# 3-[[(Aryloxy)alkyl]piperidinyl]-1,2-Benzisoxazoles as $D_2$/5-$HT_2$ Antagonists with Potential Atypical Antipsychotic Activity: Antipsychotic Profile of Iloperidone (HP 873)[1]

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A series of 3-[[(aryloxy)alkyl]piperidinyl]-1,2-benzisoxazoles was synthesized and evaluated as potential antipsychotic $D_2$/5-$HT_2$ antagonists. Most of these compounds showed potent antipsychotic-like activity in an apomorphine-induced climbing mouse paradigm, with many also showing preferential mesolimbic activity, as indicated by their weaker effects in an apomorphine-induced stereotypy model. In receptor binding assays, many displayed a moderate affinity for the $D_2$ receptor coupled with a significantly greater affinity for the 5-$HT_2$ receptor: a property that has been suggested as necessary for atypicality. From this series, compound **45**, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (iloperidone, HP 873), was further evaluated in a battery of in vivo and in vitro assays. This compound showed a 300-fold greater potency in inhibition of climbing than in inhibition of stereotypy or induction of catalepsy, and when evaluated chronically in an electrophysiological model, **45** caused a depolarization blockade of dopamine neurons in the A10 area of the rat brain but not in the A9 area. Additionally, it showed positive activity in a social interaction paradigm, suggesting potential efficacy against asociality, a component of the negative symptoms of schizophrenia. In chronic ex vivo studies, **45**, similar to clozapine, caused a down regulation of 5-$HT_2$ receptors but had no effect on the number of $D_2$ receptors. Compound **45** is currently undergoing clinical evaluation.

## Introduction

Within the last several years, among the drugs available for the treatment of schizophrenia, one drug, clozapine, has consistently stood above the rest, and it has become the standard atypical antipsychotic to which all others are compared. Besides its lack of neurological side effects, clozapine has also been found to be more effective in treating refractory patients,[2] and it appears to be efficacious in treating the anhedonia, asociality, and poverty of speech, the so-called negative symptoms of schizophrenia.[3,4] Unfortunately, due to its tendency to cause agranulocytosis in some patients, it is not the initial drug of choice and must be used with extreme caution.

Clozapine's outstanding clinical record as an antipsychotic has caused a considerable amount of discussion among clinicians, medicinal chemists, and pharmacologists as to which of its biological properties is most responsible for its unique antipsychotic profile. Besides its activity as a $D_2$ antagonist, clozapine shows affinity for a variety of different receptor sites found in the central nervous system (CNS),[5] and analyses have focused on this characteristic as a viable rationale for its unique profile. Among the hypotheses invoked, one that has attracted considerable attention was based upon clozapine's binding characteristics at the 5-$HT_2$ receptor. Support for this rationale was garnered from some clinical studies which suggested that coadministration of a 5-$HT_2$ antagonist with a typical antipsychotic apparently induced a reduction of extrapyramidal side effects (EPS).[6,7]

Furthermore, another study suggested that the addition of a 5-$HT_2$ antagonist to the treatment regimen of schizophrenics appeared to improve negative symptoms.[8] Later, in studies performed in laboratory animals, it was suggested that the key to clozapine's antipsychotic profile and other atypical antipsychotics was not merely due to a high affinity for the 5-$HT_2$ binding site but rather to the ratio of a drug's binding affinities for the $D_2$ versus 5-$HT_2$ receptor sites.[9] Thus, according to this hypothesis, those antipsychotics that displayed a $D_2$/5-$HT_2$ affinity ratio of greater than 1 would have the best possibility of exhibiting an atypical profile. Finding this rationale particularly engaging, we attempted to design and synthesize $D_2$/5-$HT_2$ receptor antagonists, with binding characteristics similar to clozapine.

Our approach was based upon some studies we reported several years ago where we described the synthesis and antipsychotic activity of a series of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles (**1**).[10,11] Therein it was suggested that the 3-(4-piperidinyl)-1,2-benzisoxazoles could be considered isosteric to 4-aroylpiperidines **2**. Additionally, our structure–activity relationship (SAR) studies had indicated that for any given substituent (R) on the piperidine nitrogen the compounds which generally gave the most potent and interesting antipsychotic profiles were those that contained a 6-fluoro-1,2-benzisoxazole moiety. Since then, workers at Janssen have reported the antipsychotic profile of the $D_2$/5-$HT_2$ antagonist risperidone (**3**), a compound which contains a 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole as a key structural component.[12,13] Results from the clinic with risperidone seem to indicate that the drug is an effective antipsychotic which may have a lower propensity to cause EPS, and it may also

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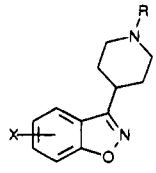
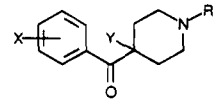
be effective against the negative symptoms of schizophrenia.[14,15]

In continuing to focus our efforts on the piperidinyl-1,2-benzisoxazoles, we decided to pursue the synthesis of a series of 3-[[(aryloxy)alkyl]piperidinyl]-1,2-benzisoxazoles (**4**). The impetus to pursue structures of this type stemmed from observations reported in the literature, where compounds such as **5**[16] and **6**[17] were described as possessing antipsychotic activity in animal models. And, similar to our previous strategy, we were interested in replacing the 4-aroylpiperidine portion, common to both structures, with the putatively isosteric 3-(4-piperidinyl)-1,2-benzisoxazole moiety. Our initial attempts produced compounds with very interesting antipsychotic profiles, and thus we embarked on a more detailed study of the series focusing mainly on the *N*-(aryloxy)alkyl substituent (R). Herein we describe the results of our studies.

