Effect of Linking Bridge Modifications on the Antipsychotic Profile of Some Phthalimide and Isoindolinone Derivatives

Mark H. Norman,*,† Douglas J. Minick,† and Greg C. Rigdon‡

Divisions of Chemistry and of Pharmacology and Molecular Therapeutics, Glaxo Wellcome Inc., Research Triangle Park, North Carolina 27709

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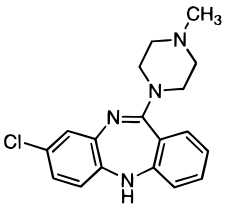
A series of phthalimide and isoindolinone derivatives bridged to 4-(1,2-benzisothiazol-3-yl)-1-piperazinyl was prepared. The compounds were evaluated *in vitro* at dopamine D_2 and serotonin 5-HT_{1a} and 5-HT_2 receptors and *in vivo* for their ability to antagonize the apomorphine-induced climbing response in mice. The effects of bridge length and conformation on the biological activity of these potential antipsychotic agents are discussed. A four-carbon spacer provided optimal activity within the two homologous series. Conformational investigations of the lead compound, isoindolinone **2**, were conducted in an attempt to account for the superior activity observed for the butyl derivatives. On the basis of NMR and molecular modeling studies, two types of folded structures were proposed and several conformationally restrained analogues were synthesized. In general, restrictions incorporated within the linking bridge were detrimental to activity.

Introduction

Since the introduction of chlorpromazine nearly 40 years ago, great progress has been made in the treatment of schizophrenia with neuroleptic drugs. A notable advancement has been the development of the dibenzodiazepine clozapine (**1**) as an atypical antipsychotic agent.[1−7] Clozapine was found to be an effective antipsychotic agent that did not induce concomitant extrapyramidal side effects. However, the clinical use of clozapine has been limited owing to the frequency with which it causes agranulocytosis, a potentially lethal blood dyscrasia.[8−10] In the search for an antipsychotic agent that is superior to clozapine, recent efforts have focused on the development of compounds that act at both dopamine and serotonin receptors.[11−18]



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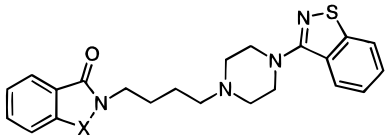

2: X = CH_2
3: X = C=O

Recently, we disclosed a series of cyclic benzamides with mixed dopamine D_2 and serotonin 5-HT_2 receptor antagonistic activity as potential atypical antipsychotic agents.[19] One of the lead compounds, 2-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]-1-isoindolinone (**2**), was selected for further evaluation. The corresponding phthalimide analogue **3**, also exhibited potent *in vivo* activities. These derivatives exhibited activities that suggested they would be useful in the treatment of schizophrenia and would have a low propensity to induce extrapyramidal side effects. To further study the structure−activity relationships within these series, we investigated the structural requirements of the bridge that links the amide or imide moiety with the piperazine benzisothiazole group. The synthesis and biological evaluation of a series of isoindolinone and phthalimide derivatives that contain modified bridging units are described herein.

Chemistry

The syntheses of phthalimide derivatives **3** and **15**−**22** are outlined in Scheme 1. Intermediates **5**−**8** were obtained from commercial suppliers, while alkylation of potassium phthalimide (**4**) with an appropriate dihalide or halo alcohol provided intermediates **9**−**13**. Small amounts of the products arising from bis-alkylation were observed in some cases. The chloro alcohol required for the preparation of the cyclopropyl derivative was obtained by the reduction of *trans*-diethyl 1,2-cyclopropanedicarboxylate with lithium aluminum hydride followed by treatment of the resulting diol with tosyl chloride and (dimethylamino)pyridine.[20] Mesylate **14** was obtained in good yield by the reaction of cyclopropyl alcohol **13** with mesyl chloride in anhydrous dichloromethane. Treatment of intermediates **5**−**12** and **14** with 3-(1-piperazinyl)-1,2-benzisothiazole in refluxing acetonitrile provided the target phthalimides **15**, **16**, **3**, and **17**−**22**, respectively.

Isoindolinone derivatives **2**, **31**−**33**, **38**, **39**, and **46**−**49** were prepared by a variety of methods, as outlined in Schemes 2−4. Condensation of ethanolamine or 3-amino-1-propanol with phthalide **23** provided the corresponding alcohols **25** and **26**, respectively (Scheme 2).[21,22] Attempts to prepare the cyclohexyl derivative **27** by employing a similar condensation using *trans*-4-aminocyclohexanol were unsuccessful. However, when this primary amine was reacted with methyl 2-(bromomethyl)benzoate (**24**)[23] and the reaction was driven to completion by the azeotropic removal of methanol, compound **27** was obtained. Treatment of alcohols **25**−**27** with either thionyl chloride or mesyl chloride provided alkylating agents **28**−**30**, respectively. The chlorides required for the synthesis of *trans*- and *cis*-2-butene derivatives were prepared by the monoreduction of phthalimide **34** followed by alkylation of isoindolinone

† Division of Chemistry.
‡ Division of Pharmacology and Molecular Therapeutics.
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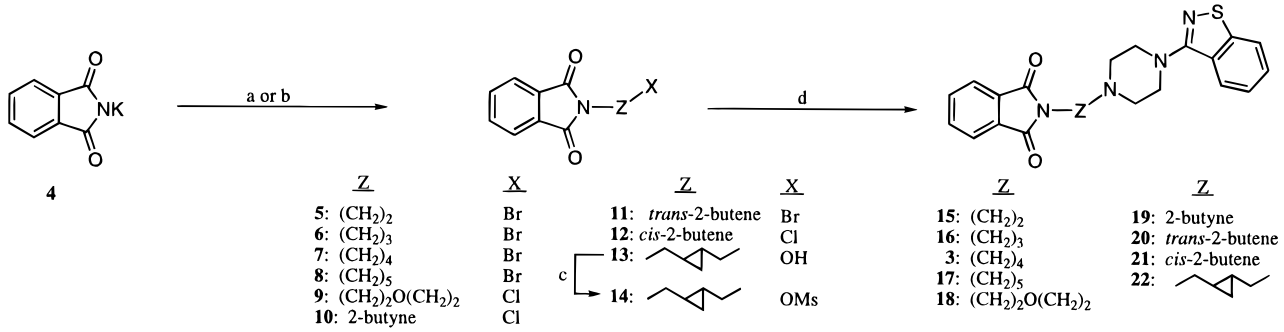
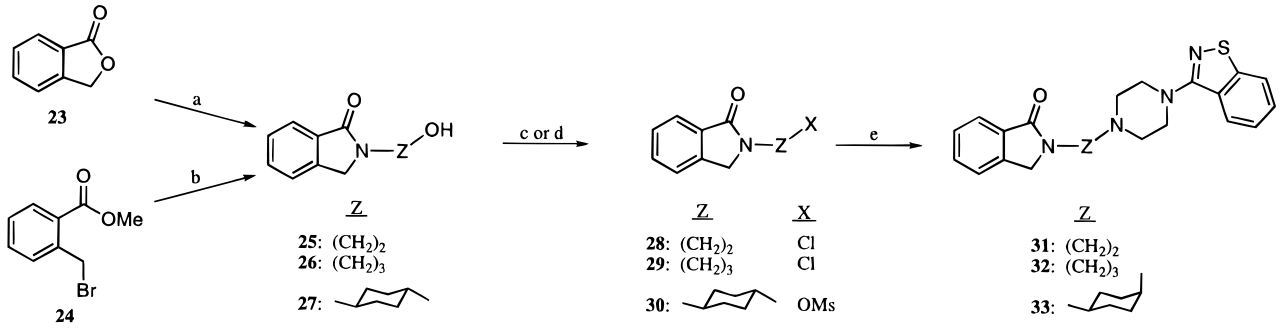
Scheme 1[a]



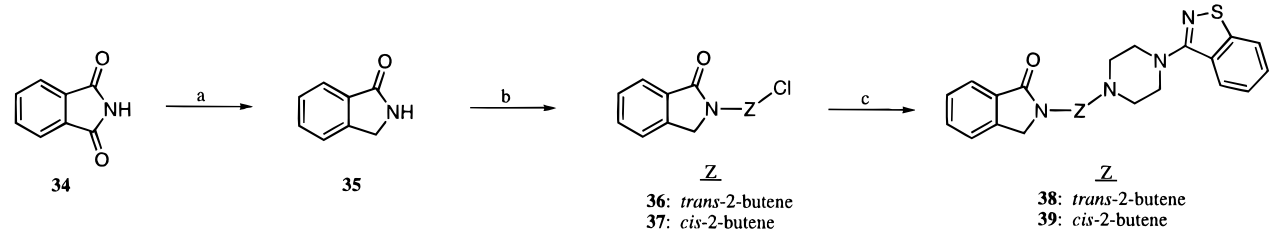
[a] Reagents: (a) 2-chloroethyl ether, 1,4-dichloro-2-butyne, or *cis*-1,4-dichloro-2-butene, 125−170 °C; (b) *trans*-1,4-dibromo-2-butene or (±)-*trans*-2-(chloromethyl)-1-cyclopropanemethanol, DMF, 125 °C−reflux; (c) Et_3N, CH_2Cl_2, MsCl, 0 °C; (d) 3-(1-piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, reflux.

