 g, 31.5 mmol, 2.5 equiv) was added to a flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet. The sodium hydride was washed with hexanes (3×), and the waste hexanes were removed each time with a pipet. To the washed sodium hydride was added anhydrous DMF (20 mL) and the resulting suspension was cooled in an ice–water bath. To the cooled reaction mixture was added a solution of 3,4-dihydro-1(2*H*)-isoquinolinone (**5**) (1.85 g, 12.6 mmol, 1.0 equiv) in anhydrous DMF (20 mL) dropwise. The reaction mixture was allowed to stir for 15 min and 1-bromo-4-chlorobutane (1.59 mL, 2.37 g, 13.8 mmol, 1.1 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir for 0.5 h. The excess sodium hydride was quenched with distilled H_2O (10 mL), the solvent was removed in vacuo, and the residue was partitioned between H_2O and EtOAc. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 5.16 g of an orange oil. The crude material was purified by flash chromatography with 3:2 hexanes–EtOAc as eluant to give 1.90 g (63%) of 2-(4-chlorobutyl)-3,4-dihydro-1(2*H*)-isoquinolinone (**16**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.83 (m, 4), 3.00 (t, 2, J = 6.6), 3.60 (m, 4), 7.18 (d, 1, J = 7.4), 7.37 (m, 2), 8.07 (dd, 1, J = 1.4, 7.7).

2-(4-Chlorobutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (17). This compound was prepared according to the method described for isoquinolinone chloride **16**. Alkylation of 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one[19] (0.46 g, 2.85 mmol) with 1-bromo-4-chlorobutane (0.393 mL, 0.586 g, 3.42 mmol, 1.2 equiv) gave 0.40 g (56%) of 2-(4-chlorobutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**17**) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 1.87 (m, 4), 2.04 (quintet, 2, J = 6.6), 2.78 (t, 2, J = 6.6), 3.40 (t, 2, J = 6.6), 3.64 (m, 4), 7.12 (d, 1, J = 7.4), 7.34 (m, 2), 7.65 (d, 1 J = 8.0).

Ethyl 2-(4-Chlorobutyl)-2,3-dihydro-3-oxo-1*H*-indazole-1-carboxylate (18). Sodium hydride (1.51 g, 50.3 mmol, 1.2 equiv of an 80% oil dispersion) was added to a flame-dried, 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and N_2 inlet. The sodium hydride was washed with hexanes (3×). To the washed sodium hydride was added anhydrous DMF (50 mL), and the resulting gray suspension was cooled in an ice–water bath. Ethyl 2,3-dihydro-3-oxo-1*H*-indazole-1-carboxylate (**7**) (8.65 g, 41.9 mmol) was added slowly with a spatula to the cooled reaction mixture. To the cooled reaction mixture was added 1-bromo-4-chlorobutane (5.31 mL, 7.91 g, 46.1 mmol, 1.1 equiv). The reaction mixture was slowly warmed to 65 °C and stirred overnight. The reaction mixture was allowed to cool and the excess sodium hydride was quenched with distilled H_2O (2 mL). The majority of the solvent was removed in vacuo and the residue was partitioned between EtOAc and distilled H_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 12.2 g of an orange oil. ^{1}H NMR of this crude material indicated that both N-alkylated and O-alkylated products were formed. Furthermore, these alkylated products were obtained as mixtures of their corresponding chlorides and bromides. The crude oil was purified by flash chromatography with 3:1 hexanes–EtOAc as eluant to give 2.00 g of ethyl 2-(4-chlorobutyl)-2,3-dihydro-3-oxo-1*H*-indazole 1-carboxylate (**18**) and ethyl 2-(4-bromobutyl)-2,3-dihydro-3-oxo-1*H*-indazole-1-carboxylate as a 60:40 mixture. The chloride/bromide ratio was determined by integration of their corresponding methylene triplets at 3.39 and 3.52 ppm, respectively. ^{1}H NMR data unique to the bromide are given in brackets: ^{1}H NMR ($CDCl_3$) δ 1.47 (t, 3, J = 7.1), 1.76 (m, 4), [3.38 (t, 2, J = 6.2)], 3.51 (t, 2, J = 6.2), 4.27 (t, 2, J = 6.8), 4.47 (q, 2, J = 7.1), 7.33 (tm, 1, J = 7.5), 7.33 (tm, 1, J = 7.5), 7.63 (ddd, 1, J = 1.3, 7.2, 8.5), 7.87 (d, 1, J = 7.0), 7.90 (d, 1, J = 8.4). This material was used as a mixture without further isolation of each halide.

2-(4-Chlorobutyl)-1(2*H*)-phthalazinone (19). Sodium hydride (2.56 g, 0.0855 mol, 1.25 equiv of an 80% oil dispersion) was placed under N_2 in a 250-mL, round-bottomed flask. The sodium hydride was washed twice with hexanes and the waste hexanes were removed. Anhydrous DMF (100 mL) was added. To this gray suspension a solution of 1-(2*H*)-phthalazinone (**8**) (10.0 g, 0.0684 mol) in anhydrous DMF (50 mL) was added and the resulting solution was allowed to stir at room temperature for 0.5 h. This anionic solution was added, via cannula, to a 500-mL, round-bottomed flask containing a solution of 1-bromo-4-chlorobutane (8.67 mL, 12.91 g, 0.0753 mol, 1.1 equiv) in anhydrous DMF (100 mL). The reaction mixture was allowed to stir at room temperature for 4 h. As the reaction proceeded, the mixture became a clear orange solution. Distilled H_2O (10 mL) was added and most of the solvent was removed with a rotary evaporator. The residue was taken up in CH_2Cl_2 and washed with H_2O (2 × 50 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated to provide 16.49 g of crude material. The product was purified by flash chromatography with 2:1 hexanes–EtOAc as eluant to give 13.11 g of a light orange oil. ^{1}H NMR indicated that the product was an 80:20 mixture of 2-(4-chlorobutyl)-1(2*H*)-phthalazinone (**19**) to its corresponding bromide, as determined by integration of the triplets at 3.56 and 3.43 ppm, respectively. ^{1}H NMR data unique to the bromide are given in brackets: ^{1}H NMR ($CDCl_3$) δ 1.75–2.08 (m, 4), [3.43 (t, 2, J = 6.4)], 3.56 (t, 2, J = 6.4), 4.24 (t, 2, J =

6.8), 7.67 (m, 1), 7.74 (m, 2), 8.13 (s, 1), 8.38 (m, 1). The chloride–bromide mixture was used without further purification.

2-(4-Bromobutyl)-4-methyl-1(2*H*)-phthalazinone (20). This compound was prepared by a method analogous to that described for phthalazinone **19**. From 4-methyl-1(2*H*)-phthalazinone (50.0 g, 0.31 mol) and 1,4-dibromobutane (80.33 g, 0.37 mol) was obtained 31.05 g (34%) of 2-(4-bromobutyl)-4-methyl-1(2*H*)-phthalazinone (**20**) as orange crystals: mp 166–172 °C; ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 4), 2.56 (s, 3), 3.58 (t, 2, J = 6.2), 4.13 (t, 2, J = 6.6), 7.88 (m, 1), 7.95 (m, 2), 8.29 (dm, 1, J = 8.7).

3-(4-Chlorobutyl)-1,2,3-benzotriazin-4(3*H*)-one (22). Sodium hydride as an 80% oil dispersion (1.53 g, 51.0 mmol) was added to a flame-dried, 100-mL, round-bottomed flask equipped with a magnetic stirring bar and N_2 inlet. The sodium hydride was washed with hexanes (3×), and the waste hexanes were removed each time with a pipet. The washed sodium hydride was cooled in an ice–water bath and 1,2,3-benzotriazin-4(3*H*)-one (**11**) (5.0 g, 34.0 mmol) in anhydrous DMF (40 mL) was added. The resulting foamy green reaction mixture was allowed to stir for 5 min, and 1-bromo-4-chlorobutane (4.31 mL, 6.41 g, 37.4 mmol, 1.1 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir for 1.5 h. The reaction was quenched with distilled H_2O (10 mL), and the solvent was removed *in vacuo* to give an orange solid. The crude material was purified by flash chromatography with 6:1 hexanes–EtOAc as eluant to give 5.67 g (70%) of 3-(4-chlorobutyl)-1,2,3-benzotriazin-4(3*H*)-one (**22**) as a colorless oil that solidified to a pale tan solid upon standing: mp 50–53 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 2), 2.10 (m, 2), 3.61 (t, 2, J = 6.4), 4.52 (t, 2, J = 6.9), 7.81 (ddd, 1, J = 7.6, 1.4, 0.6), 7.95 (ddd, 1, J = 7.6, 1.6, 0.6), 8.16 (ddt, 1, J = 8.0, 1.4, 0.6), 8.36 (dm, 1, J = 7.8); ^{13}C NMR ($CDCl_3$) δ 26.15, 29.39, 44.11, 48.76, 119.61, 124.93, 128.14, 132.24, 134.69, 144.12, 155.37. Anal. ($C_{11}H_{12}N_3OCl$) C, H, N.