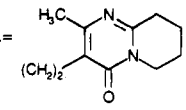


(1) R= antipsychotic pharmacophores
X= 6-F (preferred substituent)

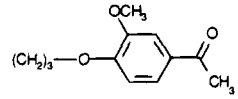


(2) Y= H; R= antipsychotic pharmacophores

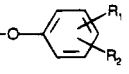
(3) X= 6-F; R=



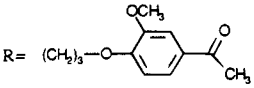
(5) Y= H; R=



(4) R=



(6) Y= OH; R=



## Chemistry

Scheme 1 illustrates the procedure used to synthesize the target structures. In the first step, novel (aryloxy)-alkyl halides **11**–**35** (Table 1) were synthesized by reacting an appropriately substituted phenol with a base, using one of several methods, to generate the derived aryl oxide ion. These in turn were reacted with a dihaloalkane to yield the desired compounds. Compound **36**, the (arylthio)alkyl halide, was synthesized similarly but using instead a thiophenol. Other (aryloxy)alkyl halides were prepared as described in the literature.[18,19]

The final step to the target 3-[[(aryloxy)alkyl]piperidinyl]-1,2-benzisoxazoles, compounds **37**–**84** (Table 2), was accomplished by the reaction of a 3-(4-piperidinyl)-1,2-benzisoxazole[11] with a suitable alkylating agent in the presence of $K_2CO_3$ in one of three solvent systems.

Compound **81**, a nitrogen congener of the series (X = NH), was synthesized as outlined in Scheme 2. Alkylation of 2-benzoxazolinone yielded the chloropropyl derivative **7**, which was subsequently acylated with acetic acid and PPA[20] to yield the 6-acyl-2-benzoxazolinone **8**. Reaction of **8** with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole gave the intermediate **9**, which after hydrolysis of the benzoxazolinone ring afforded the aminophenol **10**. Methylation of the phenol yielded the desired compound **81**.

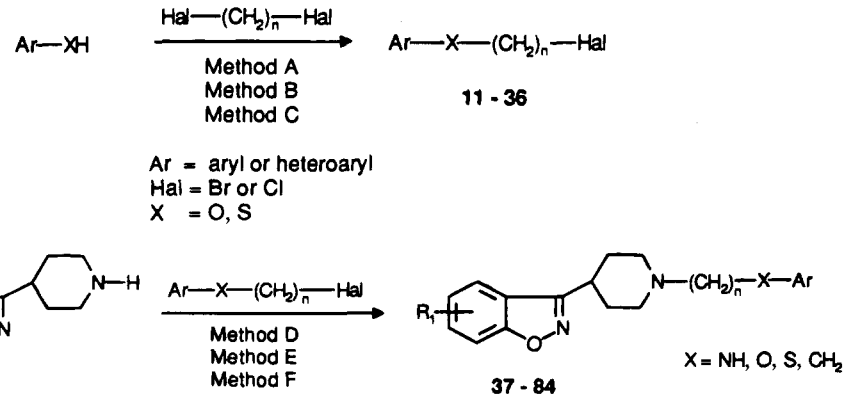
## Biological Results and Discussion

The compounds listed in Table 2 were evaluated for their potential antipsychotic activity by testing their ability to inhibit apomorphine-induced climbing behavior in mice. Inhibition of climbing would suggest that a compound was a $D_2$ antagonist, a characteristic of all clinically effective antipsychotics. Subsequently, compounds that showed good activity in the climbing mouse assay (CMA) were tested for their ability to block apomorphine-induced stereotypy in rats. Since apomorphine-induced climbing is considered to be primarily a mesolimbic mediated phenomenon, while stereotypy is thought to be stratially mediated, large diffrences between the effective doses in these assays would suggest preferential mesolimbic activity and thus a reduced potential for extrapyramidal side effects.[21,22]

The compounds were also evaluated for their affinity for $D_2$ and 5-$HT_2$ binding sites by their ability to displace [$^3$H]spiperone from rat striatum and [$^3$H]spiperone from rat frontal cortex, respectively. From these results, we were quite interested in compounds that showed a greater affinity for the 5-$HT_2$ receptor as opposed to the $D_2$ site, in particular, as cited previously, those compounds that would show a ratio of $D_2$ to 5-$HT_2$ binding greater than 1 ($D_2$/5-$HT_2$ > 1).[9] The biological results are summarized in Table 3.

The first compounds to be synthesized in the series, compounds **37**–**46**, bore the (4-acetyl-2-methoxyphenoxy)alkyl substituent on the piperidinyl nitrogen

**Scheme 1**[a]




[a] Method A: NaH, DMF, rt. Method B: $CH_3CN$, $K_2CO_3$, reflux. Method C: $(CH_3)_2CO$, $K_2CO_3$, reflux. Method D: DMF, $K_2CO_3$, 70–90 °C. Method E: $CH_3CN$, $K_2CO_3$, KI, reflux. Method F: DMF, $CH_3CN$, $K_2CO_3$, 90–100 °C.

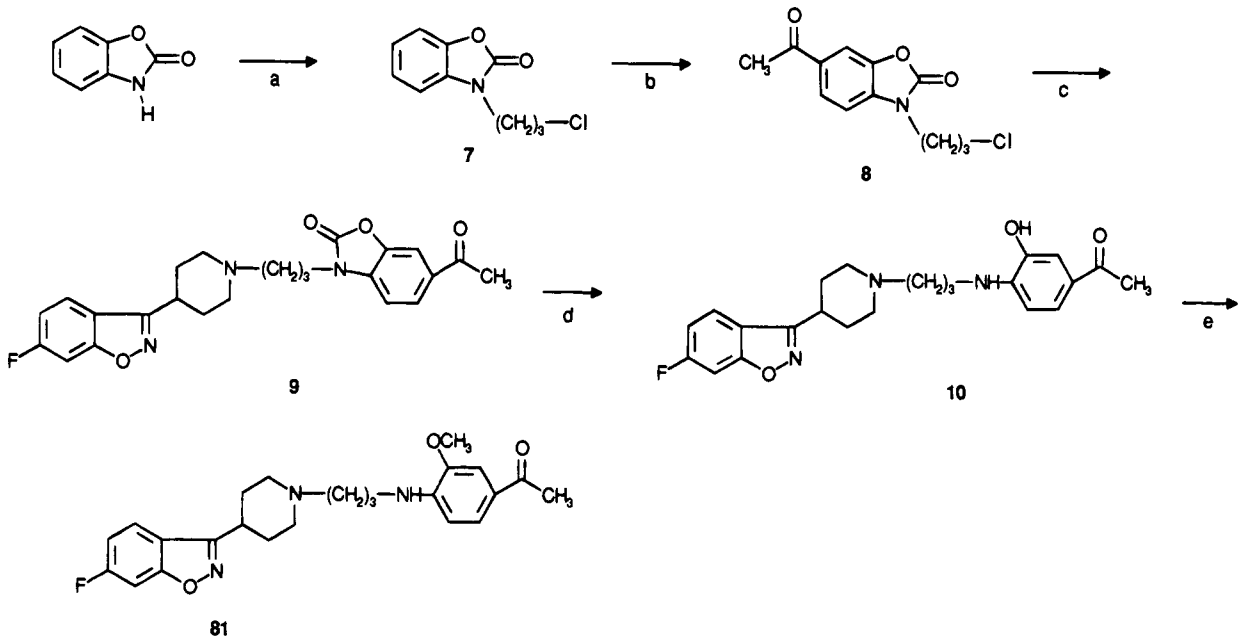
**Table 1.** (Aryloxy)alkyl Halides[a]