Scheme 2[a]



[a] Reagents: (a) ethanolamine or 3-amino-1-propanol, 205−210 °C; (b) *trans*-4-aminocyclohexanol hydrochloride, K_2CO_3, toluene, H_2O, reflux; (c) $SOCl_2$, toluene, 60 °C; (d) Et_3N, CH_2Cl_2, MsCl, 0 °C; (e) 3-(1-piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, reflux.

Scheme 3[a]



[a] Reagents: (a) HOAc, HCl, Sn, reflux; (b) *trans*- or *cis*-1,4-dichloro-2-butene, DMF, NaH, 0 °C−room temperature; (c) 3-(1-piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, reflux.

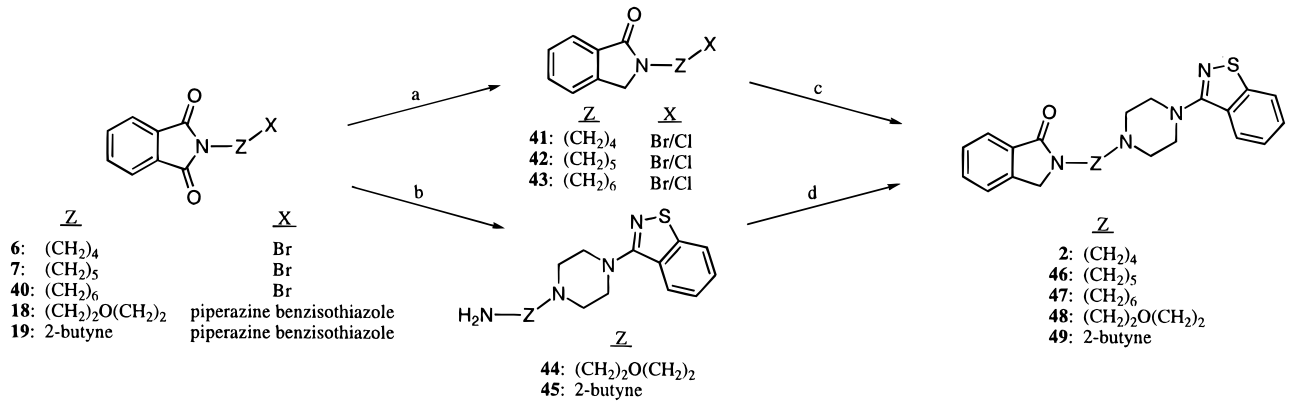
35 with either *trans*- or *cis*-1,4-dichloro-2-butene (Scheme 3). Target isoindolinones **31**−**33**, **38**, and **39** were obtained by the alkylation of 3-(1-piperazinyl)-1,2-benzisothiazole by a method analogous to that employed for the phthalimide derivatives. The reaction with the sterically hindered *trans*-mesylate **30** proceeded with inversion of configuration to provide the *cis*-cyclohexyl product **33**, albeit in poor yield.

The syntheses of the remaining isoindolinones **2** and **46**−**49** are outlined in Scheme 4. The butyl-, pentyl-, and hexylisoindolinone halides **41**−**43** were prepared by the reduction of the corresponding phthalimides with tin metal in concentrated hydrochloric acid.[24] Intermediates **41**−**43** were isolated as mixtures of bromides and chlorides and reacted with piperazine benzisothiazole to give isoindolinones **2**, **46**, and **47**. The final two isoindolinone targets (**48** and **49**) were prepared by the condensation of amines **44** and **45** (obtained from the reaction of phthalimides **18** and **19** with hydrazine hydrate) with methyl 2-(bromomethyl)benzoate (**24**). All of the target compounds, with the exception of compound **48**, were treated with ethereal hydrochloric acid and isolated as their hydrochloride salts. ^1H, ^{13}C, and difference NOE NMR spectra of the targets were consistent with N-alkylated products: No O-alkylated byproducts were observed.

Results and Discussion

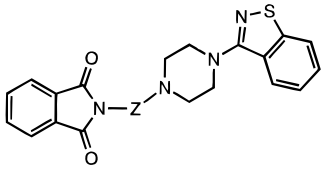
Radioligand-binding competition experiments were carried out to determine the affinities of phthalimides **3** and **15**−**22** and isoindolinones **2**, **31**−**33**, **38**, **39**, and **46**−**49** for dopamine D_2, serotonin 5-HT_{1a}, and serotonin 5-HT_2 receptors. The affinities of the compounds for dopamine D_2 receptors were determined by measuring their ability to displace [^3H]raclopride from the D_2 receptors isolated from the striata of male Sprague−Dawley rats.[25] Inhibition of the binding of [^3H]-8-hydroxy-2-(di-*n*-propylamino)tetralin to rat hippocampus tissue allowed the determination of the compounds' affinities for serotonin 5-HT_{1a} receptors,[26] while serotonin 5-HT_2 binding was measured by the displacement of [^3H]ketanserin from rat frontal cortex.[27] As an indication of potential antipsychotic activity, the compounds were evaluated *in vivo* for their ability to

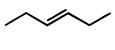
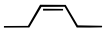
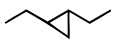
Scheme 4[a]



[a] Reagents: (a) HOAc, HCl, Sn, reflux; (b) $H_2NNH_2 \cdot H_2O$, CH_3OH, reflux; (c) 3-(1-piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, reflux; (d) **24**, toluene, 100 °C−reflux.

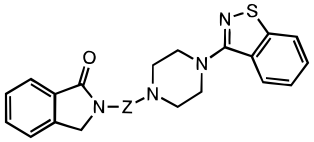
Table 1. Receptor-Binding Affinities and *in Vivo* Activities of Phthalimide Derivatives **3** and **15**−**22**

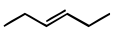


compd no.[a]	Z	receptor binding[b, c] IC_{50} (nM) D_2	$5\text{-}HT_{1a}$	$5\text{-}HT_2$	antagonism of apomorphine-induced mouse climbing[c, d] ED_{50} (mg/kg, ip)
15	$-(CH_2)_2-$	700	54	30	>25
16	$-(CH_2)_3-$	340	13	6.0	>25
3	$-(CH_2)_4-$	49	0.19	7.6	1.1 [0.5-2.4]
17	$-(CH_2)_5-$	21	2.0	1.8	27.0 [7.8-93.6]
18	$-(CH_2)_2O(CH_2)_2-$	170	54	5.4	>25
19		2800	420	43	>25
20		220	4.7	0.78	12.7 [7.2-22.4]
21		130	24	3.2	>25
22		24	19	4.0	22.9 [12.9-40.7]
haloperidol		40	7000	360	2 [1.4-2.8]
clozapine		290	2000	28	26.2 [9.4-73.2]

[a] Hydrochloride salts. [b] D_2: [^{3}H]raclopride binding. $5\text{-}HT_{1a}$: [^{3}H]-8-OH-DPAT binding. $5\text{-}HT_2$: [^{3}H]ketanserin binding. [c] For experimental protocol, see ref 19. Binding values are from single determinations. [d] 95% confidence limits are shown in brackets.[28b]

Table 2. Receptor-Binding Affinities and *in Vivo* Activities of Isoindolinone Derivatives **2**, **31**, **33**, **38**, **39**, and **46**−**49**



compd no.[a]	Z	receptor binding[b, c] IC_{50} (nM) D_2	$5\text{-}HT_{1a}$	$5\text{-}HT_2$	antagonism of apomorphine-induced mouse climbing[c, d] ED_{50} (mg/kg, ip)
31	$-(CH_2)_2-$	270	40	9.8	>25
32	$-(CH_2)_3-$	700	390	13	>25
2	$-(CH_2)_4-$	43	7.0	5.1	6.8 [3.2-14.4]
46	$-(CH_2)_5-$	44	2.7	2.2	20-25[e]
47	$-(CH_2)_6-$	9.2	0.76	0.69	11.2 [6.1-20.6]
48	$-(CH_2)_2O(CH_2)_2-$	180	220	1.7	>25
49		1100	1000	18	>25
38		44	23	1.7	17.6[e]
39		43	44	5.5	13.9[e]
33		7.6	140	120	11.7 [7.4-18.5]

[a] Hydrochloride salts. [b] D_2: [^{3}H]raclopride binding. $5\text{-}HT_{1a}$: [^{3}H]-8-OH-DPAT binding. $5\text{-}HT_2$: [^{3}H]ketanserin binding. [c] For experimental protocol, see ref 19. Binding values are from single determinations. [d] 95% confidence limits are shown in brackets.[28b] [e] Insufficient number of doses tested to determine 95% confidence limits.

antagonize the apomorphine-induced climbing response in mice.[28a] The results of these *in vitro* and *in vivo* assays for both the phthalimide and isoindolinone series are shown in Tables 1 and 2, respectively.[28b,c] The corresponding biological data for reference compounds, haloperidol and clozapine, are also included in Table 1.