2-(4-Bromobutyl)-1,3(2*H*,4*H*)-isoquinolinedione (24). Homophthalic anhydride (**12**) (15 g, 92.5 mmol) and 4-amino-1-butanol (8.54 mL, 8.26 g, 92.5 mmol, 1 equiv) were added to a three-necked, round-bottomed flask equipped with a reflux condenser, and addition funnel. The reaction mixture was heated with an oil bath at 150 °C for 2 h. The crude alcohol **23** was cooled to room temperature and phosphorous tribromide (6.0 mL, 17.1 g, 63 mmol) was added dropwise. The reaction mixture was heated slowly to 170 °C and maintained at that temperature for 45 min. The hot reaction mixture was poured onto crushed ice (150 g). The viscous organic material was separated from the ice and EtOH was added. The material became a white solid upon the addition of EtOH. The solvent was removed *in vacuo* to give a yellow solid. The solid was recrystallized from EtOH to give 17.1 g (62%) of 2-(4-bromobutyl)-1,3(2*H*,4*H*)-isoquinolinedione (**24**) as a pale yellow solid: mp 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (m, 4), 3.43 (t, 2, J = 6.5), 4.02 (t, 4, J = 7.0), 4.03 (s, 2), 7.26 (d, 1, J = 7.2), 7.43 (t, 1, J = 7.5), 7.58 (td, 1, J = 7.4, 1.4), 8.20 (d, 1, J = 7.8); ^{13}C NMR ($CDCl_3$) δ 26.26, 29.64, 32.55, 35.88, 38.66, 124.77, 126.63, 127.26, 128.66, 133.17, 133.54, 164.32, 169.44. Anal. ($C_{13}H_{14}NO_2Br$) C, H, N.

2-(4-Hydroxybutyl)-1,2-benzisothiazol-3(2*H*)-one (25). 2,2′-Dithiobis(benzoyl chloride) (**13**)[16] (18.0 g, 0.0523 mol) and CH_2Cl_2 (50.0 mL) were added to a 150-mL beaker. Chlorine gas was bubbled through this cloudy solution with stirring, giving an orange-brown mixture. To a separate flask was added a solution of 4-amino-1-butanol (10.0 g, 0.110 mol, 2.1 equiv), triethylamine (16.1 mL, 11.6 g, 0.115 mol, 2.2 equiv), and CH_2Cl_2 (50 mL). This mixture was cooled in an ice–water bath. The bis-chloride solution was slowly added to the cooled amino alcohol solution with stirring. The resulting orange mixture was washed with distilled H_2O and the organic layers were separated, dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 23.33 g of a crude red-orange oil. ^{1}H NMR of this material was consistent with 2-(4-hydroxybutyl)-1,2-benzisothiazol-3(2*H*)-one (**25**) and the compound was used without further purification.

2-(4-Chlorobutyl)-1,2-benzisothiazol-3(2*H*)-one (26). Crude 2-(4-hydroxybutyl)-1,2-benzisothiazol-3(2*H*)-one (**25**) (23.33 g, 0.104 mol) was dissolved in toluene (100 mL). The solution was placed under N_2, and thionyl chloride (8.61 mol, 14.05 g, 0.118 mol, 1.13 equiv) was added dropwise over a 15-min period. The reaction mixture was allowed to stir at room temperature for 4 h. The toluene and excess thionyl chloride were removed by distillation under reduced pressure through an inverted Hopkins condenser. The red-orange residue was purified by flash chromatography with 4:1 hexanes–EtOAc as eluant to give 7.57 g (30%, based on 2,2′-dithiobis(benzoyl chloride)) of 2-(4-chlorobutyl)-1,2-benzisothiazol-3(2*H*)-one (**26**) as a red oil: ^{1}H NMR ($CDCl_3$) δ 1.90 (m,4), 3.58 (t, 2, J = 6.1), 3.93 (t, 2, J = 6.6), 7.39 (dt, 1, J = 1.6, 6.4), 7.56 (m, 2), 8.01 (dd, 1, J = 1.0, 7.8); ^{13}C NMR ($CDCl_3$) δ 26.80, 29.26, 42.89, 44.30, 120.36, 124.57, 125.54, 126.68, 131.81, 140.06, 165.42. Anal. ($C_{11}H_{12}NOSCl$) C, H, N.

3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (28). To a solution of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)phthalimide (**30**) (12.46 g, 0.0296 mol) and MeOH (30 mL) was added 85% hydrazine hydrate (2.62 g, 1.5 equiv). The reaction mixture was heated at reflux for 3.5 h and allowed to cool to room temperature. 1 N HCl (59.0 mL) was added to the solution and the resulting white precipitate was filtered and washed with H_2O. The filtrate was made basic by the addition of 50% NaOH and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 8.1 g (94%) of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (**28**) as an orange-brown oil: ^{1}H NMR ($CDCl_3$): δ 1.38 (br s, 2), 1.55 (m, 4), 2.45 (t, 2, J = 7.4), 2.68 (t, 4, J = 5.0), 2.74 (t, 2, J = 6.8), 3.57 (t, 4, J = 5.0), 7.35 (ddd, 1, J = 1.1, 7.0, 8.1), 7.46 (ddd, 1, J = 1.1, 7.0, 8.1), 7.81 (d, 1, J = 8.1), 7.91 (d, 1, J = 8.2). This crude amine was used without further purification.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-phthalimide Hydrochloride (30). *N*-(4-Bromobutyl)phthalimide (**14**) (3.50 g, 0.0124 mol), 3-(1-piperazinyl)-1,2-benzisothiazole (2.72 g, 12.4 mmol, 1.0 equiv), triethylamine (2.24 mL, 16.1 mmol, 1.3 equiv), and acetonitrile (15 mL) were added to a 100-mL, round-bottomed flask. The cloudy orange solution was heated at reflux under N_2 for 17 h. The mixture was allowed to cool to room temperature and diluted with CH_2Cl_2. The organic solution was washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give 5.48 g of a light orange solid. This crude material was recrystallized from acetonitrile and dried in a vacuum oven to give 4.35 g of a tan powder. The hydrochloride salt was prepared by the addition of 1 N HCl in Et_2O (10.3 mL, 1.0 equiv) to a solution of the free base in EtOAc/EtOH. The salt was triturated with hot 95% EtOH and the solution was cooled. The solids were filtered, washed with cold EtOH and dried in a vacuum oven to give 4.53 g (82%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl) phthalimide hydrochloride (**30**) as an off-white powder: mp 258–260 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.72 (m, 4), 3.20 (m, 4), 3.54 (m, 6), 4.02 (br d, 2, J = 13.7), 7.44 (ddd, 1, J = 8.1, 7.0, 1.1), 7.57 (ddd, 1, J = 8.1, 7.0, 1.0), 7.85 (m, 4), 8.09 (dd, 2, J = 8.0, 4.5), 11.18 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.52, 25.25, 36.82, 46.30, 50.44, 54.98, 121.13, 122.98, 123.94, 124.56, 126.90, 128.06, 131.58, 134.33, 152.04, 162.16, 167.93. Anal. ($C_{23}H_{24}N_4O_2S$·HCl) C, H, N.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1-isoindolinone Hydrochloride (31). A 40:60 mixture of 2-(4-bromobutyl)-1-isoindolinone (**15**) and 2-(4-chlorobutyl)-1-isoindolinone (3.69 g, 15.27 mmol) was added to a 100-mL, round-bottomed flask. Triethylamine (2.77 mL, 2.01 g, 19.85 mmol, 1.3 equiv), acetonitrile (25.0 mL), and 3-(1-piperazinyl)-1,2-benzisothiazole (3.68 g, 16.80 mmol, 1.1 equiv) were added to the chloride/bromide mixture and the light orange reaction mixture was heated at reflux for 19 h under N_2. The solution was allowed to cool to room temperature and was transferred to a separatory funnel with the aid of EtOAc. The organic layers were washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give 7.31 g of a dark orange oil, which solidified upon standing. The crude solids were recrystallized from acetonitrile to give 4.38 g of free amine. The hydrochloride salt was prepared via the addition of HCl (10.8 mL of a 1 N solution in Et_2O, 1.0 equiv) to a solution of the free amine in EtOH. The salt was recrystallized from 95% EtOH to give 3.47 g (51%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1-isoindolinone hydrochloride (**31**) as an off-white powder: mp 232–233 °C; ^{1}H NMR (DMSO-d_6) δ 1.77