Ar–X–$(CH_2)_3$–Hal

| compd | Ar | X | Hal | method | mp, °C | formula[b] |
|---|---|---|---|---|---|---|
| **11** | 2-(OH)-4-($COCH_3$)$C_6H_3$ | O | Cl | *g* | 101–103 | $C_{11}H_{13}ClO_3$ |
| **12** | 4-($COCH_3$)$C_6H_4$ | O | Br | A | oil | |
| **13** | 2-($CH_3$)-4-($COCH_3$)$C_6H_3$ | O | Br | A | 59–61 | $C_{12}H_{15}BrO_2$ |
| **14** | 2-($SCH_3$)-4-($COCH_3$)$C_6H_3$ | O | Br | B | 120–122 | $C_{12}H_{15}BrOS$ |
| **15** | 2-($NHCH_3$)-4-($COCH_3$)$C_6H_3$ | O | Cl | A | 115–117 | $C_{12}H_{16}ClNO_2$ |
| **16** | 2-($N(CH_3)_2$)-4-($COCH_3$)$C_6H_3$ | O | Cl | A | oil | |
| **17** | 2,6-($OCH_3$)$_2$-4-($COCH_3$)$C_6H_2$ | O | Br | A | oil | |
| **18** | 2-(OH)-4-(CH(OH)$CH_3$)$C_6H_3$ | O | Cl | *g* | 107–109 | $C_{11}H_{15}ClO_3$ |
| **19** | 2-($OCH_3$)-4-($CO_2C_2H_5$)$C_6H_3$ | O | Br | B | oil | |
| **20** | 2-($OCH_3$)-4-($CO(CH_2)_3CH_3$)$C_6H_3$ | O | Br | B | oil | |
| **21** | 2-($OCH_3$)-4-(COPh)$C_6H_3$ | O | Br | A | 81–83 | $C_{17}H_{17}BrO_3$[c] |
| **22** | 2-($OCH_3$)-4-($COCF_3$)$C_6H_3$ | O | Cl | *g* | 45–47 | $C_{12}H_{12}ClF_3O_3$ |
| **23** | 2-($OCH_3$)-4-($CON(CH_3)_2$)$C_6H_3$ | O | Br | B | oil | |
| **24** | 2-($OCH_3$)-4-($CONH_2$)$C_6H_3$ | O | Br | B | 171–172 | $C_{11}H_{14}ClNO_3$[d] |
| **25** | 2-($OCH_3$)-4-($C_2H_5$)$C_6H_3$ | O | Cl | B | oil | |
| **26** | 2-($OCH_3$)-4-(CN)$C_6H_3$ | O | Br | B | 99–101 | $C_{11}H_{12}BrNO_2$[e] |
| **27** | 3-($CH_3$)-4-($COCH_3$)$C_6H_3$ | O | Br | A | oil | |
| **28** | 2-($COCH_3$)-4-($CH_3$)$C_6H_3$ | O | Br | B | oil | |
| **29** | 2-($OCH_3$)-4-(Br)$C_6H_3$ | O | Cl | C | 52–54 | $C_{10}H_{12}BrClO_2$ |
| **30** | 2-($OCH_3$)-5-($NHCOCH_3$)$C_6H_3$ | O | Cl | A | 112–114 | $C_{12}H_{16}ClNO_3$ |
| **31** | 2-($NHCOCH_3$)-4-($COCH_3$)$C_6H_3$ | O | Cl | C | 124–126 | $C_{13}H_{16}ClNO_3$[f] |
| **32** | 2-($NH_2$)$C_6H_4$ | O | Cl | A | oil | |
| **33** | 2-($NHCH_3$)$C_6H_4$ | O | Cl | A | 115–117 | $C_{10}H_{14}ClNO$ |
| **34** | 7-($OCH_3$)-1-tetralon-6-yl | O | Cl | C | oil | |
| **35** | 5-($OCH_3$)indol-6-yl | O | Cl | A | 73–75 | $C_{12}H_{14}ClNO_2$ |
| **36** | 2-($OCH_3$)-4-($COCH_3$)$C_6H_4$ | S | Cl | C | 53–55 | $C_{12}H_{15}ClO_2S$ |

[a] Starting phenols were purchased or prepared by literature methods. [b] Compounds were analyzed for C, H, and N and were within ±0.4% of theoretical values, unless noted. [c] C: calcd, 58.47; found, 59.03. [d] C: calcd, 45.85; found, 46.66. [e] C: calcd, 48.91; found, 49.49. [f] C: calcd, 57.89; found, 57.08. [g] See the Experimental Section for details.

**Scheme 2**[a]

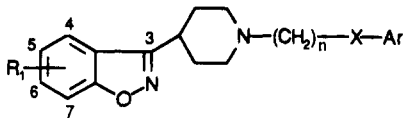



[a] (a) NaH, DMF, $Br(CH_2)_3Cl$, 5 °C to rt; (b) $CH_3CO_2H$, PPA, 100 °C; (c) $CH_3CN$, $K_2CO_3$, KI, 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole; (d) 10% NaOH, reflux, 5% HCl; (e) NaH, DMF, $CH_3I$, 5 °C.

with three variations in the length of the alkyl side chain and four different substituents on the 1,2-benzisoxazole ring. The choices of the preferred substituents on the benzisoxazole ring were based upon our previous studies.