Initially, we were interested in studying the effect of the length of the bridging unit on biological activity. As additional methylene groups were added to extend the length of the spacer, both the isoindolinone and phthalimide series exhibited similar trends. Receptor-binding affinities (especially dopamine D_2) and *in vivo* activities increased from ethyl to propyl to butyl (Table 1, **15**, **16**, and **3**; Table 2, **31**, **32**, and **2**). In both series, dopamine D_2 and serotonin $5\text{-}HT_2$ receptor binding affinities were maintained or continued to increase with the pentyl derivatives; however, the *in vivo* activity of these analogues declined (compounds **17** and **46**). The homologous isoindolinone hexyl analogue **47** exhibited both reduced solubility and *in vivo* activity. Introduction of an oxygen in the middle of the five-atom bridge also resulted in reduced activity (compounds **18** and **48**). These data indicated that the butyl bridge provided optimal activity.

To gain insight into possible reasons for the superior activity of butyl analogues **3** and **2**, investigations were

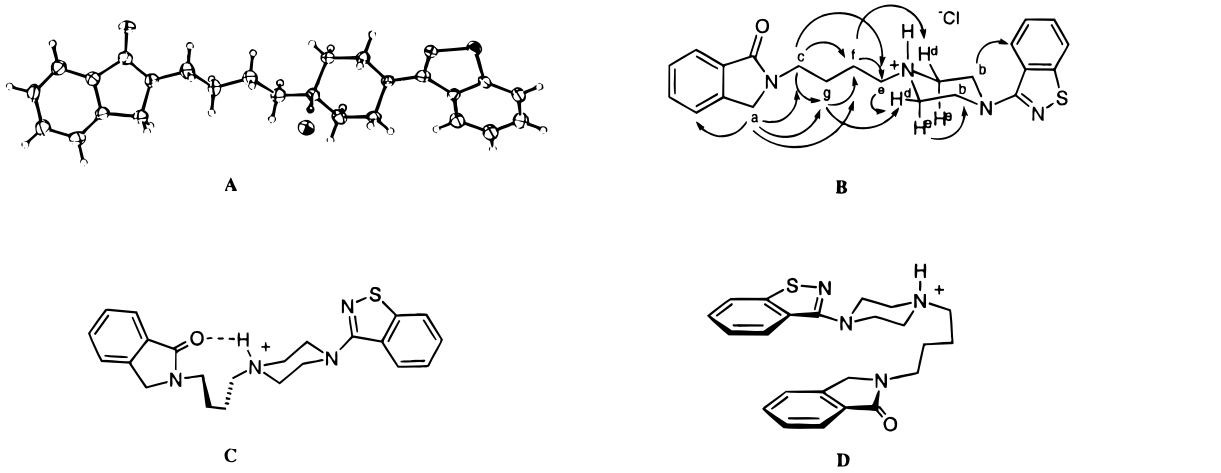


Figure 1. (A) ORTEP representation of the X-ray crystal structure of isoindolinone **2**. (B) Extended conformation of isoindolinone **2**. Significant NOE signals are indicated. (C) Proposed folded, intramolecular hydrogen-bonded conformation of isoindolinone **2**. (D) Proposed folded conformation of isoindolinone **2** with interactions between the two terminal aromatic groups.

undertaken to study some physical and spectral properties of the isoindolinone series. Conformational information was obtained for isoindolinone **2** via an X-ray crystal structure and ^{1}H NMR data. Crystals suitable for X-ray analysis were obtained by recrystallization from ethanol, and the crystal structure was determined.[29] The resultant ORTEP representation of **2** is shown in Figure 1A. In the solid state, the compound exists in an extended conformation with the methylene bridging units in an antiperiplanar arrangement. NMR data, on the other hand, suggested that the conformation in solution was quite different. 2D-NOE experiments were conducted in deuterated chloroform, and the significant NOE signals are indicated in Figure 1B. If the compound was in its extended conformation, the interactions between H_a-H_f and H_c-H_e would not be expected to exist. In a folded or "kinked" conformation, the closer spatial arrangements of these protons could explain the observed NOE signals. Two types of folded conformations are proposed and illustrated in Figure 1C,D. In a folded conformation, such as shown in Figure 1C, an intramolecular hydrogen bond between the protonated piperazine and the amide carbonyl may help stabilize the folded conformation, while a $\pi-\pi$ interaction between the two aromatic termini may help form a conformation of the type shown in Figure 1D. ^{1}H NMR studies in different solvents also supported the possibility of a folded conformation. In deuterium oxide, the signals for the two center methylene groups (g and f) are broadened and appear as a single multiplet, indicating that a fast equilibrium exists between open (Figure 1B) and folded (Figure 1C,D) conformations. However, in deuterated chloroform the corresponding methylene signals are sharp and separated by 0.2 ppm, suggesting that a folded conformation may predominate.

In addition to this spectral data, molecular modeling studies were undertaken to further investigate the conformational preference of isoindolinone **2**. To obtain a qualitative picture of the conformational space open to **2**, four Monte Carlo conformational searches were conducted using MacroModel (version 4.5) with the MM2* force field.[30] Conformational preferences for both the free base and the hydrochloride salt of **2** were investigated using the parameters for either a water or chloroform continuum. All flexible bonds were allowed to rotate, the simulations were conducted for 500 iterations, and conformations that were within 4 kJ of the lowest energy conformation were examined. The results of the experiments showed that three general families of conformations were obtained (two types of folded conformations and open conformations). The folded conformations corresponded to the previously proposed conformations, and representatives for each type are illustrated in Figure 2. The greatest variety of conformations was predicted for the free base of isoindolinone **2** in chloroform. In this case, a mixture of open (Figure 2A) and folded (Figure 2B,C) conformations was produced, and no clear conformational preference was observed. In the other experiments, however, the lowest energy conformations were generally of the type in Figure 2B, wherein an intramolecular hydrogen-bonding interaction between the carbonyl and the protonated piperazine dominated, or of the type in Figure 2C, wherein a $\pi-\pi$ interaction was favored. In chloroform, conformations of the type in Figure 2B predominated for the hydrochloride salt of **2**, while a mixture of both types of folded conformations were obtained when water was used in the calculations. When the free base of **2** was examined in water, all of the conformations were similar to the type in Figure 2C. In general, these modeling results suggested that, although isoindolinone **2** is very flexible, a preference may exist for the folded conformations.

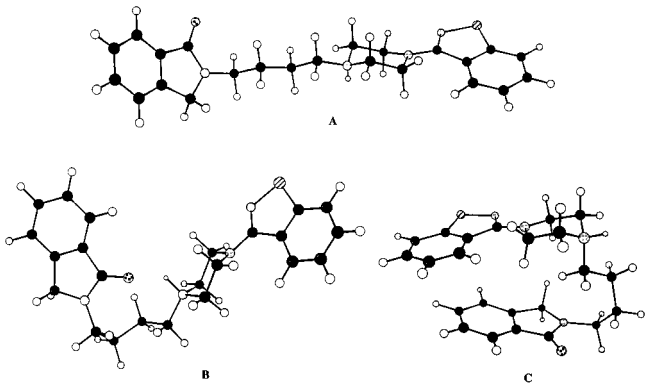


Figure 2. Representative low-energy conformations of isoindoline **2** obtained from Monte Carlo conformational computations: (A) "open" conformation of **2** free base, (B) "folded" hydrogen-bonded conformation of **2** hydrochloride, (C) "folded" conformation of **2** hydrochloride with a $\pi-\pi$ interaction.

As a second phase of these investigations, several analogues containing conformationally constrained four-atom bridging units were prepared in attempts to alter the position of the terminal pharmacophores (i.e., compounds **19**−**22**, **33**, **38**, **39**, and **49**). The butynyl derivatives **19** and **49**, where a folded conformation might be inhibited, exhibited decreased activities both *in vitro* and *in vivo*. The *trans*-2-butene analogues **20** and **38** were 2.5−11.5 times less active in the mouse climbing assay than their saturated counterparts **3** and **2**, respectively. Changing the configuration of the double bond to give *cis*-2-butenes **21** and **39** gave mixed results. While phthalimide **21** showed reduced *in vivo* activity, isoindolinone **39** exhibited a similar pharmacological profile to compound **2**. The phthalimide containing the cyclopropyl unit was 10 times as potent at the dopamine D_2 receptor as the *trans*-2-butene derivative but only one-half as active *in vivo* (compounds **22** and **20**, respectively). The *cis*-cyclohexyl bridge of compound **33** creates a folded conformation that brings the piperazine benzisothiazole and isoindolinone group in close proximity. This restricted conformation resulted in increased dopamine D_2 affinity, decreased affinities to the serotonin receptors, and slightly reduced *in vivo* activity.