(m, 4), 3.23 (m, 4), 3.57 (m, 6), 4.05 (br d, 2, J = 13.8), 4.52 (s, 2), 7.48 (m, 2), 7.60 (d, 3, J = 8.9), 7.69 (d, 1, J = 7.5), 8.12 (t, 2, J = 7.6), 11.32 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.49, 25.05, 40.96, 46.29, 49.41, 50.43, 55.12, 121.15, 122.65, 123.30, 123.96, 124.57, 126.92, 127.74, 128.07, 131.17, 132.33, 141.84, 152.06, 162.19, 167.34. Anal. ($C_{23}H_{26}N_4OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3,4-dihydro-1(2*H*)-isoquinolinone Hydrochloride (32).** 2-(4-Chlorobutyl)-3,4-dihydro-1(2*H*)-isoquinolinone (**16**) (1.90 g, 7.99 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (2.10 g, 9.59 mmol, 1.2 equiv), triethylamine (1.56 mL, 1.13 g, 11.2 mmol, 1.4 equiv), and acetonitrile (25 mL) were added to a 100-mL, round-bottomed flask equipped with a magnetic stirring bar, condenser, and N_2 inlet. The reaction mixture was heated at reflux under N_2 for 30 h. The reaction was incomplete as indicated by TLC; therefore, additional portions of 3-(1-piperazinyl)-1,2-benzisothiazole (0.350 g, 1.60 mmol, 0.2 equiv) and triethylamine (0.670 mL, 0.486 g, 4.81 mmol, 0.6 equiv) were added and the reaction mixture was heated at reflux for an additional 24 h. The solution was allowed to cool to room temperature and transferred to a separatory funnel with the aid of EtOAc. The solution was washed with saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 5.2 g of an orange oil. The crude material was purified by flash chromatography with EtOAc/0.1% triethylamine as eluant to give 2.26 g of an orange oil. The free base was taken up in EtOAc, and HCl (5.37 mL of a 1 N solution in Et_2O, 1.0 equiv) was added. The resulting salt was recrystallized from EtOH to give 2.0 g (55%) of the title compound as a light orange solid: mp 229–231 °C; ^{1}H NMR (DMSO-d_6) δ 1.66 (m, 2), 1.78 (m, 2), 3.00 (t, 2, J = 6.6), 3.27 (m, 4), 3.52 (m, 8), 4.07 (br d, 2, J = 13.0), 7.31 (d, 1, J = 8.0), 7.37 (dd, 1, J = 1.5, 7.4), 7.48 (dt, 2, J = 1.2, 7.5), 7.60 (dt, 1, J = 0.8, 7.5), 7.88 (dd, 1, J = 1.1, 7.5), 8.12 (t, 2, J = 7.9), 10.68 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.46, 24.37, 27.36, 45.36, 45.69, 46.31, 50.44, 55.22, 121.14, 123.95, 124.56, 126.60, 126.91, 127.17, 127.26, 128.06, 129.15, 131.45, 138.60, 152.05, 162.17, 163.17. Anal. ($C_{24}H_{26}N_4OS$·HCl) C, H, N.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one Hydrochloride (33). This compound was prepared according to the method described for compound **32**. Alkylation of 2-(4-chlorobutyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (0.40 g, 1.59 mmol) with 3-(1-piperazinyl)-1,2-benzisothiazole (0.52 g, 2.39 mmol, 1.5 equiv) gave 0.45 g of the free base, which was purified by flash chromatography with 2:1 EtOAc–hexanes/0.1% triethylamine as eluant. The hydrochloride salt was prepared, recrystallized from EtOH, and dried in a vacuum oven to give 227 mg (30%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one hydrochloride (**33**) as a beige solid: mp 215–217 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.67 (m, 2), 1.81 (m, 2), 1.99 (quintet, 2, J = 6.7), 2.73 (t, 2, J = 7.0), 3.18 (t, 2, J = 6.4), 3.27 (m, 4), 3.53 (m, 6), 4.08 (br d, 2, J = 13.0), 7.25 (dd, 1, J = 1.2, 7.5), 7.33 (td, 1, J = 7.5, 1.4), 7.42 (td, 1, J = 7.4, 1.6), 7.48 (ddd, 1, J = 1.1, 7.0, 8.1), 7.51 (dd, 1, J = 1.6, 7.4), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 8.13 (t, 2, J = 9.1), 10.92 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.61, 25.55, 29.30, 29.58, 45.59, 45.69, 46.35, 50.46, 55.23, 121.15, 123.95, 124.57, 126.59, 126.91, 127.94, 128.07, 128.24, 130.51, 136.25, 137.09, 152.06, 162.16, 169.78. Anal. ($C_{25}H_{30}N_4OS$·HCl) C, H, N.

Ethyl 2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2,3-dihydro-3-oxo-1*H*-indazole-1-carboxylate Hydrochloride (34). A 60:40 mixture of ethyl 2-(4-chlorobutyl)-2,3-dihydro-3-oxo-1*H*-indazole 1-carboxylate (**18**) and ethyl 2-(4-bromobutyl)-2,3-dihydro-3-oxo-1*H*-indazole 1-carboxylate (3.13 g, 9.68 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (3.84 g, 17.5 mmol, 1.8 equiv), triethylamine (2.44 mL, 1.77 g, 17.5 mmol, 1.8 equiv), and acetonitrile (30.0 mL) were added to a 50-mL, round-bottomed flask equipped with a magnetic stirring bar, condenser, and N_2 inlet. The reaction mixture was heated at reflux under N_2 overnight. The reaction mixture was allowed to cool to room temperature and partitioned between EtOAc and saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 7.18 g of an oily tan solid. The crude material was purified by flash chromatography with 2:1 EtOAc–hexanes followed by EtOAc to give 2.97 g of the free base as a yellow oil. To a solution of the free base in EtOAc was added HCl (6.2 mL of a 1 N solution in Et_2O, 1.0 equiv). The resulting hydrochloride salt was recrystallized from EtOH to give 0.52 g (8%) of ethyl 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3-dihydro-3-oxo-1*H*-indazole-1-carboxylate hydrochloride (**34**) as a beige solid: mp 189–190 °C; ^{1}H NMR (DMSO-d_6) δ 1.41 (t, 2, J = 7.1), 1.66 (br s, 3), 3.23 (m, 6), 3.42 (br t, 2, J = 12.1), 3.53 (br d, 2, J = 12.0), 4.05 (br d, 2, J = 13.2), 4.15 (m, 2), 4.44 (q, 2, J = 7.1), 7.46 (m, 2), 7.60 (ddd, 1, J = 0.9, 7.1, 8.0), 7.78 (ddd, 1, J = 1.3, 7.2, 8.5), 7.84 (ddd, 1, J = 0.8, 1.3, 7.7), 7.94 (d, 1, J = 8.4), 8.12 (t, 2, J = 6.9), 10.53 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 14.05, 20.36, 24.51, 45.78, 46.27, 50.41, 54.90, 64.10, 115.39, 117.86, 121.14, 123.37, 123.95, 124.57, 124.90, 126.91, 128.07, 133.88, 142.68, 150.63, 152.05, 162.15, 163.75. Anal. ($C_{25}H_{29}N_5O_3S$·HCl) C, H, N.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2-dihydro-3*H*-indazol-3-one Hydrochloride Hydrate (35). Ethyl 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3-dihydro-3-oxo-1*H*-indazole-1-carboxylate (**34**) (1.88 g, 3.92 mmol) and potassium hydroxide (23.7 mL of a 0.67 M solution in EtOH) were added to a 300-mL, round-bottomed flask equipped with a magnetic stirring bar, N_2 inlet, and condenser. The reaction mixture was placed under N_2 and heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was partitioned between EtOAc and saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 1.37 g of the crude product as an orange oil. The crude material was purified by flash chromatography with 92:8 CH_2Cl_2/MeOH as eluant to give 1.03 g of the free base as a light yellow solid. To a solution of the free base in EtOAc and CH_2Cl_2 was added HCl (2.53 mL of a 1 N solution in Et_2O, 1.0 equiv). The hydrochloride salt was recrystallized from EtOH/Et_2O to give 0.36 g (20%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2-dihydro-3*H*-indazol-3-one hydrochloride hydrate (**35**) as a white solid: mp 80–90 °C (softens), 125–145 °C (effervesces); ^{1}H NMR (DMSO-d_6) δ 1.77 (m, 4), 3.25 (m, 4), 3.44 (m, 2), 3.56 (br d, 2, J = 11.4), 3.87 (t, 2, J = 6.0), 4.06 (br d, 2, J = 13.3), 7.11 (ddd, 1, J = 0.8, 7.1, 8.0), 7.28 (dt, 1, J = 8.3, 0.8), 7.47 (ddd, 1, J = 1.1, 6.4, 8.2), 7.52 (ddd, 1, J = 1.2, 6.5, 8.3), 7.60 (ddd, 1, J = 1.1, 7.0, 8.2), 7.65 (dt, 1, J = 7.9, 1.1), 8.12 (t, 2, J = 7.8), 10.40 (br s, 1), 10.70 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.31, 25.04, 42.41, 46.33, 50.49, 54.94, 112.12, 117.20, 120.80, 121.15, 122.87, 123.96, 124.58, 126.91, 128.08, 131.20, 145.91, 152.06, 160.58, 162.16. Anal. ($C_{22}H_{25}N_5OS$·HCl·0.75H_2O) C, H, N, H_2O.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1(2*H*)-phthalazinone Hydrochloride (36). This compound was prepared according to a method analogous to that described for compound **30**. From 3-(1-piperazinyl)-1,2-benzisothiazole (3.93 g, 0.0179 mol, 1.1 equiv) and an 80:20 mixture of 2-(4-chlorobutyl)-1(2*H*)-phthalazinone and 2-(4-bromobutyl)-1(2*H*)-phthalazinone (**19**) (4.00 g, 0.163 mol) was obtained 7.75 g of crude material, which was purified by flash chromatography with 3:1 EtOAc–hexanes as eluant. The hydrochloride salt was prepared, recrystallized from EtOH/H_2O, and dried in a vacuum oven to give 4.09 g (55%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl-1(2*H*)-phthalazinone hydrochloride (**36**) as a white crystalline solid: mp 252–253 °C; ^{1}H NMR (DMSO-d_6) δ 1.83 (m, 4), 3.22 (m, 4), 3.61 (br q, 4, J = 10.5), 4.25 (d, 2, J = 13.2), 4.20 (t, 1, J = 5.9), 7.47 (ddd, 1, J = 8.1, 7.0, 1.1), 7.59 (ddd, 1, J = 8.1, 7.0, 1.1), 7.89 (m, 1), 7.96 (m, 2), 8.12 (tt, 2, J = 7.6, 1.4), 8.28 (dm, 1, J = 7.8), 8.48 (d, 1, J = 0.7), 11.16 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.35, 25.29, 46.32, 49.43, 50.46, 55.11, 121.12, 123.94, 124.55, 125.71, 126.78, 126.91, 126.99, 128.06, 129.28, 132.00, 133.45, 138.01, 152.05, 158.36, 162.16. Anal. ($C_{23}H_{25}N_5OS$·HCl) C, H, N.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-methyl-1(2*H*)-phthalazinone Hydrochloride Hydrate (37). This compound was prepared according to the method outlined for compound **30**. The crude product obtained from the reaction of 2-(4-bromobutyl)-4-methyl-1(2*H*)-phthalazinone (**20**) (2.48 g, 8.4 mmol) and 3-(1-piperazinyl)-1,2-benzisothiazole (1.93 g, 8.80 mmol, 1.05 equiv) was purified by recrystal-