When tested, compounds **37–39** and **41–46** showed significant activity in the CMA with only compound **40** containing a 6-chloro substituent and a 2-carbon chain being relatively weak (Table 3). In contrast, compound **45** which contained a 6-fluoro substituent with a 3-carbon chain was the most potent in the assay, being approximately equipotent to haloperidol and considerably more potent than clozapine. Additionally, several of these comopunds exhibited relatively large separations of the $ED_{50}$'s between the stereotypy and the CMA assays (stereotypy/CMA ratio), with compound **45** showing the most favorable difference of over 360 times, as compared to about 50 times for risperidone. Also, when evaluated in receptor binding, these compounds, except for compound **42**, another 6-chloro analog, displayed the desired receptor binding profile that was sought. Thus, compounds **37–41** and **43–46** all showed greater affinity for the 5-$HT_2$ receptor than for the $D_2$ site. Indeed, compound **45** showed a very high affinity for the 5-$HT_2$

**Table 2.** 3-[[(Aryloxy)alkyl]piperidinyl]-1,2-benzisoxazoles



| compd | $R_1$ | $n$ | X | Ar | method | mp, °C | formula[a] |
|---|---|---|---|---|---|---|---|
| **37** | H | 2 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | D | 127–129 | $C_{23}H_{26}N_2O_4 \cdot C_4H_4O_4$[c,d] |
| **38** | H | 3 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | D | 99–101 | $C_{24}H_{28}N_2O_4$ |
| **39** | H | 4 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | D | 99–101 | $C_{25}H_{30}N_2O_4$ |
| **40** | 6-Cl | 2 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 133–135 | $C_{23}H_{25}ClN_2O_4$ |
| **41** | 6-Cl | 3 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 116–118 | $C_{24}H_{27}ClN_2O_4$ |
| **42** | 6-Cl | 4 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 139–141 | $C_{25}H_{29}ClN_2O_4 \cdot C_4H_4O_4$[c] |
| **43** | 5-F | 3 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 103–105 | $C_{24}H_{27}FN_2O_4$ |
| **44** | 6-F | 2 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | D | 132–134 | $C_{23}H_{25}FN_2O_4$ |
| **45** | 6-F | 3 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | D | 118–120 | $C_{24}H_{27}FN_2O_4$ |
| **46** | 6-F | 4 | O | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | D | 88–90 | $C_{25}H_{29}FN_2O_4$ |
| **47** | 6-F | 3 | O | 2-(OH)-4-($COCH_3$)$C_6H_3$ | E | 122–124 | $C_{23}H_{25}FN_2O_4$ |
| **48** | 6-F | 3 | O | 4-($COCH_3$)$C_6H_4$ | E | 111–112 | $C_{23}H_{25}FN_2O_3$ |
| **49** | 6-F | 3 | O | 2-($CH_3$)-4-($COCH_3$)$C_6H_3$ | F | 185–187 | $C_{24}H_{27}FN_2O_3 \cdot 0.5C_4H_4O_4$[c] |
| **50** | 6-F | 3 | O | 2-($SCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 151–153 | $C_{24}H_{27}FN_2O_3S$ |
| **51** | 6-F | 3 | O | 2-($NHCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 150–152 | $C_{24}H_{28}FN_3O_3$ |
| **52** | 6-F | 3 | O | 2-($N(CH_3)_2$)-4-($COCH_3$)$C_6H_3$ | E | 94–96 | $C_{25}H_{30}FN_3O_3$[e] |
| **53** | 6-F | 3 | O | 2-($NHCOCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 108–110 | $C_{25}H_{28}FN_3O_4$ |
| **54** | 6-F | 3 | O | 2-($OC_2H_5$)-4-($COCH_3$)$C_6H_3$ | *b* | 112–114 | $C_{25}H_{29}FN_2O_4$ |
| **55** | 6-F | 3 | O | 2,6-($OCH_3$)$_2$-4-($COCH_3$)$C_6H_2$ | E | 107–108 | $C_{25}H_{29}FN_2O_5$ |
| **56** | 6-F | 3 | O | 2-($OCH_3$)-4-($CH(OH)CH_3$)$C_6H_3$ | *b* | 136–138 | $C_{24}H_{29}FN_2O_4$ |
| **57** | 6-F | 3 | O | 2-(OH)-4-($CH(OH)CH_3$)$C_6H_3$ | E | 142–144 | $C_{23}H_{27}FN_2O_4$ |
| **58** | 6-F | 3 | O | 2-($OCH_3$)-4-($COC_2H_5$)$C_6H_3$ | E | 118–119 | $C_{25}H_{29}FN_2O_4$ |
| **59** | 6-F | 3 | O | 2-($OCH_3$)-4-($CO(CH_2)_3CH_3$)$C_6H_3$ | E | 79–80 | $C_{27}H_{33}FN_2O_4$[f] |
| **60** | 6-F | 3 | O | 2-($OCH_3$)-4-($COC_6H_5$)$C_6H_3$ | E | 128–130 | $C_{29}H_{29}FN_2O_4$ |
| **61** | 6-F | 3 | O | 2-($OCH_3$)-4-($COCF_3$)$C_6H_3$ | E | 94–96 | $C_{24}H_{24}F_4N_2O_4$ |
| **62** | 6-F | 3 | O | 2-($OCH_3$)-4-($CONH_2$)$C_6H_3$ | E | 163–164 | $C_{23}H_{26}FN_3O_4$[g] |
| **63** | 6-F | 3 | O | 2-($OCH_3$)-4-($CON(CH_3)_2$)$C_6H_3$ | E | 126–127 | $C_{25}H_{30}FN_3O_4$ |
| **64** | 6-F | 3 | O | 2-($OCH_3$)-4-($C(=CH_2)CH_3$)$C_6H_3$ | *b* | 192–194 | $C_{24}H_{29}FN_2O_3 \cdot HCl$ |
| **65** | 6-F | 3 | O | 2-($OCH_3$)-4-($C(=NOH)CH_3$)$C_6H_3$ | *b* | 168–170 | $C_{24}H_{28}FN_3O_4$ |
| **66** | 6-F | 3 | O | 2-($OCH_3$)-4-($C(=NNH_2)CH_3$)$C_6H_3$ | *b* | 106–108 | $C_{24}H_{29}FN_4O_3$ |
| **67** | 6-F | 3 | O | 2-($OCH_3$)-4-($C_2H_5$)$C_6H_3$ | E | 150–152 | $C_{24}H_{29}FN_2O_3$ |
| **68** | 6-F | 3 | O | 2-($OCH_3$)-4-(CN)$C_6H_3$ | E | 107–108 | $C_{23}H_{24}FN_3O_3$ |
| **69** | 6-F | 3 | O | 2-($OCH_3$)-4-(Br)$C_6H_3$ | E | 88–90 | $C_{22}H_{24}BrFN_2O_3$ |
| **70** | 6-F | 3 | O | 2-($OCH_3$)$C_6H_4$ | E | 169–170 | $C_{22}H_{25}FN_2O_3 \cdot C_4H_4O_4$[c] |
| **71** | 6-F | 3 | O | 3-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 193–195 | $C_{24}H_{27}FN_2O_4 \cdot HCl$ |
| **72** | 6-F | 3 | O | 3-($CH_3$)-4-($COCH_3$)$C_6H_3$ | F | 113–114 | $C_{24}H_{27}FN_2O_3$ |
| **73** | 6-F | 3 | O | 2-($COCH_3$)-4-($CH_3$)$C_6H_3$ | F | 92–93 | $C_{24}H_{27}FN_2O_3$ |
| **74** | 6-F | 3 | O | 2-($OCH_3$)-5-($NHCOCH_3$)$C_6H_3$ | F | 205–206 | $C_{24}H_{28}FN_3O_4 \cdot 0.5C_4H_4O_4$[c] |
| **75** | 6-F | 3 | O | 2-($OCH_3$)-5-($NH_2$)$C_6H_3$ | *b* | 94–95 | $C_{22}H_{26}FN_3O_3$ |
| **76** | 6-F | 3 | O | 3-($COCH_3$)$C_6H_4$ | E | 172–174 | $C_{24}H_{25}FN_2O_3 \cdot C_4H_4O_4$[c] |
| **77** | 6-F | 3 | O | 2-($NH_2$)$C_6H_4$ | E | 252–255 | $C_{21}H_{24}FN_3O_2 \cdot 2HCl$ |
| **78** | 6-F | 3 | O | 2-($NHCH_3$)$C_6H_4$ | E | 180–182 | $C_{22}H_{26}FN_3O_2 \cdot 0.5C_4H_4O_4$[c] |
| **79** | 6-F | 3 | O | $C_6H_5$ | E | 78–80 | $C_{21}H_{23}FN_2O_2$ |
| **80** | 6-F | 3 | S | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | E | 93–95 | $C_{24}H_{27}FN_2O_3S$[h] |
| **81** | 6-F | 3 | NH | 2-($OCH_3$)-4-($COCH_3$)$C_6H_3$ | *b* | 96–98 | $C_{24}H_{28}FN_3O_3$ |
| **82** | 6-F | 1 | $CH_2$ | 6-($COCH_3$)-1,4-benzodioxan-2-yl | *b* | 122–123 | $C_{23}H_{23}FN_2O_4$ |
| **83** | 6-F | 3 | O | 7-($OCH_3$)-1-tetralon-6-yl | E | 129–131 | $C_{26}H_{29}FN_2O_4$ |
| **84** | 6-F | 3 | O | 5-($OCH_3$)indol-6-yl | E | 156–158 | $C_{24}H_{25}FN_3O_2$ |