Although modeling and spectral data suggest that a folded conformation may exist in solution, no clear conclusions can be made based on the biological results of the conformationally restricted derivatives. On one hand, the weak *in vitro* and *in vivo* activities of the butynyl derivatives **19** and **49** suggested that an extended conformation may not be favorable. Furthermore, the fact that the cyclohexyl derivative **33** retains high affinity to the dopamine D_2 receptor and possesses significant biological activity in the mouse climbing assay may point to a folded structure as a bioactive conformation. However, if a folded conformation is required for good activity, then the relatively potent activities of the butenyl derivatives (especially **20** and **38**) are difficult to rationalize. Perhaps there is an optimum conformation and distance between the terminal pharmacophores that can be obtained in the flexible butyl derivative **2** but cannot be obtained by the restrained analogues. Additional experiments will be necessary to further elucidate the conformational preference of these potential antipsychotic agents. Toward this end, we are currently conducting a series of infrared spectroscopy experiments with the homologous series of isoindolinones (**31**, **32**, and **2**) in hopes of gaining additional insight into the nature of the intramolecular interactions.

In summary, a series of phthalimide and isoindolinone piperazine benzisothiazoles with a variety of different bridging units were prepared and evaluated as potential antipsychotic agents. A four-carbon spacer provided optimal activity within the two homologous series (i.e., compounds **3** and **2**). Conformational studies of isoindolinone **2** indicated a linear arrangement of the molecule in the solid state, but a folded structure was suggested by ^{1}H NMR and molecular modeling analysis. Results of these investigations led us to prepare several derivatives in which the linking bridge contained conformational restraints that restricted the orientations of the two terminal pharmacophores. In general, the restrictions imposed in the linking unit were detrimental to activity; however, a few observations are notable. The weak activity of the butynyl derivatives **19** and **49** and the relatively good activity of cyclohexylisoindolinone **33** supported the possibility of a folded bioactive conformation; however, the good activities of the butenyl derivatives **20** and **38** discount the necessity of completely folded structure. Further experiments are currently underway in attempts to gain additional insight into the structural and conformational requirements of this series.

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), CH_2Cl_2, toluene, pyridine, and dimethyl sulfoxide (DMSO) were obtained in Sure/Seal bottles from Aldrich Chemical Co. 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 and flush chromatography were performed using EM Science silica gel 60 (230−400-mesh ASTM). The term flush chromatography refers to the technique of applying suction to the bottom of a chromatography column to increase the flow rate of the eluant. Thin-layer chromatography (TLC) was performed with Analtech silica gel FG TLC plates (250 μm). ^{1}H NMR spectra were determined with superconducting FT-NMR spectrometers operating at 200, 300, and 500 MHz. ^{13}C NMR spectra were measured at 50.29 or 75.43 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in hertz (Hz). 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 bromide was prepared according to the method described by Yevich et al.[31] Phthalimides **5**−**8** were obtained form commercial suppliers, and compounds **2**, **3**, and **41** were prepared as described previously.[19]

(±)-*trans*-2-(Chloromethyl)-1-cyclopropanemethanol. (±)-*trans*-1,2-Cyclopropanedimethanol [32] (4.0 g, 0.039 mol), tosyl chloride (TsCl) (8.96 g, 0.047 mol, 1.2 equiv), (dimethylamino)pyridine (DMAP) (5.30 g), and anhydrous CH_2Cl_2 (75.0 mL) were added to an oven-dried, 500-mL, round-bottomed flask. The reaction mixture was placed under N_2 and allowed to stir at room temperature for 24 h. Additional portions of the reagents were added, TsCl (2.24 g), DMAP (1.0 g), and CH_2Cl_2 (1.0 mL). The solution was allowed to stir at room temperature for an additional 6 d. Triethylamine (5.43 mL, 3.95 g, 0.039 mol, 1.0 equiv) was added, and the solution was allowed to stir for 24 h. The mixture was heated at reflux for 1.5 h, and the solvent was removed with a rotary evaporator, yielding a sticky tan solid. This crude material was purified by flash chromatography with 1:1 hexanes−EtOAc followed by 19:1 EtOAc−MeOH as eluant to give 1.85 g (39%) of (±)-*trans*-2-(chloromethyl)-1-cyclopropanemethanol. ^{1}H NMR ($CDCl_3$): δ 0.65 (tm, 2, J = 8.0), 1.15 (m, 2), 1.40 (br t, 1, J = 5.0), 3.42 (m, 2), 3.55 (m, 2). A portion of the starting diol (0.87 g) was recovered.

***N*-[2-(2-Chloroethoxy)ethyl]phthalimide (9).** Potassium phthalimide (15.0 g, 0.081 mol) as a fluffy powder and 2-chloroethyl ether (28.5 mL, 34.74 g, 0.243 mol, 3.0 equiv) as a colorless oil were added to a 250-mL, round-bottomed flask. The reaction mixture was heated under N_2 with an oil bath at 170 °C for 19 h. As the mixture was heated, the solution became more liquid in consistency and brown in color. The mixture was removed from the oil bath, and distilled H_2O was added. The solution was allowed to cool to room temperature and extracted with CH_2Cl_2. The organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to give

36.1 g of a dark-orange-brown oil. This crude material was purified by flush chromatography with 3:1 hexanes−EtOAc as eluant to give 13.53 g (67%) of a light-orange oil, which quickly solidified upon standing. An analytically pure white powder was obtained by recrystallization from EtOAc. Mp: 67−70 °C. ^{1}H NMR ($CDCl_3$): δ 3.54 (dt, 2, J = 6.2, 0.8), 3.72 (dt, 2, J = 5.9, 0.6), 3.75 (dt, 2, J = 5.8, 0.9), 3.89 (dt, 2, J = 5.4, 1.2), 7.71 (m, 2), 7.83 (m, 2). ^{13}C NMR ($CDCl_3$): δ 37.14, 42.70, 67.92, 70.61, 123.27, 132.06, 133.97, 168.27. Anal. ($C_{12}H_{12}NO_3Cl$) C, H, N.

***N*-(4-Chloro-2-butynyl)phthalimide (10), (*E*)-*N*-(4-Bromo-2-butenyl)phthalimide (11), and (*Z*)-*N*-(4-Chloro-2-butenyl)phthalimide (12).** These compounds were prepared according to the method described for compound **9**. ^{1}H NMR, ^{13}C NMR, and combustion analyses were consistent with the title compounds. See supporting information for additional information.

(±)-*trans*-*N*-[[2-(Hydroxymethyl)cyclopropyl]methyl]phthalimide (13). Potassium phthalimide (1.44 g, 7.62 mmol), (±)-*trans*-2-(chloromethyl)-1-cyclopropanemethanol (1.59 g, 13.20 mmol, 1.7 equiv), and anhydrous DMF (50.0 mL) were placed in a 100-mL, round-bottomed flask. The resulting cloudy suspension was heated at reflux for 20 h. The reaction mixture was allowed to cool to room temperature, and most of the DMF was removed *in vacuo* with a rotary evaporator. The residue was taken up in CH_2Cl_2 and washed with two portions of H_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 3.55 g of a dark-orange oil. This crude material was purified by flash chromatography with 5:1 hexanes−EtOAc as eluant to give 1.12 g (64%) of (±)-*trans*-*N*-[[2-(hydroxymethyl)cyclopropyl]methyl]phthalimide (**13**) as a white powder. Mp: 117−118 °C. ^{1}H NMR ($CDCl_3$): δ 0.48 (ddd, 1, J = 13.6, 10.3, 5.2), 0.65 (ddd, 1, J = 13.6, 10.3, 5.0), 1.17 (m, 2), 1.52 (br s, 1), 3.45 (m, 2), 3.59 (dd, 2, J = 7.0, 2.2), 7.70 (m, 2), 7.84 (m, 2). ^{13}C NMR ($CDCl_3$): δ 8.99, 16.17, 20.68, 41.57, 66.09, 123.43, 132.12, 133.95, 168.48. Anal. ($C_{13}H_{13}NO_3$) C, H, N.

(±)-*trans*-[2-(Phthalimidomethyl)-1-cyclopropyl]methyl Methanesulfonate (14). (±)-*trans*-*N*-[[2-(Hydroxymethyl)cyclopropyl]methyl]phthalimide (1.04 g, 4.50 mmol), triethylamine (0.94 mL, 0.68 g, 6.75 mmol, 1.5 equiv), and anhydrous CH_2Cl_2 (14.0 mL) were added to a 50-mL, round-bottomed flask. The solution was placed under a N_2 atmosphere and cooled with an ice−water bath. To this cooled mixture was added a solution of mesyl chloride (0.52 mL, 0.77 g, 6.75 mmol, 1.5 equiv) in CH_2Cl_2 (2.0 mL). Upon this addition, the white alcohol suspension became a clear, light-orange solution, which was allowed to stir at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and washed with saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 1.40 g of an off-white solid. This material was purified by flash chromatography on silica gel with 1:1 hexanes−EtOAc as eluant to give 1.29 g (93%) of (±)-*trans*-[2-(phthalimidomethyl)-1-cyclopropyl]methyl methanesulfonate (**14**) as a white powder. Mp: 118−121 °C. ^{1}H NMR ($CDCl_3$): δ 0.65 (dt, 1, J = 8.6, 5.4), 0.83 (dt, 1, J = 8.4, 5.4), 1.33 (m, 2), 2.94 (s, 3), 3.58 (dd, 1, J = 14.2, 7.2), 3.65 (dd, 1, J = 14.2, 6.9), 3.99 (dd, 1, J = 10.8, 7.5), 4.09 (dd, 1, J = 10.8, 7.0), 7.74 (m, 2), 7.86 (m, 2). ^{13}C NMR ($CDCl_3$): δ 9.97, 16.90, 17.26, 37.79, 40.86, 73.22, 123.29, 132.09, 134.02, 168.29.