lization from acetonitrile to give 2.89 g of the free base as a light orange solid. The hydrochloride salt was prepared, recrystallized from 95% EtOH, and dried in a vacuum oven to give 2.71 g (68%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-methyl-1(2*H*)-phthalazinone hydrochloride hydrate (**37**) as an off-white powder: mp 228–230 °C; ^{1}H NMR (DMSO-d_6) δ 1.80 (br s, 4), 2.56 (s, 3), 3.20 (m, 4), 3.52 (m, 4), 4.04 (br d, 2, J = 13.3), 4.14 (m, 2), 7.45 (t, 1, J = 7.5), 7.59 (t, 1, J = 7.5), 7.87 (m, 1), 7.98 (d, 2, J = 3.7), 8.11 (dd, 2, J = 7.8, 4.9), 8.29 (d, 1, J = 7.7), 11.08 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 18.55, 20.37, 25.31, 46.36, 49.14, 50.51, 55.13, 121.15, 123.95, 124.57, 125.61, 126.14, 126.90, 128.08, 129.15, 131.75, 133.31, 143.46, 152.06, 158.19, 162.15. Anal. ($C_{24}H_{27}N_5OS$·HCl·0.25H_2O) C, H, N.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-Dioxide Hydrochloride (38). This compound was prepared according to a method analogous to that described for compound **30** from 3-(1-piperazinyl)-1,2-benzisothiazole (1.23 g, 5.61 mmol) and 2-(4-bromobutyl)-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (**21**)[35] (1.78 g, 5.59 mmol). The crude product was purified by flash chromatography with 3:2 EtOAc–hexanes as eluant to give 2.52 g of an off-white solid. The hydrochloride salt was prepared, recrystallized from EtOH/H_2O, and dried in a vacuum oven to give 1.73 g (63%) of the title compound (**38**) as an off-white solid: mp 222.5–224 °C [lit.[35] mp 224–226 °C]; ^{1}H NMR (DMSO-d_6) δ 1.85 (br s, 4), 3.14–3.68 (m, 8), 3.81 (br t, 2, J = 5.4), 4.09 (br d, 2, J = 12.9), 7.48 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.6), 8.09 (m, 5), 8.35 (dm, 1, J = 7.7), 10.74 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.75, 25.59, 38.41, 46.68, 50.80, 55.13, 121.53, 121.88, 124.36, 124.95, 125.44, 126.68, 127.30, 128.45, 135.62, 136.13, 137.02, 152.43, 158.96, 162.55. Anal. ($C_{22}H_{24}N_4O_3S_2$·HCl) C, H, N.

3-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2,3-benzotriazin-4(3*H*)-one Hydrochloride (39). 3-(4-Chlorobutyl)-1,2,3-benzotriazin-4(3*H*)-one (**22**) (2.00 g, 8.41 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (1.85 g, 8.41 mmol, 1.0 equiv), triethylamine (1.52 mL, 1.11 g, 10.9 mmol, 1.3 equiv), and acetonitrile (25 mL) were added to a 50-mL, round-bottomed flask equipped with a magnetic stirring bar, condenser, and N_2 inlet. The reaction mixture was heated at reflux under N_2 for 17 h. The reaction was incomplete as indicated by TLC; therefore, additional portions of 3-(1-piperazinyl)-1,2-benzisothiazole (0.184 g, 0.84 mmol, 0.1 equiv) and triethylamine (0.59 mL, 0.428 g, 4.23 mmol, 0.5 equiv) were added and the reaction mixture was heated at reflux for an additional 4 h. The solution was allowed to cool to room temperature and transferred to a separatory funnel with the aid of CH_2Cl_2 (75 mL). The solution was washed with saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give a crude orange oil. The crude material was purified by flash chromatography with 1:1 EtOAc–hexanes to give 1.25 g of an oil that solidified upon standing. A portion of the free base (0.63 g, 1.50 mmol) was dissolved in CH_2Cl_2 and HCl (1.5 mL of a 1 N solution in Et_2O, 1.0 equiv) was added. The hydrochloride salt was recrystallized from EtOH/H_2O to give 0.44 g (23%) of 3-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2,3-benzotriazin-4(3*H*)-one hydrochloride (**39**) as a beige solid: mp 244–245 °C; ^{1}H NMR (DMSO-d_6) δ 1.89 (m, 4), 3.24 (m, 4), 3.43 (br t, 2, J = 11.9), 3.59 (br t, 2, J = 11.1), 4.07 (br d, 2, J = 11.4), 4.46 (t, 2, J = 6.5), 7.47 (tm, 1, J = 7.5), 7.60 (tm, 1, J = 7.5), 7.96 (ddd, 1, J = 1.3, 7.2, 7.9), 8.12 (m, 3), 8.24 (dd, 1, J = 0.7, 8.1), 8.29 (ddd, 1, J = 0.5, 1.4, 7.9), 10.5 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.36, 25.52, 46.33, 48.50, 50.49, 55.02, 119.24, 121.15, 123.96, 124.54, 124.57, 126.91, 127.94, 128.08, 132.89, 135.35, 143.66, 152.06, 154.78, 162.16. Anal. ($C_{22}H_{24}N_6OS$·HCl) C, H, N.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,3(2*H*,4*H*)-isoquinolinedione Hydrochloride Hydrate (40). 2-(4-Bromobutyl)-1,3(2*H*,4*H*)-isoquinolinedione (**24**) (9.74 g, 33 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (7.96 g, 36.3 mmol, 1.1 equiv), triethylamine (5.52 mL, 4.0 g, 39.6 mmol, 1.2 equiv), and acetonitrile (50.0 mL) were added to a round-bottomed flask equipped with magnetic stirring bar, condenser, and N_2 inlet. The reaction mixture was heated at reflux for 3.5 h. The crude mixture was adsorbed onto silica gel and purified by flash chromatography with 2:1 EtOAc–hexanes followed by EtOAc as eluant to give 11.9 g of the free base as an orange oil. To a solution of the free base in EtOAc was added HCl (27.4 mL of a 1 N solution in Et_2O, 1.0 equiv). The resulting hydrochloride salt was recrystallized from EtOH/H_2O to give 6.57 g (40%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-1,3(2*H*,4*H*)-isoquinolinedione hydrochloride hydrate (**40**) as an orange solid: mp 190–195 °C; ^{1}H NMR (DMSO-d_6) δ 1.64 (m, 2), 1.75 (m, 2), 3.10–3.60 (m, 4), 3.91 (q, 2, J = 6.8), 4.05 (br d, 2, J = 13.0), 7.55 (m, 4), 8.12 (m, 4), 10.60 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.57, 24.66, 36.02, 38.53, 46.32, 50.44, 55.12, 121.13, 123.94, 124.57, 124.84, 126.90, 127.20, 127.48, 127.93, 128.06, 133.46, 135.41, 152.06, 162.15, 164.53, 170.08. Anal. ($C_{24}H_{26}N_4O_2S$·HCl·0.5H_2O) C, H, N, H_2O.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3(2*H*)-one Hydrochloride (41). This compound was prepared according to the method described for compound **30**. From 2-(4-chlorobutyl)-1,2-benzisothiazol-3(2*H*)-one (**26**) (6.61 g, 0.0273 mol), and 3-(1-piperazinyl)-1,2-benzisothiazole (6.78 g, 0.0309 mol, 1.13 equiv) was obtained 14.16 g of a dark orange oil. This crude material was purified by flash chromatography with 4:1 EtOAc–CH_2Cl_2 as eluant, followed by recrystallization of the free amine from 95% EtOH to yield 3.68 g of an off-white powder. The hydrochloride salt was prepared, recrystallized from 95% EtOH, and dried in a vacuum oven to give 2.81 g (22%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3(2*H*)-one hydrochloride (**41**) as an off-white powder: mp 215–216 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (br s, 4), 3.19 (m, 4), 3.49 (m, 4), 3.87 (m, 2), 4.02 (br d, 2, J = 13.4), 7.44 (m, 2), 7.57 (ddd, 1, J = 1.1, 7.0, 8.0), 7.68 (ddd, 1, J = 1.3, 7.1, 8.4), 7.86 (dq, 1, J = 7.8, 0.7), 8.00 (dt, 1, J = 8.1, 0.9), 8.09 (m, 2), 11.15 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.26, 26.27, 42.34, 46.29, 50.45, 54.93, 121.12, 121.91, 123.94, 124.05, 124.55, 125.47, 125.54, 126.90, 128.06, 131.75, 140.38, 152.04, 162.16, 164.34. Anal. ($C_{22}H_{24}N_4OS_2$·HCl) C, H, N.