[a] Compounds were analyzed for C, H, and N and are within ±0.4% of theoretical values, unless noted. [b] See the Experimental Section for details. [c] Fumarate salt. [d] C: calcd, 63.52; found, 63.00. [e] C: calcd, 68.32; found, 67.74. [f] N: calcd, 5.98; found, 6.39. [g] C: calcd, 64.62; found, 64.20. [h] C: calcd, 65.14; found, 64.66.

receptor with an $IC_{50}$ of 9.0 nM while exhibiting a modest affinity of 110 nM for the $D_2$ receptor. This yielded a $D_2$/5-$HT_2$ ratio of 12 as compared to approximately 17 for clozapine, 14 for risperidone, and 0.1 for haloperidol.

From this initial series of compounds, it appeared that a 6-fluoro substituent on the 1,2-benzisoxazole ring imparted the best antipsychotic profile, a result that was consistent with our previous finding.[11] Additionally, when comparing compounds **44**–**46**, it appeared that a propyl chain between the piperidine nitrogen and aryloxy terminus was preferred. Given this information, **45** became the lead compound. Thus, our tactic for further studying the structure–activity relationships within the series was to keep the 6-fluoro-3-(1-propyl-4-piperidinyl)-1,2-benzisoxazole functionality constant while varying the aryloxy substituent bonded at the propyl terminus of the piperidine nitrogen.

Initially we looked to modifying the 2-methoxy substituent of the lead compond **45**, and compounds **47**–**55** reflect those modifications. Demethylation to afford **47** resulted in a compound that was extremely potent in the CMA but likewise in stereotypy, suggesting less mesolimbic selectivity than **45**. Additionally, **47** showed very high affinity for the $D_2$ receptor, in fact the highest affinity in the series, and while its affinity for the 5-$HT_2$ site was also quite high, the potent $D_2$ affinity resulted in a smaller $D_2$/5-$HT_2$ ratio when compared to **45**.