***N*-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]phthalimide Hydrochloride (15).** *N*-(2-Bromoethyl)phthalimide (**5**) (3.48 g, 13.7 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (3.00 g, 13.7 mmol, 1.0 equiv), triethylamine (2.29 mL, 16.0 mmol, 1.2 equiv), and acetonitrile (30 mL) were added to a 100-mL, round-bottomed flask. The cloudy orange solution was heated at reflux under N_2 for 3.5 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 5.78 g of a viscous orange oil. This crude material was recrystallized from acetonitrile and dried in a vacuum oven to give 1.86 g of a tan powder. The filtrate was concentrated, and the resulting residue was purified by flash chromatography on silica gel with hexanes−EtOAc as eluant to give an additional 0.71 g of the free base as a light-yellow solid. The hydrochloride salt was prepared by the addition of 1 N HCl in Et_2O (6.5 mL, 1.0 equiv) to a solution of the free base in EtOAc−CH_2Cl_2. The salt was recrystallized from EtOH. The solids were filtered, washed with cold EtOH, and dried in a vacuum oven to give 2.07 g (48%) of 2-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-phthalimide hydrochloride (**15**) as off-white flakes. Mp: 248−250 °C dec. ^{1}H NMR (DMSO-d_6): δ 3.32 (m, 7), 3.52 (m, 1), 3.75 (m, 1), 4.01 (m, 1), 4.09 (m, 1), 7.46 (t, 1, J = 7.6), 7.59 (t, 1, J = 7.6), 7.87 (m, 4), 8.09 (d, 1, J = 8.1), 8.14 (d, 1, J = 8.1). ^{13}C NMR (DMSO-d_6): δ 33.04, 47.16, 51.55, 54.11, 122.12, 124.11, 125.02, 125.59, 127.89, 129.09, 132.91, 135.36, 153.06, 163.05, 168.90. Anal. ($C_{21}H_{20}N_4O_2S$·HCl) C, H, N.

***N*-[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]propyl]phthalimide Hydrochloride (16), *N*-[5-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]pentyl]phthalimide Hydrochloride (17), *N*-[2-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethoxy]ethyl]phthalimide Hydrochloride (18), *N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-butynyl]phthalimide Hydrochloride (19), (*E*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-butenyl]phthalimide Hydrochloride (20), and (*Z*)-*N*-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-butenyl]phthalimide Hydrochloride Hydrate (21).** These compounds were prepared by the procedure analogous to that used for compound **15**. ^{1}H NMR, ^{13}C NMR, and combustion analyses were consistent with the title compounds. See supporting information for additional information.

(±)-*trans*-*N*-[[2-[[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]methyl]cyclopropyl]methyl]phthalimide Hydrochloride Hydrate (22). (±)-*trans*-[2-(Phthalimidomethyl)-1-cyclopropyl]methyl methanesulfonate (**14**) (1.17 g, 3.78 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (0.912 g, 4.16 mmol, 1.1 equiv), triethylamine (0.633 mL, 0.459 g, 4.54 mmol, 1.2 equiv), and CH_3CN (10.0 mL) were added to a 100-mL, round-bottomed flask. The cloudy solution was placed under N_2 and heated at reflux for 3.5 h. An additional portion of the piperazine benzisothiazole (0.083 g, 0.10 equiv) was added, and heating was continued for a total of 20 h. The solution was allowed to cool to room temperature, and CH_2Cl_2 was added. The solution was washed with saturated K_2CO_3, and the organic layers were dried over $MgSO_4$, filtered, and concentrated to give 1.92 g of a viscous orange oil. This crude material was purified by flash chromatography with 2:1 hexanes−EtOAc as eluant to give 1.30 g of the free base. The hydrochloride salt was prepared, recrystallized from EtOH−H_2O, and dried in a vacuum oven to give 1.11 g (61%) of (±)-*trans*-*N*-[[2-[[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]methyl]-cyclopropyl]methyl]phthalimide hydrochloride hydrate (**22**) as an off-white powder. Mp: 246−248 °C. ^{1}H NMR (DMSO-d_6): δ 0.74 (m, 2), 1.29 (m, 2), 3.12 (br s, 2), 3.20−3.67 (m, 8), 4.05 (m, 2), 7.45 (t, 1, J = 7.5), 7.58 (t, 1, J = 7.5), 7.18 (m, 4), 8.09 (d, 2, J = 8.2), 11.12 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 9.64, 12.01, 17.07, 46.24, 49.87, 50.22, 58.47, 121.16, 123.02, 124.01, 124.61, 126.93, 128.11, 131.67, 134.37, 152.08, 162.16, 168.02. Anal. ($C_{24}H_{24}N_4O_2S$·HCl·0.5H_2O) C, H, N, H_2O.

Methyl 2-(Bromomethyl)benzoate (24). 2-(Bromomethyl)benzoyl bromide was obtained by bromination of *o*-toluoyl chloride using the method of Davies and Perkin.[23] The crude 2-(bromomethyl)benzoyl bromide (0.184 mol) was taken up in CH_2Cl_2 (40 mL), and the solution was cooled in an ice−water bath. Absolute MeOH (15 mL) was added, and the reaction mixture was allowed to warm to room temperature and stir for 0.5 h. The solution was washed with saturated K_2CO_3 and extracted with EtOAc. The organic layers were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 42.08 g of a pale-yellow oil. This material was used without further purification. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3), 4.96 (s, 2), 7.40 (m, 3), 7.97 (m, 1).

2-(2-Hydroxyethyl)-1-isoindolinone (25). This compound was prepared according to a modified procedure of Murata.[21] Ethanolamine (50.1 g, 0.82 mL) was added to a 300-mL, round-bottomed flask equipped with a Dean−Stark trap, a reflux condenser, a magnetic stirring bar, and a nitrogen inlet. Phthalide (110.0 g, 0.82 mol, 1.0 equiv) was then added as a light-tan powder with stirring. The resulting slurry was

placed under N_2 and heated in an oil bath at 150 °C for 4 h. The oil bath temperature was increased to 205−210 °C, and the melt was heated for an additional 17 h. Water (12 mL) was collected in the Dean−Stark trap. The product solidified upon cooling to give a light-brown solid. The crude material was taken up in hot toluene, and the solution was filtered hot. The solids that formed upon cooling were filtered, washed with cold toluene, and dried in a vacuum oven to give 129.75 g (88%) of 2-(2-hydroxyethyl)-1-isoindolinone (**25**) as a light-tan powder. Mp: 117−119 °C (lit.[21] mp 119−120 °C). ^{1}H NMR ($CDCl_3$): δ 3.28 (br s, 1), 3.69 (m, 2), 3.85 (m, 2), 4.46 (s, 2), 7.40 (m, 3), 7.73 (m, 1). ^{13}C NMR ($CDCl_3$): δ 45.84, 51.63, 61.30, 122.60, 123.44, 127.91, 131.34, 132.44, 141.53, 169.55. Anal. ($C_{10}H_{11}NO_2$) C, H, N.

2-(3-Hydroxypropyl)-1-isoindolinone (26). This compound was prepared according to the method described for compound **25**. By employing 3-amino-1-propanol as the amino alcohol, 2-(3-hydroxypropyl)-1-isoindolinone (156.83 g, 86%) was obtained. ^{1}H NMR ($CDCl_3$): δ 1.91 (quintet, 2, J = 6.2), 3.55 (br s, 2), 3.74 (t, 2, J = 6.2), 3.82 (br s, 1), 4.38 (s, 2), 7.47 (m, 3), 7.80 (m, 1). ^{13}C NMR ($CDCl_3$): δ 30.85, 38.81, 50.39, 58.37, 122.73, 123.64, 128.12, 131.45, 132.30, 141.18, 169.67. Anal. ($C_{11}H_{13}NO_2$) C, H, N.