2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,4(2*H*,3*H*)-phthalazinedione Hydrochloride (42). Sodium hydride (0.102 g of an 80% oil dispersion, 3.39 mmol, 1 equiv) was added to a flame-dried, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and N_2 inlet. The sodium hydride was washed with hexanes (3×), and anhydrous DMF (10 mL) was added. The suspension was cooled in an ice–water bath. Phthalhydrazide (0.549 g, 3.39 mmol) and 8-(1,2-benzisothiazol-3-yl)-8-aza-5-azoniaspiro[4.5]decane bromide[16] (1.2 g, 3.39 mmol, 1.0 equiv) were added and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled in an ice–water bath and the excess sodium hydride was quenched with distilled H_2O (5.0 mL). The solvent was removed in vacuo and the residue was partitioned between EtOAc and H_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 0.63 g of the crude material. This crude material was combined with an additional 1.3 g of the crude material obtained from a previous run. The aqueous phases of both reactions were also combined and washed with CH_2Cl_2. The CH_2Cl_2 was dried over $MgSO_4$, filtered, and removed *in vacuo* to obtain an additional 0.34 g of crude material. The crude material was purified by flash chromatography with 94:6 CH_2Cl_2–MeOH to give 0.64 g of the free base as a white solid. To a solution of the free base in chloroform was added HCl (1.47 mL of a 1 N solution in Et_2O, 1.0 equiv). The resulting hydrochloride salt was recrystallized from EtOH/H_2O to give 0.429 g (13%) of 2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-1,4(2*H*,3*H*)-phthalazinedione hydrochloride (**42**) as a white solid: mp 242–245 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.81 (br s, 4), 3.26 (m, 4), 3.45 (br t, 2, J = 12.0), 3.57 (br d, 2, J = 11.5), 4.06 (m, 4), 7.47 (ddd, 1, J = 0.8, 7.2, 8.1), 7.60 (ddd, 1, J = 1.0, 7.1, 8.1), 7.90 (m, 2), 7.98 (m, 1), 8.12 (t, 2, J = 7.2), 8.25 (m, 1), 10.69 (br s, 1), 11.70 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.37, 25.14, 46.33, 48.32, 50.45, 55.12, 121.13, 123.93, 124.07, 124.55, 126.41, 126.90, 128.06, 128.71, 132.22, 133.03, 150.23, 152.05, 157.15, 162.15. Anal. ($C_{23}H_{25}N_5O_2S$·HCl) C, H, N.

3-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4(3*H*)-quinazolinone Hydrochloride (43). Methyl 2-(*N*,*N*-

dimethyl-*N'*-formamidinyl)benzoate (**29**)[22] (0.621 g, 3.01 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (**28**) (0.960 g, 3.31 mmol, 1.1 equiv), *p*-toluenesulfonic acid (0.1 g), and anhydrous 1,4-dioxane (45 mL) were added to a flame-dried, 250-mL, round-bottomed flask equipped with a magnetic stirring bar, condenser, and N_2 inlet. The reaction mixture was heated at reflux for 1 h, allowed to cool to room temperature, and concentrated to give an orange oil. The oil was dissolved in a solution of EtOAc and CH_2Cl_2 and washed with saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 1.41 g of a tan solid. The crude material was purified by flash chromatography with 24:1 CH_2Cl_2–MeOH as eluant to give 1.02 g of a white solid. To a solution of the free base in EtOAc was added HCl (2.43 mL of a 1 N solution in Et_2O, 1.0 equiv). The hydrochloride salt was recrystallized from EtOH/H_2O to give 0.810 g (59%) of 3-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4(3*H*)-quinazolinone hydrochloride (**43**) as a white solid: mp 238–240 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.80 (br s, 4), 3.28 (m, 4), 3.47 (br t, 2, J = 12.6), 3.58 (br d, 2, J = 12.0), 4.05 (br s, 3), 4.08 (m, 1), 7.47 (ddd, 1, J = 1.1, 6.9, 8.1), 7.58 (qm, 2, J = 8.4), 8.12 (t, 3, J = 8.0), 8.18 (ddd, 3, J = 0.6, 1.6, 8.0), 8.46 (s, 1), 10.86 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.24, 25.78, 45.25, 46.31, 50.42, 54.89, 121.12, 121.48, 123.94, 124.56, 125.97, 126.90, 126.97, 127.11, 128.06, 134.22, 147.87, 147.96, 152.05, 160.17, 162.16. Anal. ($C_{23}H_{25}N_5OS$·HCl) C, H, N.

(±)-*cis*-2-(Methoxycarbonyl)-1-cyclohexanecarboxylic acid (45). (±)-*cis*-1,2-Cyclohexanedicarboxylic anhydride (**44**) (10.0 g, 64.9 mmol) and MeOH (2.76 mL, 2.18 g, 68.1 mmol, 1.05 equiv) were added to a round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. The reaction mixture was heated with an oil bath at 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature and the excess MeOH was removed in vacuo to obtain 12.0 g (100%) of (±)-*cis*-2-(methoxycarbonyl)-1-cyclohexanecarboxylic acid as an oil that became a white solid upon standing: mp 63–66 °C; ^{1}H NMR ($CDCl_3$) δ 1.35–1.65 (m, 4), 1.80 (m, 2), 2.03 (m, 2), 2.86 (m, 2), 3.68 (s, 3); ^{13}C NMR ($CDCl_3$) δ 23.63, 23.75, 25.96, 26.26, 42.34, 42.48, 51.71, 174.04, 179.71. Anal. ($C_9H_{14}O_4$) C, H.

(±)-*cis*-Methyl 2-(Hydroxymethyl)-1-cyclohexanecarboxylate (46). (±)-*cis*-2-(Methoxycarbonyl)-1-cyclohexanecarboxylic acid (**45**) (11.7 g, 63.0 mmol) and anhydrous THF (35.0 mL) was added to a flame-dried, 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, septum, and N_2 inlet. The reaction mixture was cooled with an ice–water bath containing rock salt. Borane–THF complex (69.0 mL of a 1 M solution in THF, 69.0 mmol, 1.1 equiv) was slowly added via a syringe over a 25-min period to the cooled reaction mixture. The stirred solution was allowed to warm to room temperature overnight. The reaction mixture was cooled with an ice–water bath, and distilled H_2O (55 mL) and K_2CO_3 (17 g) were added. The layers were separated and the aqueous phase was extracted with EtOAc followed by Et_2O. The organic layers were combined, washed with saturated sodium chloride, dried over $MgSO_4$, filtered, and concentrated to give 10.9 g of an oil. The crude material was purified by flash chromatography with 2:1 hexanes–EtOAc to give 6.47 g (59%) of (±)-*cis*-methyl 2-(hydroxymethyl)-1-cyclohexanecarboxylate (**46**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.30–1.75 (m, 7), 1.89 (m, 1), 1.97 (t, 1, J = 6.0), 2.02 (m, 1), 2.76 (m, 1), 3.63 (m, 2), 3.68 (s, 3); ^{13}C NMR ($CDCl_3$) δ 23.55, 26.22, 26.34, 40.65, 42.32, 51.44, 64.27, 175.75. Anal. ($C_9H_{16}O_3$) C, H.