When the 2-methoxy group of **45** was replaced with a hydrogen as in **48**, it resulted in a compound that was

**Table 3.** In Vivo and in Vitro Antipsychotic Activity of 3-[[(Aryloxy)alkyl]piperidinyl]-1,2-benzisoxazoles

| | inhibtn of apomorphine-induced | | inhibtn of ligand binding | | |
|---|---|---|---|---|---|
| compd | climbing: $ED_{50}$, mg/kg ip[a] | stereotypy: $ED_{50}$, mg/kg ip[b] | $D_2$ $IC_{50}$ (nM)[c] | 5-$HT_2$ $IC_{50}$ (nM)[d] | $IC_{50}$ ratio $D_2$/5-$HT_2$ |
| **37** | 7.4 (6.6–8.0)[e] | NT[f] | 969 | 26 | 37.3 |
| **38** | 0.67 (0.59–0.75) | 20.8 (14.4–30.1) | 168 | 3.5 | 48 |
| **39** | 1.6 (1.5–1.8) | 17.0 (9.8–29.5) | 66 | 34 | 1.9 |
| **40** | >20 | NT | 940 | 45 | 20.9 |
| **41** | 3.3 (2.8–3.7) | >80 | 111 | 4.9 | 23 |
| **42** | 2.4 (2.2–2.6) | 9.7 (3.5–26.7) | 110 | 143 | 0.8 |
| **43** | 5.2 (4.7–5.8) | >80 | 455 | 122 | 3.7 |
| **44** | 5.3 (4.8–5.8) | >80 | 427 | 67 | 6.4 |
| **45** | 0.095 (0.090–0.101) | 34.8 (22.0–55.1) | 110 | 9.0 | 12.2 |
| **46** | 0.68 (0.58–0.79) | 7.5 (5.7–9.9) | 23 | 8.5 | 2.7 |
| **47** | 0.054 (0.050–0.058) | 0.7 (0.47–1.1) | 8.6 | 2.9 | 3.0 |
| **48** | 0.84 (0.75–0.95) | 5.7 (3.9–8.1) | 16 | 5.5 | 2.9 |
| **49** | 0.25 (0.23–0.27) | 31.4 (19.4–50.9) | 66 | 67 | 1.0 |
| **50** | ~20 | NT | 295 | 170 | 1.7 |
| **51** | 0.15 (0.14–0.16) | 47.6 (31.4–72.1) | 250 | 42 | 5.9 |
| **52** | 0.15 (0.14–0.16) | 4.3 (2.6–7.4) | 116 | 16 | 7.7 |
| **53** | 0.049 (0.046–0.052) | 21.1 (4.0–102.5) | 107 | 20 | 5.4 |
| **54** | 0.56 (0.51–0.61) | 14.5 (8.4–25.2) | 127 | 3.8 | 33.4 |
| **55** | 0.72 (0.65–0.80) | 13.6 (12.0–15.5) | 45 | <10 | 4.5 |
| **56** | 0.12 (0.11–0.13) | 22.7 (18.0–28.7) | 727 | 22 | 33.0 |
| **57** | 0.058 (0.055–0.062) | 3.6 (2.8–4.5) | >1000 | 53 | |
| **58** | 0.77 (0.70–0.84) | >20 | 135 | 11 | 12.3 |
| **59** | 0.78 (0.71–0.85) | 16.9 | 242 | 89 | 2.7 |
| **60** | 18.1 (16.5–20.2) | >80 | 460 | 241 | 1.9 |
| **61** | 2.2 (2.1–2.4) | >20 | 169 | 38 | 4.4 |
| **62** | 1.6 (1.6–1.8) | 22.7 (18.0–28.7) | 59 | 0.9 | 65.6 |
| **63** | 0.72 (0.59–0.85) | 26.7 (21.8–32.8) | 127 | 5.2 | 24.4 |
| **64** | 0.55 (0.52–0.58) | ~25 | 221 | 20 | 11.0 |
| **65** | 1.1 (1.0–1.3) | >80 | 90 | 0.7 | 128 |
| **66** | 0.64 (0.62–0.67) | 17.4 (7.7–39.3) | 107 | 20 | 5.4 |
| **67** | 0.18 (0.16–0.20) | 9.5 (0.3–81.0) | 213 | 16 | 13.3 |
| **68** | 1.0 (0.84–1.2) | 15.7 (9.9–24.7) | 111 | 45 | 2.5 |
| **69** | 1.6 (1.5–1.8) | 15.3 (9.2–25.6) | 262 | 49 | 5.4 |
| **70** | 0.48 (0.45–0.52) | 9.7 (6.0–15.6) | 66 | 5.2 | 12.7 |
| **71** | 0.28 (0.27–0.29) | 8.2 (6.5–10.4) | 237 | 23 | 10.3 |
| **72** | 1.2 (1.0–1.3) | 52.3 (44.5–61.4) | 182 | 36 | 5.1 |
| **73** | 5.6 (5.1–6.2) | 25.1 (21.6–29.2) | 336 | 153 | 2.2 |
| **74** | 0.60 (0.53–0.66) | 30.1 (23.7–38.2) | 147 | 3.8 | 38.7 |
| **75** | 0.16 (0.14–0.17) | ~13.0 | 112 | 2.0 | 56.0 |
| **76** | 0.39 (0.35–0.43) | 6.4 (6.0–15.6) | 454 | 63 | 7.2 |
| **77** | 0.42 (0.40–0.44) | 5.5 (3.1–9.9) | 40 | 40 | 1.0 |
| **78** | 0.81 (0.73–0.88) | 22.3 (16.5–30.2) | 246 | 17 | 17.4 |
| **79** | 0.62 (0.50–0.75) | 7.1 (5.6–9.0) | 364 | 33 | 11.0 |
| **80** | ~2.0 | 13.6 (12.0–15.5) | 571 | 41 | 13.9 |
| **81** | 0.26 (0.25–0.28) | 9.3 (6.1–14.0) | 58 | 18 | 3.4 |
| **82** | 13.7 (12.0–15.9) | >80 | >1000 | 91 | |
| **83** | 2.3 (2.1–2.6) | 25.0 (4.0–167) | 97 | <10 | |
| **84** | 2.7 (2.3–3.1) | 8.6 (6.4–11.4) | 118 | 3.2 | 36.9 |
| clozapine | 23.2 (21.1–25.9) | >40 | 830 | 50 | 16.6 |
| haloperidol | 0.11 (0.10–0.13) | 0.6 (0.40–0.80) | 18 | 170 | 0.1 |
| risperidone | 0.062 (0.047–0.077) | 3.2 (2.1–4.8) | 37.5 | 2.6 | 14.4 |

[a] Mouse. [b] Rat. [c] $D_2$ = dopamine $D_2$; binding was determined in rat striatum using [$^3$H]spiperone as ligand with a specific activity of 20–30 Ci/mmol and concentration of approximately 0.4 nM. $IC_{50}$ values were determined from seven-point concentration curves done in duplicate. Specific binding was determined with (+)-butaclamol. [d] 5-$HT_2$ = serotonin 5-$HT_2$; binding was determined in rat cortex using [$^3$H]spiperone as ligand with a specific activity of 20–30 Ci/mmol and concentration of approximately 1.5 nM. $IC_{50}$ values were determined from seven-point concentration curves done in duplicate. Specific binding was determined with 5 $\mu$M methysergide. [e] 95% confidence limits are shown in parentheses. [f] Not tested.

somewhat weaker in the CMA but more potent in the stereotypy model, suggesting that this compound would possess less mesolimbic selectivity than the lead structure. Additionally, it was approximately 1 order of magnitude more potent at the $D_2$ binding site when compared to **45**. In compound **49** a methyl group was introduced at the 2-position of the aromatic ring, and this resulted in good activity in the CMA and also gave a favorable stereotypy/CMA ratio of 125. However, unlike **45**, the compound showed equipotent affinity at the dopamine and serotonin receptors.