***trans*-2-(4-Hydroxy-1-cyclohexyl)-1-isoindolinone (27).** Methyl 2-(bromomethyl)benzoate (**24**) (30.00 g, 0.131 mol), *trans*-4-aminocyclohexanol hydrochloride (20.85 g, 0.137 mol, 1.05 equiv), K_2CO_3 (27.15 g, 0.196 mol, 1.5 equiv), toluene (110 mL), and H_2O (20 mL) were added to a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a Dean−Stark trap. The two-phase mixture was heated at reflux for 19 h. The toluene−water azeotrope was collected, and the H_2O was not allowed to re-enter the reaction pot. Fresh toluene (300 mL) was added, and the toluene−MeOH azeotrope was removed through the Dean−Stark trap. After an additional 24 h of heating, the solution was decanted from the salts into a clean, round-bottomed flask. The solvent was removed with a rotary evaporator to give 25.16 g of a viscous orange oil. This crude material was purified by flash chromatography with EtOAc−0.1% triethylamine as eluant to give 11.88 g (39%) of *trans*-2-(4-hydroxy-1-cyclohexyl)-1-isoindolinone (**27**) as an off-white solid. Mp: 133−134 °C. ^{1}H NMR ($CDCl_3$): δ 156 (m, 4), 1.41 (m, 3), 2.11 (m, 2), 3.66 (m, 1), 4.26 (tt, 1, J = 11.5, 3.9), 4.32 (s, 2), 7.47 (m, 3), 7.84 (dd, 1, J = 7.7, 1.6). ^{13}C NMR ($CDCl_3$): δ 29.02, 34.46, 46.04, 49.67, 69.90, 122.68, 123.60, 128.01, 131.12, 133.12, 141.12, 165.11. Anal. ($C_{14}H_{17}NO_2$) C, H, N.

2-(2-Chloroethyl)-1-isoindolinone (28). 2-(2-Hydroxyethyl)-1-isoindolinone (**25**) (117.95 g, 0.666 mol) and toluene (400 mL) were added to a 1-L, round-bottomed flask. The solution was cooled with an ice−water bath, and thionyl chloride (55.0 mL, 89.7 g, 0.754 mol, 1.13 equiv) was added dropwise over a 0.5-h period. The slurry was allowed to stand at room temperature for 4 h with periodic swirling. A condenser was attached, and the reaction mixture was heated at 60 °C for 3 h. The toluene and excess thionyl chloride were removed by distillation under aspirator pressure. The hot residue was poured into petroleum ether (500 mL), forming a brown solid. The crude solid was filtered and taken up in hot toluene. The solution was filtered hot, and the hot toluene solution was poured into petroleum ether (300 mL) with stirring. The solid that formed was filtered, washed with petroleum ether, and dried in a vacuum oven to give 103.08 g of a powdery tan solid. A second crop of 15.99 g was obtained, which gave a total of 119.07 g (91%) of 2-(2-chloroethyl)-1-isoindolinone (**28**). Mp: 80−81 °C (lit.[21] mp 81−82 °C). ^{1}H NMR ($CDCl_3$): δ 3.80 (t, 2, J = 5.4), 3.96 (t, 2, J = 5.4), 4.57 (s, 2), 7.50 (m, 3), 7.86 (m, 1). ^{13}C NMR (DMSO-d_6): δ 7.50, 48.74, 54.98, 128.01, 128.60, 133.08, 136.68, 137.15, 147.11, 172.80. Anal. ($C_{10}H_{10}NOCl$) C, H, N.

2-(3-Chloropropyl)-1-isoindolinone (29). This compound was prepared according to the method described for compound **28**. By employing 2-(3-hydroxypropyl)-1-isoindolinone (**26**) (127.53 g), 130.94 g (94%) of the crude chloride was obtained. A small sample (5 g) was purified by flash chromatography with 4:1 hexanes−EtOAc as eluant to give 4.29 g of an analytically pure, white solid. Mp: 56−57.5 °C. ^{1}H NMR ($CDCl_3$): δ 2.15 (quintet, 2, J = 6.7), 3.58 (t, 2, J = 6.5), 3.74 (t, 2, J = 6.9), 4.41 (s, 2), 7.46 (m, 3), 7.81 (m, 1). ^{13}C NMR ($CDCl_3$): δ 31.29, 40.17, 42.22, 50.57, 122.71, 123.63, 128.68, 131.36, 132.68, 141.11, 168.75. Anal. ($C_{11}H_{12}NOCl$) C, H, N.

2-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-1-isoindolinone Hydrochloride (31). 2-(2-Chloroethyl)-1-isoindolinone (**28**) (6.03 g, 30.82 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (6.76 g, 30.82 mmol, 1.0 equiv), triethylamine (5.15 mL, 3.74 g, 36.99 mmol, 1.2 equiv), and CH_3CN (30.0 mL) were added to a 100-mL, round-bottomed flask. The resulting orange mixture was placed under N_2 and heated at reflux for 24 h. The solution was allowed to cool to room temperature and transferred to a separatory funnel with the aid of EtOAc. The dark-orange solution was washed with saturated K_2CO_3, and the organic layers were dried over $MgSO_4$, filtered, and concentrated to give 13.44 g of an orange oil. This crude material was purified by flash chromatography with 5:1 EtOAc−hexanes as eluant to give 7.15 g of 2-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-2,3-dihydro-1*H*-isoindol-1-one (**31**).

The free amine was taken up in acetone, and HCl (24.5 mL of a 1 N solution in ether, 1.0 equiv) was added. The salt was recrystallized twice from 95% EtOH to give 3.05 g (24%) of the hydrochloride salt as an off-white powder. Spectral and analytical data indicated 1 equiv of HCl and 0.5 equiv of EtOH. Mp: 264−267 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.03 (t, 3, J = 6.9), 3.48 (m, 7), 3.70 (br d, 2, J = 11.0), 4.02 (m, 4), 4.60 (s, 2), 7.55 (m, 6), 8.10 (t, 2, J = 9.2), 11.28 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 8.50, 36.51, 46.17, 49.66, 50.49, 52.88, 55.94, 121.10, 122.84, 123.34, 124.01, 124.55, 126.81, 127.71, 128.05, 131.48, 131.86, 142.24, 152.06, 162.09, 168.00. Anal. ($C_{21}H_{22}N_4OS\cdot HCl\cdot 0.5C_2H_6O$) C, H, N.

2-[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]propyl]-1-isoindolinone Hydrochloride (32), (*E*)-2-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-butenyl]-1-isoindolinone Hydrochloride (38), (*Z*)-2-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-butenyl]-1-isoindolinone Hydrochloride Hydrate (39), 2-[5-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]pentyl]-1-isoindolinone Hydrochloride (46), and 2-[6-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]hexyl]-1-isoindolinone Hydrochloride (47). These compounds were prepared following the procedure described for compound **31**. ^{1}H NMR, ^{13}C NMR, and combustion analyses were consistent with the title compounds. See supporting information for additional information.

(±)-*cis*-2-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-1-cyclohexyl]-1-isoindolinone Hydrochloride Monohydrate (33). *trans*-2-(4-Hydroxy-1-cyclohexyl)-1-isoindolinone (**27**) (3.94 g, 0.017 mol) was taken up in anhydrous CH_2Cl_2 (150 mL), and triethylamine (13.56 mL, 2.59 g, 0.025 mol, 1.5 equiv) was added. The orange solution was placed under N_2 and cooled in an ice−water bath. To this stirred solution was slowly added a mixture of mesyl chloride (1.98 mL, 2.93 g, 0.025 mol, 1.5 equiv) in anhydrous CH_2Cl_2 (3.0 mL). The reaction mixture was allowed to stir at 0−5 °C for 1.25 h. An additional portion of CH_2Cl_2 was added, and the solution was washed with saturated K_2CO_3. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 5.40 g (96%) of *trans*-4-(1-oxo-2-isoindolinyl)-1-cyclohexyl methanesulfonate (**30**) as an orange solid.

This solid (5.27 g, 0.017 mL), 3-(1-piperazinyl)-1,2-benzisothiazole (3.92 g, 0.079 mol, 1.05 equiv), triethylamine (2.85 mL, 2.07 g, 0.020 mol, 1.2 equiv), and CH_3CN (20 mL) were combined, placed under N_2, and heated at reflux for 2.5 d. The mixture was allowed to cool to room temperature and washed with saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 8.29 g of a viscous orange oil. This crude material was purified by flash chromatography with EtOAc as eluant. The material isolated was purified further by flash chromatography with 2:1 EtOAc−hexanes as eluant yielding 0.224 g of a sticky orange oil. The hydrochloride salt of this free base was formed, recrystallized from EtOH, and dried in a vacuum oven to give 0.120 g (2%, based on *trans*-2-(4-hydroxy-1-cyclohexyl)-1-

isoindolinone) of (±)-*cis*-2-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-1-cyclohexyl]-1-isoindolinone hydrochloride monohydrate (**33**) as light-peach crystals. Mp: 231−232 °C. ^{1}H NMR (DMSO-d_6): δ 1.72 (m, 2), 1.95 (m, 2), 2.20 (m, 2), 2.35 (m, 2), 3.33 (m, 2), 3.45 (m, 1), 3.77 (br d, 2, J = 13.4), 3.85 (br d, 2, J = 12.2), 4.05 (br d, 2, J = 13.4), 4.20 (quintet, 1, J = 3.7), 4.74 (s, 2), 7.46 (m, 2), 7.58 (m, 3), 7.67 (d, 1, J = 7.3), 8.11 (dd, 2, J = 8.0, 4.7), 10.80 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 23.37, 25.25, 45.96, 47.95, 48.75, 62.03, 121.17, 122.51, 123.15, 123.91, 124.56, 126.93, 127.69, 128.07, 131.13, 132.37, 142.06, 152.09, 162.15, 167.08. Anal. ($C_{25}H_{28}N_4OS\cdot HCl\cdot H_2O$) C, H, N, H_2O.