(±)-*cis*-Methyl 2-Formyl-1-cyclohexanecarboxylate (47). (±)-*cis*-Methyl 2-(hydroxymethyl)-1-cyclohexanecarboxylate (**46**) (7.20 g, 41.8 mmol), anhydrous dimethyl sulfoxide (42 mL), anhydrous CH_2Cl_2 (200 mL), and triethylamine (29.1 mL, 21.2 g, 209 mmol, 5 equiv) were added to a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, and N_2 inlet. The reaction mixture was cooled with an ice-water bath and sulfur trioxide pyridine complex (26.6 g, 167 mmol, 4.0 equiv) was added in three equal portions at 5-min intervals. The reaction mixture was allowed to stir for 1.5 h. Distilled H_2O (200 mL) was added and the aqueous and organic phases were separated. The aqueous phase was extracted with CH_2Cl_2. The organic layers were combined and concentrated to give a pale orange liquid. The product was partitioned between distilled H_2O and Et_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 7.45 g of a light yellow oil. The crude product was purified by flash chromatography with 12:1 hexanes–EtOAc as eluant to give 4.98 g (70%) of (±)-*cis*-methyl 2-formyl-1-cyclohexanecarboxylate (**47**) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 4), 1.80 (m, 2), 1.96 (m, 2), 2.65 (m, 1), 2.87 (m, 1), 3.68 (s, 3), 9.69 (s, 1).

(±)-*cis*-4a,5,6,7,8,8a-Hexahydro-1(2*H*)-phthalazinone (48) and (±)-*trans*-4a,5,6,7,8,8a-Hexahydro-1(2*H*)-phthalazinone (49). (±)-*cis*-Methyl 2-formyl-1-cyclohexanecarboxylate (**47**) (11.9 g, 69.8 mmol), 95% EtOH (120 mL), and hydrazine hydrate (9.0 g, 154 mmol, 2.2 equiv) as an 85% aqueous solution were added to a round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and N_2 inlet. The reaction mixture was heated at reflux for 0.5 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between distilled H_2O (100 mL) and EtOAc (300 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 7.79 g (74%) of a pale yellow oil that was determined to be a 3:1 mixture of (±)-*cis*-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (**48**) and (±)-*trans*-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (**49**) by integration of the corresponding imine signals at 7.01 and 6.98 ppm, respectively. This crude material was used without further purification; however in separate runs purification by flash chromatography with 2:1 hexanes–EtOAc as eluant provided pure samples of each of the isomers. *cis*-Isomer **48**: mp 67–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.36–1.82 (m, 8), 2.54 (m, 1), 2.69 (m, 1), 7.01 (d, 1, J = 7.0), 8.38 (br s, 1); ^{13}C NMR ($CDCl_3$) δ 23.61, 24.02, 24.24, 25.35, 35.04, 38.15, 149.44, 170.90. Anal. ($C_8H_{12}N_2O$) C, H, N. *trans*-Isomer **49**: mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (m, 4), 1.90 (m, 3), 2.06 (m, 1), 2.19 (m, 1), 2.36 (m, 1), 6.98 (s, 1), 8.36 (br s, 1); ^{13}C NMR ($CDCl_3$) δ 25.13 (2 carbons), 25.22, 28.34, 37.39, 39.62, 150.63, 170.58. Anal. ($C_8H_{12}N_2O$) C, H, N.

(±)-*cis*-2-(4-Chlorobutyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (50) and (±)-*trans*-2-(4-Chlorobutyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (51). Sodium hydride (3.07 g of an 80% oil dispersion, 103 mmol, 2 equiv) was added to a flame-dried, 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, N_2 inlet, and septum. The sodium hydride was washed with hexanes (3×) and anhydrous DMF (30 mL) was added. The suspension was cooled in an ice–water bath and a (3:1) mixture of (±)-*cis*-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (**48**) and (±)-*trans*-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (**49**) (7.79 g, 51.2 mmol) in anhydrous DMF (40.0 mL) was slowly added. After the addition of phthalazinone was complete, 1-bromo-4-chlorobutane (6.47 mL, 9.65 g, 56.3 mmol, 1.1 equiv) was added dropwise. After 15 min, the excess sodium hydride was quenched with distilled H_2O (30 mL) and the solvent was removed in vacuo. Ethyl acetate was added to the residue and the organic layers were washed with H_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 14.0 g of an orange oil. The crude material was purified by flash chromatography with 6:1 hexanes–EtOAc as eluant to give 3.02 g of (±)-*cis*-2-(4-chlorobutyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (R_f = 0.13) as a colorless oil and 3.78 g of (±)-*trans*-2-(4-chlorobutyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (R_f = 0.20) as a colorless oil. *cis*-Isomer **50**: ^{1}H NMR ($CDCl_3$) δ 1.25–1.71 (m, 8), 1.77 (quintet, 4, J = 3.2), 2.48 (q, 1, J = 6.4), 2.67 (m,1), 3.55 (m, 2), 3.78 (m, 2), 7.03 (dd, 1, J = 1.0, 2.6); ^{13}C NMR ($CDCl_3$) δ 22.71, 23.25, 23.51, 24.29, 24.98, 29.15, 34.04, 37.06, 44.95, 46.10, 149.21, 167.53. Anal. ($C_{12}H_{19}N_2OCl$) C, H, N. *trans*-Isomer **51**: ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 4), 1.79 (m, 7), 2.10 (m, 2), 2.34 (m, 1), 3.56 (m, 2), 3.73 (m, 1), 3.84 (m, 1), 7.02 (s, 1); ^{13}C NMR ($CDCl_3$) δ 25.03, 25.21, 25.54, 25.66, 28.42, 29.67, 37.52, 39.92, 44.61, 47.14, 150.58, 168.66. Anal. ($C_{12}H_{19}N_2OCl$) C, H, N.

(±)-*cis*-2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone Hydrochloride (52). (±)-*cis*-2-(4-Chlorobutyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (**50**) (1.05 g, 4.33 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (1.04 g, 4.76 mmol, 1.1 equiv), triethylamine (0.725 mL, 0.526 g, 5.20 mmol, 1.2 equiv), and

acetonitrile (10 mL) were added to a round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and N_2 inlet. The reaction mixture was heated at reflux for 6 h. The reaction was not complete according to TLC; therefore, additional portions of 3-(1-piperazinyl)-1,2-benzisothiazole (0.19 g, 0.2 equiv) and triethylamine (0.12 mL, 87 mg, 0.86 mmol, 0.2 equiv) were added and the reaction mixture was allowed to reflux overnight. The reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered and concentrated to give 2.54 g of an orange oil. The crude material was purified by flash chromatography with 2:1 EtOAc–hexanes followed by EtOAc to give 1.05 g of the free base as a yellow oil. To a solution of the free base in EtOAc was added HCl (2.47 mL of a 1 N solution in Et_2O, 1.0 equiv). The hydrochloride salt was recrystallized from EtOH to give 0.58 g (29%) of the title compound as a white solid. The hydrochloride salt contained 10% of the *trans* isomer: mp 191–193 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.32 (m, 1), 1.46 (m, 3), 1.58 (m, 5), 1.73 (m, 3), 2.73 (m, 1), 3.25 (m, 4), 3.46 (br d, 2, J = 12.4), 3.55 (br d, 3, J = 14.7), 3.70 (m, 2), 4.06 (br d, 2, J = 14.2), 7.16 (d, 1, J = 1.1), 7.20 (d, 1, J = 2.6), 7.48 (ddd, 1, J = 1.1, 7.0, 8.1), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 8.12 (t, 2, J = 8.1), 10.83 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.18, 22.76, 23.22, 23.54, 24.34, 24.87, 34.03, 37.13, 46.28 (2 carbons), 50.41, 55.12, 121.14, 123.95, 124.56, 126.91, 128.07, 149.42, 152.06, 162.16, 167.65. Anal. ($C_{23}H_{31}N_5OS$·HCl) C, H, N.