Replacement of the oxygen with sulfur as in the thioether **50** yielded a much less active compound in all assays, suggesting that there was a steric constraint for the 2-substituent. This hypothesis was reinforced by the activity of **51**, which has the smaller 2-methylamino substituent. Compound **51** showed robust activity in CMA, almost equipotent to **45**, and with a similar large stereotypy/CMA ratio of over 300. However, unlike **45**, it displayed a weaker affinity for the 5-$HT_2$ receptor being approximately 1 order of magnitude less potent. Compound **53**, which possessed a 2-acetamide function, was remarkable for its potency in the CMA, as it was one of the most potent in the series, being slightly more potent than risperidone and almost twice as potent as the lead compound.

Compounds **56**–**69** illustrate the effect of modifying the 4-acetyl moiety. For example, reduction of the

ketone of **45** resulted in the alcohol **56**, which showed an in vivo profile similar to that of **45** but was somewhat less potent in the in vitro assays. Demethylation of this compound afforded the phenol **57**, which, similar to the test results found with the demethylated ketone **47**, gave a compound more active in the CMA but which also showed increased potency in stereotypy.

Increasing the size of the alkyl portion of the ketone by one or three carbon atoms as in compounds **58** and **59** or substituting a phenyl for the methyl group as in **60** reduced activity, particularly in the CMA. These results would also seem to suggest that the 4-acyl position is sensitive to steric factors.

Compound **61** illustrates the result of electronically altering the 4-acyl position, by replacing it with a trifluoromethyl ketone. This functionality would be somewhat sterically similar to **45**; however, it would be significantly more electron-withdrawing than the methyl ketone. This change resulted in a compound that was approximately 20 times less potent than **45** in the CMA and less potent in binding to the 5-$HT_2$ receptor. Such results would suggest that the greater electron density afforded by the methyl group is preferred for optimum activity.

Replacement of the methyl ketone by a carboxamido group as in **62** produced a compound that showed one of the most potent affinities for the 5-$HT_2$ receptor and displayed a very high $D_2$/5-$HT_2$ ratio of approximately 65; however, it was considerably less active in the in vivo CMA model when compared to **45**.

In compounds **64–66**, the effect of introducing $\pi$ bond substitutes for the carbonyl of **45** was studied. Surprisingly, these compounds retained relatively good activity. Interestingly, the oxime **65**, although less potent in the in vivo tests, showed similar $D_2$ binding as **45** but was approximately 1 order of magnitude more potent at the 5-$HT_2$ receptor. In fact, this compound along with **62** was the most potent of the series in their affinity for this receptor site.

Substituting other atoms or functional groups for the 4-acetyl group produced compounds **67–70**; note that compound **67** represents an analog of **45** where the acetyl is reduced to an ethyl group, while compound **70** is devoid of a substituent at this position. All of these compounds retained relatively good potential antipsychotic activity in the assays but did not show as nearly a favorable bias toward preferential mesolimbic activity as did **45**, nor did they show as high an affinity for the 5-$HT_2$ binding site, except for **70**. Thus, it would appear that the acetyl function at the 4-position is needed for the preferred antipsychotic profile.

Compounds **71–75** provide examples with two substituents in the phenoxy ring at positions other than the 2 and 4. Structure **71** shows the effect of moving the methoxy group of compound **45** from the 2-position to the 3-position. This compound retained relatively good activity in the CMA but was more potent than **45** in the stereotypy assay.

A few examples of monosubstituted phenoxy compounds were also synthesized and are represented by compounds **76–78**. While all showed potential antipsychotic activity, none could be considered serious challengers to the lead compound. Also, it should be noted that the phenoxy compound **79**, with no phenyl ring substituents, showed an unremarkable profile compared to other compounds of the series.

Isosteric replacement of the phenoxy group of **45** with either a thiophenoxy, compound **80**, or an anilino group, as in **81**, did not improve upon the activity of the lead compound. Of the two analogs, compound **81** manifested the more interesting profile as it possessed a better stereotypy/CMA ratio. It is interesting to note that a similar trend was observed when the 2-methoxy group of **45** was replaced with a 2-methylthio (**50**) or 2-methylamino (**51**) group, respectively.

In the bicyclic structure **82**, the effect of linking the two oxygens of **45** by a carbon bridge in the form of a 1,4-benzodioxan is shown. This compound showed much weaker activity and was one of the weakest members of the series when tested in vivo. On the other hand, building the 4-keto function of **45** into a ring, via the tetralone **83**, and thus constraining the carbonyl in a ring system resulted in a more active compound but still considerably less interesting than **45**, when comparing the in vivo data.

Finally, the indolyl analog **84** was synthesized to observe the effect of using the 5-membered ring of the indole as a constrained isostere for the carbonyl of **45**. Although the compound showed weaker activity and reduced mesolimbic selectivity compared to **45**, its receptor binding characteristics were similar to the lead compound.

In conclusion, our studies suggest that the 3-[[(aryloxy)alkyl]piperidinyl]-1,2-benisoxazoles described here provided a class of compounds that showed significant activity in pharmacological models predictive of antipsychotic activity. Additionally, many showed biological profiles that were consistent with potential atypical activity as indicated by mesolimbic selectivity and moderate affinity for the $D_2$ receptor as well as a higher affinity for the 5-$HT_2$ receptor. Furthermore, structure–activity studies within this series indicate that a 6-fluoro substituent in the 1,2-benzisoxazole ring coupled with a 3-(4-acetyl-2-methoxphenyl)propoxy substituent at the piperidine nitrogen provided the optimal potential antipsychotic profile as embodied in **45**. Thus, the initial testing results suggested that **45** would be expected to be an effective antipsychotic with a potential for reduced EPS liability. Upon the basis of these results, compound **45** (HP 873, iloperidone) was chosen for further evaluation.