1-Isoindolinone (35). Phthalimide (30.0 g, 0.204 mol) was placed in a 500-mL, round-bottomed flask with glacial acetic acid (150.0 mL), concentrated HCl (75.0 mL), and tin metal (58.08 g, 0.489 mL, 2.4 equiv). The creamy slurry was heated in an oil bath at reflux. As the solution was heated, the phthalimide dissolved, resulting in a light-yellow solution. The reaction mixture was allowed to heat at reflux for 2 h, the solution was filtered hot, and the tin shavings were washed with fresh acetic acid. The majority of the acetic acid was removed with a rotary evaporator, resulting in a light-yellow creamy solution. This material was taken up in CH_2Cl_2 and washed with distilled H_2O and a saturated sodium chloride solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 17.61 g of a light-yellow solid. This crude material was purified by flash chromatography with EtOAc as eluant to give 11.93 g (47%) of 1-isoindolinone (**35**) as a light-yellow powder. Mp: 150−151 °C (lit.[33] mp 150−152 °C). ^{1}H NMR ($CDCl_3$): δ 4.48 (s, 2), 7.48 (m, 2), 7.57 (m, 1), 7.76 (br s, 1), 7.88 (m, 1). ^{13}C NMR ($CDCl_3$): δ 45.83, 123.16, 123.64, 127.95, 131.69, 143.72, 172.35. Anal. (C_8H_7NO) C, H, N.

(*E*)-2-(4-Chloro-2-butenyl)-1-isoindolinone (36). Sodium hydride (1.54 g of an 80% oil dispersion, 1.25 equiv) was placed under N_2 in an oven-dried, 500-mL, round-bottomed flask. The sodium hydride was washed with hexanes (2×), and the waste hexanes were removed with a pipet. Anhydrous DMF (100 mL) was added to the washed sodium hydride. To this gray suspension was added a solution of 1-isoindolinone (5.47 g, 0.041 mol) in dry DMF (50.0 mL). In a separate oven-dried, 500-mL, round-bottomed flask, *trans*-1,4-dichloro-2-butene (13.51 g, 0.103 mol, 2.5 equiv) and dry DMF (100.0 mL) were placed. This solution was cooled in an ice−water bath, and the 1-isoindolinone solution was slowly added via a cannula. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stir for 0.5 h. The majority of the DMF was removed with a rotary evaporator, and the residue was taken up in CH_2Cl_2 and washed several times with H_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 20.12 g of a dark-orange oil. This crude material was purified by flash chromatography with 1:1 hexanes−EtOAc as eluant to give 6.48 g (71%) of (*E*)-2-(4-chloro-2-butenyl)-1-isoindolinone (**36**) as a light-yellow oil. The ^{1}H and ^{13}C NMR spectra of this material were consistent for the N-alkylated product. ^{13}C NMR ($CDCl_3$): δ 43.45, 43.99, 49.61, 122.78, 123.79, 128.08, 129.26, 129.56, 131.43, 132.54, 141.16, 168.28.

(*Z*)-2-(4-Chloro-2-butenyl)-1-isoindolinone (37). This compound was prepared according to the method described for compound **36**. Alkylation of 1-isoindolinone (**35**) (5.75 g, 0.043 mol) with *cis*-1,4-dichloro-2-butene (6.25 g, 0.047 mol, 1.1 equiv) in anhydrous DMF provided 3.43 g (36%) of (*Z*)-2-(4-chloro-2-butenyl)-1-isoindolinone (**37**) after purification by flash chromatography. ^{1}H, ^{13}C, and difference NOE NMR spectra of the light-orange oil were consistent with the N-alkylated product. ^{13}C NMR ($CDCl_3$): δ 38.42, 38.50, 49.57, 122.77, 123.75, 128.08, 129.01, 129.44, 131.43, 132.44, 141.15, 168.26.

2-(5-Chloropentyl)- and 2-(5-Bromopentyl)-1-isoindolinone (42) and 2-(6-Chlorohexyl)- and 2-(6-Bromohexyl)-1-isoindolinone (43). These compounds were prepared by the method described for compound **35**. See supporting information for additional information.

2-[2-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethoxy]-ethyl]-1-isoindolinone (48). *N*-[2-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethoxy]ethyl]phthalimide (**18**) (7.45 g, 0.017 mol) was placed in a 100-mL, round-bottomed flask and taken up in MeOH (20 mL). To this stirred solution was added dropwise hydrazine hydrate (1.49 g of an 85% solution in H_2O, 0.025 mol, 1.5 equiv), and the mixture was heated at reflux under N_2 for 2 h. The reaction mixture was allowed to cool to room temperature, and 1 N HCl (50.0 mL) was added. The resulting precipitate was filtered and washed with distilled 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 5.31 g of 3-[4-[2-(2-aminoethoxy)ethyl]-1-piperazinyl]-1,2-benzisothiazole (**44**) as a viscous orange oil.

A solution of toluene (100 mL) and **44** (5.31 g, 0.017 mol) was heated in an oil bath at 100−110 °C. A solution of methyl 2-(bromomethyl)benzoate (**24**) (3.97 g, 0.017 mL, 1.0 equiv) and toluene (25 mL) was added to the amine solution dropwise, over a 15−20-min period. The reaction mixture was heated under N_2 for 0.75 h after the addition was complete. The solution was allowed to cool to room temperature and washed with saturated K_2CO_3. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 6.22 g of a red-orange oil. This crude material was purified by flash chromatography with EtOAc−0.2% triethylamine as eluant followed by recrystallization from an EtOAc−EtOH solution to give 0.95 g (13% based on **24**) of **48** as a tan solid. ^{1}H NMR indicated a small amount of EtOAc present in the sample. Mp: 108−110 °C. ^{1}H NMR ($CDCl_3$): δ 2.69 (m, 6), 3.49 (br t, 4, J = 5.0), 3.66 (t, 2, J = 5.6), 3.74 (dt, 2, J = 1.0, 5.2), 3.82 (br t, 2, J = 4.7), 4.57 (s, 2), 7.34 (ddd, 1, J = 8.2, 7.0, 1.1), 7.47 (m, 4), 7.82 (m, 3). ^{13}C NMR ($CDCl_3$): δ 42.36, 49.80, 51.55, 53.28, 57.82, 68.59, 69.77, 120.53, 122.63, 123.57, 123.85, 127.50, 127.87, 127.97, 131.23, 132.71, 141.64, 152.73, 163.74, 168.55. Anal. ($C_{23}H_{26}N_4O_2S\cdot 0.15C_4H_8O_2$) C, H, N.

2-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-2-butynyl]-1-isoindolinone Hydrochloride (49). 3-[4-(4-Amino-2-butynyl)-1-piperazinyl]-1,2-benzisothiazole (**45**) was prepared according to the method described above for compound **44**. From *N*-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-2-butynyl)phthalimide (**19**) (12.54 g, 0.630 mol), hydrazine hydrate (2.66 g of an 85% aqueous solution), and MeOH (30 mL), 6.23 g (72.3%) of 3-[4-(4-amino-2-butynyl)-1-piperazinyl]-1,2-benzisothiazole was obtained as a crude orange oil.

Amine **45** (6.23 g, 0.022 mol) was taken up in toluene (50 mL). To the stirred mixture was added a solution of methyl 2-(bromomethyl)benzoate (**24**). The resulting orange solution was heated at reflux under N_2 for 18 h. The reaction mixture was allowed to cool to room temperature and transferred to a separatory funnel. The solution was washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give an orange oil. This crude material was purified by flash chromatography on flash silica gel with 3:1 EtOAc−hexanes as eluant. The hydrochloride salt of the pure free base was prepared by the addition of 1 N HCl. The salt was recrystallized from EtOH−EtOAc and dried in a vacuum oven to give 0.24 g (3%) of 2-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-2-butynyl]-1-isoindolinone hydrochloride (**49**) as an off-white powder. Mp: 194−196 °C. ^{1}H NMR (DMSO-d_6): δ 3.40 (m, 3), 3.51 (m, 3), 4.08 (m, 2), 4.22 (br s, 2), 4.59 (s, 2), 4.61 (s, 2), 7.48 (m, 2), 7.58 (m, 1), 7.63 (m, 2), 7.71 (dt, 1, J = 7.5, 1.0), 8.10 (dt, 1, J = 8.2, 0.9), 8.14 (dt, 1, J = 8.2, 0.9), 12.00 (s, 1). ^{13}C NMR (DMSO-d_6): δ 31.32, 44.53, 49.05, 49.85, 73.23, 84.95, 121.13, 122.91, 123.54, 123.98, 124.56, 126.91, 127.96, 128.07, 131.42, 131.70, 141.76, 152.03, 162.15, 166.80. Anal. ($C_{23}H_{22}N_4OS\cdot HCl$) C, H, N.