(±)-*trans*-2-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone Hydrochloride (53). 3-(1-Piperazinyl)-1,2-benzisothiazole (2.92 g, 13.3 mmol, 1.3 equiv), triethylamine (2.16 mL, 1.57 g, 15.5 mmol, 1.5 equiv), acetonitrile (20 mL), and (±)-*trans*-2-(4-chlorobutyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone (**51**) (2.49 g, 10.3 mmol) were added to a round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and N_2 inlet. The reaction mixture was heated at reflux for 24 h under N_2. The reaction was not complete according to TLC; therefore, additional portions of 3-(1-piperazinyl)-1,2-benzisothiazole (0.450 g, 2.05 mmol, 0.2 equiv) and triethylamine (0.72 mL, 0.52 g, 5.14 mmol, 0.5 equiv) were added and the reaction mixture was heated at reflux for an additional 24 h. The reaction mixture was allowed to cool to room temperature and EtOAc was added. The organic layers were washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give 6.2 g of an orange oil. The crude product was purified by flash chromatography with EtOAc as eluant to give 2.72 g of the free base as a pale yellow solid. To a solution of the free base in EtOAc was added HCl (6.41 mL of a 1 N solution in Et_2O, 1.0 equiv). The resulting hydrochloride salt was recrystallized from EtOH to give 2.25 g (47%) of (±)-*trans*-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4a,5,6,7,8,8a-hexahydro-1(2*H*)-phthalazinone hydrochloride (**53**) as an off-white solid: mp 186–188 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (m, 4), 1.61 (br q, 2, J = 6.6) 1.71 (m, 4), 1.97 (m, 2), 2.19 (m, 2) , 3.24 (m, 4), 3.47 (br t, 2, J = 13.0), 3.54 (br d, 2, J = 11.1), 3.69 (td, 2, J = 2.5, 6.5), 4.06 (br d, 2, J = 13.7), 7.16 (d, 1, J = 1.1), 7.48 (ddd, 1, J = 1.1, 7.0, 8.1), 7.60 (ddd, 1, J = 1.1, 7.0, 8.0), 8.12 (t, 2, J = 7.9), 10.8 (br s, 1); ^{13}C NMR (DMSO-d_6) δ 20.14, 24.45, 24.65, 24.87, 25.35, 27.59, 36.68, 38.82, 46.25, 46.30, 50.41, 55.15, 121.13, 123.95, 124.56, 126.91, 128.06, 151.05, 152.06, 162.15, 168.07. Anal. ($C_{23}H_{31}N_5OS$·HCl) C, H, N.

Pharmacology. Radioligand Binding Assays: Dopamine D_2. The radioligand binding assay of Köhler *et al.*[24] was employed with modifications. The striata from male Sprague–Dawley rats were dissected, placed in cold 50 mM Tris buffer (pH 7.7, 1 mL/ 20 mg), and homogenized with a polytron. The homogenate was centrifuged at 48000g for 10 min. The pellet was homogenized and centrifuged a second time. The final pellet was resuspended in cold incubation buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 μM pargyline, pH 7.4). The binding assay was performed using the D_2 antagonist [^{3}H]raclopride at a final assay concentration of 1 nM. Specific binding was defined as the total binding minus the nonspecific binding obtained in the presence of (+)-butaclamol (1 μM). Compounds were screened at 10 μM final assay concentration and the concentration that inhibited specific binding by 50% (IC_{50}) was determined. Using Incubation Buffer for all assay additions, the total assay volume was 0.5 mL. After a 60-min incubation at 25 °C the assay was stopped by rapid filtration through a presoaked GF/B filter followed by washing twice with cold 50 mM Tris buffer. Radioactivity was determined using a LKB Betaplate scintillation counter.

Serotonin 5-HT_{1a}. The radioligand binding assay of Peroutka[25] was employed with modifications. The hippocampuses from male Sprague–Dawley rats were dissected, placed in cold 50 mM Tris buffer (pH 7.7, 1 mL/ 50 mg), and homogenized with a polytron. The homogenate was centrifuged at 45000g for 10 min. The supernatant was discarded, and the pellet was resuspended in Tris buffer (1 mL/ 50 mg). The homogenate was incubated at 37 °C for 10 min and centrifuged at 45000g for 10 min, and the resulting pellet was resuspended in cold incubation buffer (50 mM Tris, 4 mM $CaCl_2$, 10 μM pargyline, 0.1% ascorbic acid, pH 7.4). The binding assay was performed using the 5-HT_{1a} agonist [^{3}H]-8-OH-DPAT at a final concentration of 0.3 nM. Specific binding was defined as the total binding minus the nonspecific binding obtained in the presence of serotonin (10 μM). Compounds were screened at 10 μM, and the concentration that inhibited specific binding by 50% (IC_{50}) was determined. Using incubation buffer for all assay additions, the total assay volume was 0.5 mL. After a 30-min incubation at 25 °C, the assay was stopped by rapid filtration through a presoaked GF/B filter followed by washing twice with cold 50 mM Tris buffer (4 mL). Radioactivity was determined using a LKB Betaplate scintillation counter.

Serotonin 5-HT_2. The radioligand binding assay of Leysen *et al.*[26] was employed with modifications. The frontal cortexes from male Sprague–Dawley rats were dissected, placed in cold 0.25 M sucrose solution (10 mL/g), and homogenized with a glass-Teflon homogenizer. The homogenate was centrifuged at 1000g for 10 min. The supernatant was saved and the pellet was washed by homogenizing briefly in sucrose solution (5 mL/ g). The homogenate was again centrifuged at 1000g for 10 min. The pellet was discarded and the supernatants were combined and diluted with 50 mM Tris buffer (pH 7.7). The supernatant solution was centrifuged at 37000g for 10 min. The resulting pellet was resuspended in cold 50 mM Tris buffer (40 mL/g), and the homogenate was centrifuged at 37000g for 10 min. The pellet was resuspended in cold 50 mM Tris Buffer (30 mL/g). The binding assay was performed using the 5-HT_2 antagonist [^{3}H]ketanserin at a final concentration of 0.5 nM. Specific binding was defined as the total binding minus the nonspecific binding obtained in the presence of ketanserin (1 μM). Compounds were screened at 10 μM, and the concentration that inhibited specific binding by 50% (IC_{50}) was determined. Using Tris buffer for all assay additions, the total assay volume was 0.5 mL. After a 40-min incubation at 25 °C the assay was stopped by rapid filtration through a presoaked GF/B filter followed by washing twice with cold 50 mM Tris buffer (4 mL). Radioactivity was determined using a LKB Betaplate scintillation counter.

Behavioral Screens. General. Subjects were male, CD-1 mice from Charles River Laboratories weighing 20–25 g, housed in group cages, and fed food and water *ad lib*. The procedures used followed the U.S. Public Health Service guidelines for the care and use of laboratory animals. Vehicle was 0.5% methyl cellulose and dosing volume was 0.5–2.0 mL/ 100 g body weight. Apomorphine hydrochloride was dissolved in 0.0001 N HCl.

Antagonism of Apomorphine-Induced Climbing and Stereotypy.[27] Mice were acclimated to round, wire-mesh cages for at least 30 min prior to initiation of testing. Test compounds or vehicle were given 60 min (po) prior to sc apomorphine hydrochloride (5 mg/kg), N = 6/dose group. Starting 5 min after apomorphine administration and continuing at 5-min intervals for 30 min, subjects were scored for climbing and stereotyped behavior. Climbing was scored as follows: all four feet on the floor of the cage, 0; one to three feet on the wall of the cage, 1; and all four feet off the cage floor, 2. Stereotypy scores were as follows: resting or moving about the cage without constant sniffing, 0; hyperactivity with constant sniffing, 1; hyperactivity, sniffing, licking, 2; licking

and biting mesh, 3; and intensely gnawing mesh, 4. Scores for the six observation periods were averaged for each subject. Percent antagonism of apomorphine effect was calculated by dividing the score from treated subjects by the score form control animals -1×100. ED_{50} values were calculated by the method of Litchfield and Wilcoxin.[36]

Induction of Catalepsy. The method employed to measure catalepsy was a modification of that used by Tedeschi for rat.[32] Test compound was given 60 min (po) before an all-or-none assessment of catalepsy. The mouse was placed with forepaws on top of a 1-in. high rubber stopper and was scored as cataleptic if it remained there for 15 s. No vehicle-treated mice scored as cataleptic. ED_{50} values were calculated by the method of Litchfield and Wilcoxin.[36]

Acknowledgment. The authors thank Ms. Flora Tang for the determination of the receptor binding data, and Mr. Richard Harper and Dr. Gerald Pollard for their excellent technical assistance in the determination of data obtained from the *in vivo* behavioral models. We also acknowledge Dr. Ching Wang and Mr. Walter Faison for conducting the electrophysiology studies and Ms. Laura Mansberg for proofreading this document.