Pharmacology. Both *in vitro* (receptor-binding affinities) and *in vivo* (antagonism of apomorphine-induced mouse climbing) activities of test compounds **2**, **3**, **15**−**22**, **31**−**33**, **38**, **39**, and **46**−**49** were determined by the methods previously reported.[19]

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Supporting Information Available: Crystal data, positional parameters, bond lengths, and bond angles for the single-crystal X-ray structure of **2** as well as complete experimental details and spectral data for compounds **10**−**12**, **16**−**21**, **32**, **38**, **39**, **46**, and **47** (21 pages). Ordering information is given on any current masthead page.

References

(1) Simpson, G. M.; Verga, E. Clozapine-A New Antipsychotic Agent. *Curr. Ther. Res.* **1974**, *16*, 679−686.
(2) 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 1−9.
(3) Lowe, J. A., III; Seeger, T. F.; Vinick, F. J. Atypical Antipsychotics - Recent Findings and New Perspectives. *Med. Res. Rev.* **1988**, *8*, 475−497.
(4) Jann, M. W. Clozapine. *Pharmacotherapy* **1991**, *11*, 179−195.
(5) Bablenis, E.; Weber, S. S.; Wagner, R. L. Clozapine: A Novel Antipsychotic Agent. *DICP* **1989**, *23*, 109−115.
(6) Meltzer, H. Y. Novel Approaches to the Pharmacotherapy of Schizophrenia. *Drug Dev. Res.* **1986**, *9*, 23−40.
(7) Kane, J.; Honigfeld, G.; Singer, J.; Meltzer, H. Clozapine for the Treatment-Resistant Schizophrenic. A Double-Blind Comparison With Chlorpromazine. *Arch. Gen. Psychiatry* **1988**, *45*, 789−796.
(8) Griffith, R. W.; Saameli, K. Letter: Clozapine and Agranulocytosis. *Lancet* **1975**, 2, 657.
(9) 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.
(10) Clozaril. *Physicians' Desk Reference*, 48th ed.; Medical Economics Data Production Co.: Montvale, NJ, 1994; pp 2042−2046.
(11) 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. Pharmacol. Exp. Ther.* **1989**, *251*, 238−246.
(12) Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. Pharmacology of Risperidone (R 64 766), A New Antipsychotic With Serotonin-S_2 and Dopamine-D_2 antagonistic properties. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 685−693.
(13) Perrone, R.; Berardi, F.; Colabufo, N. A.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Vanotti, E.; Govoni, S. Mixed 5-HT$_{1A}$/D_2 Activity of a New Model of Arylpiperazines: 1-Aryl-4-[3-(1,2-dihydronaphthalen-4-yl)-*n*-propyl]piperazines. 1. Synthesis and Structure-Activity Relationships. *J. Med. Chem.* **1994**, *37*, 99−104.
(14) Hrib, N. J.; Jurcak, J. G.; Burgher, K. L.; Conway, P. G.; Hartman, H. B.; Kerman, L. L.; Roehr, J. E.; Woods, A. T. Benzisoxazole- and Benzisothiazole-3-carboxamides and Potential Atypical Antipsychotic Agents. *J. Med. Chem.* **1994**, *37*, 2308−2314.
(15) Fontenla, J. A.; Osuna, J.; Rosa, E.; Castro, M. E.; G-Ferreiro, T.; Loza-Garcia, I.; Calleja, J. M.; Sanz, F.; Rodriguez, J.; Ravina, E.; Fueyo, J.; F-Masaguer, C.; Vidal, A.; de Ceballos, M. L. Synthesis and Atypical Antipsychotic Profile of some 2-(2-Piperidinoethyl)benzocycloalkanones as Analogues of Butyrophenone. *J. Med. Chem.* **1994**, *37*, 2564−2573.
(16) Phillips, S. T.; de Paulis, T.; Baron, B. M.; Siegel, B. W.; Seeman, P.; Van Tol, H. H. M.; Guan, H.-C.; Smith, H. E. Binding of 5*H*-Dibenzo[*b,e*][1,4]diazepine and Chiral 5*H*-Dibenzo[*a,d*]cycloheptene Analogues of Clozapine to Dopamine and Serotonin Receptors. *J. Med. Chem.* **1994**, *37*, 2686−2696.
(17) Mewshaw, R. E.; Abreu, M. E.; Silverman, L. S.; Mathew, R. M.; Tiffany, C. W.; Bailey, M. A.; Karbon, E. W.; Ferkany, J. W.; Kaiser, C. Examination of the D_2/5-HT$_2$ Affinity Ratios of Resolved 5,6,7,8,9,10-Hexahydro-7,10-iminocyclohept[*b*]indoles: An Enantioselective Approach Toward the Design of Potential Atypical Antipsychotics. *J. Med Chem.* **1993**, *36*, 3073−3076.
(18) Hrib, N. J.; Jurcak, J. G.; Huger, F. P.; Errico, C. L.; Dunn, R. W. Synthesis and Biological Evaluation of a Series of Substituted N-Alkoxyimides and amides as Potential Atypical Antipsychotic Agents. *J. Med. Chem.* **1991**, *34*, 1068−1072.
(19) Norman, M. H.; Rigdon, G. C.; Navas, F., III; Cooper, B. R. Cyclic Benzamides as Mixed Dopamine D_2/Serotonin 5-HT$_2$ Receptor Antagonists: Potential Atypical Antipsychotic Agents. *J. Med. Chem.* **1994**, *37*, 2552−2563.
(20) Treatment of *trans*-1,2-cyclopropanedimethanol with tosyl chloride−DMAP is reported to give the corresponding dichloride (Hwang, C. K.; Li, W. S.; Nicolaou, K. C. Reactions of Hydroxyl Groups with Tosylchloride-Dimethylaminopyridine System. Direct Synthesis of Chlorides from Hydroxycompounds. *Tetrahedron Lett.* **1984**, *25*, 2295−2296). In our hands, however, only the monochlorinated product was obtained.
(21) Murata, K. Preparation, Polymerization, and Copolymerization of N-Vinyl Phthalimidine. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1752−1755.
(22) Kato, K.; Yoshida, M. Diels-Alder Reaction of N-Vinylimides. *Nipon Kagaku Zasshi*, **1966**, *87*, 1098−1100.
(23) Davies, W.; Perkins, W. H. The Chlorination and Bromination of the Toluic Acids and the Preparation of Phthalaldehydic Acids. *J. Chem. Soc.* **1922**, *121*, 2202−2215.
(24) Lee, G. E.; Wragg, W. R. 5-(and 6-)Chloro-1-Oxoisoindoline Derivatives. U.K. Patent 1,036,274, July 20, 1966.
(25) Köhler, C.; Hall, H.; Ögren, S. O.; 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.
(26) 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.
(27) 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. Binding Properties, Brain Distribution, and Functional Role. *Mol. Pharmacol.* **1982**, *21*, 301−314.
(28) (a) 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. (b) ED_{50}s (doses required for 50% of maximal response) were calculated on percent antagonism or percent inhibition by the method of Litchfield, J. T.; Wilcoxon, F. Simplified Method of Evaluating Dose-effect Experiments. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99−113 (Pharm/PCS Software, Philadelphia, PA). (c) IC_{50}s (concentrations that inhibited specific binding by 50%) were calculated by the method of Monod, J.; Changeux, J.-P.; Jocob, F. Allosteric Proteins and Cellular Control Systems *J. Mol. Biol.* **1963**, *6*, 306−329.
(29) The X-ray crystal structure of isoindolinone **2** was determined by J. D. Ferrara of Molecular Structure Corp., 3200A Research Forest Dr., The Woodlands, TX.
(30) MacroModel, version 4.5, Department of Chemistry, Columbia University, New York, NY 10027. See: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. MarcroModel - An Integrated Software System for Modeling Organic and Bioorganic Molecules Using Molecular Mechanics. *J. Comput. Chem.* **1990**, *11*, 440−467. Note: The version of MM2* employed in these calculations did not contain sufficient parameters for the benzisothiazole heterocycle. Therefore, a bond length of 1.653 Å (obtained from the single X-ray analysis of isoindolinone **2**) and an estimated force constant of 3.0 mdyn/Å were added to the parameter set for the N−S bond of the benzisothiazole ring.
(31) 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.
(32) Ashton, W. T.; Meurer, L. C.; Cantone, C. L.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wagner, A. F.; Walton, E.; Tolman, R. L. Synthesis and Antiherpetic Activity of (±)-9-[[(Z)-2-(Hydroxymethyl)cyclopropyl]-methyl]quanine and Related Compounds. *J. Med. Chem.* **1988**, *31*, 2304−2315.
(33) Chapman, J. M., Jr.; Cocolas, G. H.; Hall, I. H. Hypolipidemic Activity of Phthalimide derivatives. 3. A Comparison of Phthalimide and 1,2-Benzisothiazolin-3-one 1,1-dioxide Derivatives to Phthalimidine and 1,2-Benzisothiazoline 1,1-dioxide congeners. *J. Med Chem.* **1983**, *26*, 243−246.

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