References

(1) Barnes, D. M. Biological Issues in Schizophrenia. *Science* **1987**, *235*, 430–433.
(2) Hughes, S. New Directions in Antipsychotic Research. *Scrip Magazine* **1992**, *7*, 50–52.
(3) Sitsen, J. M. A. *Current Trends in Antipsychotic Research*; PJB Publications: Richmond, Surrey, Engl., 1990.
(4) Lader, M. Clinical Pharmacology of Antipsychotic Drugs. *J. Int. Med. Res.* **1989**, *17*, 1–16.
(5) Jain, A. K.; Kelwala, S.; Gershon, S. Antipsychotic Drugs in Schizophrenia: Current Issues. *Int. Clin. Psychopharmacol.* **1988**, *3*, 1–30.
(6) Hollister, L. E. Old and New Approaches to Drug Treatment of Schizophrenia. *Drug Dev. Res.* **1986**, *9*, 9–21.
(7) Lowe, J. A.; Seeger, T. F.; Vinick, F. J. Atypical Antipsychotics – Recent Findings and New Perspectives. *Med. Res. Rev.* **1988**, *8*, 475–497.
(8) Vinick, F. J.; Kozlowski, M. R. Atypical Antipsychotic Agents. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed. Academic Press: New York, 1986; Vol. 21, pp 1–10.
(9) (a) Jann, M. W. Evaluations of New Drugs, Clozapine. *Pharmacotherapy* **1991**, *11*, 179–195. (b) Bablenis, E.; Weber, S. S.; Wagner, R. L. Clozapine: A Novel Antipsychotic Agent. *DICP, Ann. Pharmacother.* **1989**, *23*, 109–115.
(10) Meltzer, H. Y. Novel Approaches to the Pharmacotherapy of Schizophrenia. *Drug Dev. Res.* **1986**, *9*, 23–40.
(11) Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H. The Clozaril Collaborative Study Group. Clozapine for the Treatment-resistant Schizophrenic. *Arch. Gen. Psychiatry* **1988**, *45*, 789–796.
(12) (a) Lieberman, J. A.; John, C. A.; Kane, J. M.; Rai, K.; Pisciotta, A. V.; Saltz, B.L.; Howard, A. Clozapine-induced Agranulocytosis: Non-cross-reactivity with Other Psychotropic Drugs. *J. Clin. Psychiatry* **1988**, *49*, 271–277. (b) Clozaril. In the *Physicians' Desk Reference*, 48th ed.; Medical Economics Data Production Company: Montvale, NJ, 1994; pp 2042–2046.
(13) Meltzer, H. Y.; Matsubara, S.; Lee, J.-C. Classification of Typical and Atypical Antipsychotic Drugs on the Basis of Dopamine D-1, D-2 and Serotonin$_2$ pK_i Values. *J. Pharm. Exp. Ther.* **1989**, *251*, 238–246.
(14) Bersani, G.; Bressa, G. M.; Meco, G.; Marini, S; Pozzi, F. Combined Serotonin-5-HT_2 and Dopamine-D_2 antagonism in Schizophrenia: Clinical, Extrapyramidal and Neuroendocrine Response in a Preliminary Study with Risperidone (R64766). *Human Psychopharmacol.* **1990**, *5*, 225–231.
(15) Castelao, J. F.; Ferreira, L.; Gelders, Y. G.; Heylen, S. L. E. The Efficacy of the D2 and 5-HT2 Antagonist Risperidone (R64,766) in the Treatment of Chronic Psychosis: An Open Dose-finding Study. *Schizophr. Res.* **1989**, *2*, 411–415.
(16) Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L., Jr. Synthesis and Biological Evaluation of 1-(1,2-Benzisothiazol-3-yl)- and (1,2-Benzisoxazol-3-yl)piperazine Derivatives as Potential Antipsychotic Agents. *J. Med. Chem.* **1986**, *29*, 359–369.
(17) Norman, M. H.; Kelley, J. L.; Hollingsworth, E. B. Conformationally Restricted Analogues of Remoxipride as Potential Antipsychotic Agents. *J. Med. Chem.* **1993**, *36*, 3417–3423.
(18) Davies, R. V.; Iddon, B.; Suschitzky, H.; Gittos, M. W. Intramolecular Cyclisation of 2-Phenylethyl Isocyanates. *J. Chem. Soc. Perkin Trans. 1* **1978**, 180–184.
(19) Gilman, N. W. 2-Benzazepines. III. Improved Synthesis of 2,3,4,5-Tetrahydro-2-benzazepin-1-one. *Synth. Commun.* **1982**, *12*, 373–380.
(20) Wyrick, S. D.; Voorstad, P. J.; Cocolas, G.; Hall, I. H. Hypolipidemic Activity of Phthalimide Derivatives. 7. Structure–Activity Studies of Indazolone Analogues. *J. Med. Chem.* **1984**, *27*, 768–772.
(21) Alternatively phthalhydrazone **9** could be prepared by the condensation of 2-acetylbenzoic acid with hydrazine hydrate in refluxing ethanol.
(22) Gupton, J. T.; Miller, J. F.; Bryant, R. D.; Maloney, P. R.; Foster, B. S. The Preparation of Aromatic Amidino Esters and Their Reaction with Primary Amines. *Tetrahedron* **1987**, *43*, 1747–1752.
(23) Brown, H. C.; Cha, J. S.; Nazer, B.; Yoon, N. M. Exceptionally Facile Reduction of Acyclic and Alicyclic Carboxylic Acids to Aldehydes by Thexylchloroborane–Dimethyl Sulfide. *J. Am. Chem. Soc.* **1984**, *106*, 8001–8002.
(24) Köhler, C.; Hall, H.; Ögren, S.; Gawell, L. Specific *in vitro* and *in vivo* binding of ^{3}H-Raclopride: A Potent Substituted Benzamide Drug with High Affinity for Dopamine D-2 Receptors in the Rat Brain. *Biochem. Pharmacol.* **1985**, *34*, 2251–2259.
(25) Peroutka, S. J. Pharmacological Differentiation and Characterization of 5-HT_{1a}, 5-HT_{1b}, and 5-HT_{1c} Binding Sites in Rat Frontal Cortex. *J. Neurochem.* **1986**, *47*, 529–540.
(26) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. ^{3}H-Ketanserin (R 41 468), a Selective ^{3}H-Ligand for Serotonin$_2$ Receptor Binding Sites. *Mol. Pharmacol.* **1982**, *21*, 301–314.
(27) Costall, B.; Naylor, R. J.; Nohria, V. Climbing Behaviour Induced by Apomorphine in Mice: A Potential Model for the Detection of Neuroleptic Activity. *Eur. J. Pharmacol.* **1978**, *50*, 39–50.
(28) (a) Seeman, P. Dopamine Receptors and the Dopamine Hypothesis of Schizophrenia. *Synapse* **1987**, *1*, 133–152. (b) Rigdon, G. C.; Wang, C. M. Serotonin Uptake Blockers Inhibit the Firing of Presumed Serotonergic Dorsal Raphe Neurons In Vitro. *Drug Dev. Res.* **1991**, *22*, 135–140.
(29) (a) McMillen, B. A.; Scott, S. M.; Davanzo, E. A. Reversal of Neuroleptic-induced Catalepsy by Novel Aryl-piperazine Anxiolytic Drugs. *J. Pharm. Pharmacol.* **1988**, *40*, 885–887. (b) Corne, S. J.; Pickering, R. W.; Warner, B. T. A Method for Assessing the Effects of Drugs on the Central Actions of 5-Hydroxytryptamine. *Br. J. Pharmacol.* **1963**, *20*, 106–120.
(30) Janssen, P. A. J. Does Ritanserin, A Potent Serotonin-S_2 Antagonist, Restore Energetic Functions During the Night? *J. R. Soc. Med.* **1987**, *80*, 409–413.
(31) Puech, A. J.; Rioux, P.; Poncelet, M.; Brochet, D.; Chermat, R.; Simon, P. Pharmacological Properties of New Antipsychotic Agents: Use of Animal Models. *Neuropharmacology* **1981**, *20*, 1279–1284.
(32) Tedeschi, D. H.; Tedeschi, R. F.; Cook, L.; Mattis, P. A.; Fellows, E. J. The Neuropharmacology of Trifluoperazine: A Potent Psychotherapeutic Agent. *Arch. Int. Pharmacodyn.* **1959**, *122*, 129–143.
(33) Cooper, B. R.; Breese, G. R.; Howard, J. L.; Grant, L. D. Effect of Central Catecholamine Alterations by 6-Hydroxydopamine on Shuttlebox Avoidance Acquisition. *Physiol. Behav.* **1972**, *9*, 727–731.
(34) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(35) Ishizumi, K.; Antoku, F.; Maruyama, I.; Kojima, A. Imide Derivatives, Their Production and Use. Eur. Pat. Appl. 0196096, October 1, 1986.
(36) Litchfield, J. T.; Wilcoxin, F. Simplified Method of Evaluating Dose-effect Experiments. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99–113.