**Additional Biological Activity of Compound 45.** In order to more fully develop the profile of **45**, further biological assays were conducted. The compound was tested in other in vivo models[23] and compared to standards as shown in Table 4.

Compound **45** displayed good activity in the pole climb avoidance assay in rats, a conditioned avoidance paradigm which ostensibly discriminates neuroleptics from purely sedative drugs. In this assay, it showed potency similar to that of risperidone in avoidance responses, with a favorable 7-fold difference between the doses that inhibit responding versus escape failures, suggesting that the activity is not due strictly to sedative properties. When tested in intracranial self-stimulation in rats, an assay predictive of potential antipsychotic activity,[24] the compound was more potent than clozapine and comparable to haloperidol and risperidone.

A compound's tendency to induce catalepsy has been

**Table 4.** Additional Comparative in Vivo Pharmacology of **45**

| test[a] | **45** | haloperidol | clozapine | risperidone |
|---|---|---|---|---|
| pole climb avoidance (rat)[b] | | | | |
| avoidance | 0.70 (0.46–0.85) | 0.043 (0.039–0.048) | 11.3 (9.5–13.2) | 0.48 (0.48–0.52) |
| escape failures | 5.2 (3.6–8.9) | 0.22 (0.19–0.25) | 29.3 (25.4–35.1) | 1.3 (1.1–1.4) |
| intracranial self-stimulation (rat)[b] | 0.15 (0.12–0.17) 1.03 (0.89–1.18)[c] | 0.077 (0.073–0.081) | 7.4 (7.2–7.7) | 0.13 (0.11–0.15) |
| catalepsy (rat)[b] | 30.7 (19.6–48.0) | 0.65 (0.39–1.09)[d] | 0% at 80 | 5.7 (3.7–8.6) |
| social interaction (rat)[e] | 31% at 1.0 | −26% at 0.25 | 39% at 10.0 | 27% at 0.5 |
| antagonism of L-5-hydroxytryptophan (5-HTP) head twitch[f] | 0.07 (0.056–0.088) | 0.29 (0.25–0.33) | 0.43 (0.37–0.51) | NT[g] |

[a] $ED_{50}$ (95% confidence limits) or percent activity at dose, ip mg/kg, unless otherwise noted. [b] Pretreatment time was 60 min. [c] $ED_{50}$, mg/kg po. [d] Pretreatment time was 120 min. [e] Pretreatment time was 30 min. [f] Compounds administered 30 min post-5 HTP. [g] Not tested.

suggested as predictive of its potential to cause EPS liability.[25] When evaluated in this model, **45** had a weak effect, and catalepsy was evident only at doses much greater than the therapeutic doses predicted by the in vivo assays. Thus, the $ED_{50}$ to cause catalepsy is over 300 times the $ED_{50}$ that inhibits apomorphine-induced climbing (Table 3) and over 40 times the $ED_{50}$ that inhibits avoidance responses in the pole climb avoidance.

The effects of **45** in a modified social interaction paradigm indicate that, similar to clozapine and risperidone, it significantly increased social interaction, whereas haloperidol significantly reduced it. It has been suggested that a positive effect in this model may be predictive of a compound's potential to improve social withdrawal, which is a component of the negative symptoms of schizophrenia.[26]

Compound **45** is extremely potent in antagonizing the effects of the serotonin precursor 5-HTP, when evaluated in the 5-HTP-induced head twitch in rats. Activity in this assay is suggestive of serotonin 5-$HT_2$ antagonist properties, and iloperidone is about 6 times more potent than clozapine in this model. This finding is consistent with the high affinity than **45** shows in the binding assay for the 5-$HT_2$ receptor site.

In has been shown by Chiodo and Bunney[27] and Wang and White[28] that it is possible to predict antipsychotic efficacy and potential side effect liability by observing the electrophysiological profile of a drug on the dopamine (DA) neurons in the mesolimbic (A10) and nigrostriatal (A9) regions, respectively, of the rat brain. Thus, it was shown by utilizing extracellular single-unit recording techniques that all compounds that were effective antipsychotics, both classic and atypical, would cause, upon repeated administration, a tonic depolarization inactivation of the A10 DA neurons. Such a result would support the hypothesis that the symptoms of schizophrenia are predominantely due to excess DA activity in the mesolimbic area of the brain. However, it was also shown that typical antipsychotics, those known to have EPS liability, such as haloperidol, would additionally cause a depolarization inactivation of the DA neurons in the A9 area of the brain. As this area of the brain has been linked to motor function, the inhibition of these neurons provided a rationale for the EPS liability of the typical antipsychotics. Compound **45** was studied in extracellular dopamine single-unit sampling at 5.0 and 10.0 mg/kg and compared to clozapine and haloperidol. The results (Table 5) show that, similar to clozapine and haloperidol, **45** shows a significant decrease in the number of spontaneously active DA neurons in the A10 area of the brain. However, similar to clozapine and unlike haloperidol,

**Table 5.** Chronic Single-Dopamine Neuron Sampling of **45** in Rats[a]

| compd | dose (mg/kg ip) | *N* | no. of A10 units[b] | percent change | no. of A9 units[b] | percent change |
|---|---|---|---|---|---|---|
| control[c] | | 10 | 10.4 (±0.8) | | 8.9 (±0.7) | |
| **45** | 5.0 | 10 | 6.1 (±0.9) | −41[d] | 16.1 (±1.9) | 81[d] |
| | 10.0 | 10 | 6.6 (±1.3) | −40[d] | 12.2 (±2.1) | 45 |
| control | | 11 | 8.8 (±0.4) | | 10.0 (±0.4) | |
| clozapine | 20.0 | 6 | 1.8 (±0.3) | −79[d] | 13.7 (±0.6) | 37[e] |
| control | | 10 | 10.4 (±0.8) | | 9.0 (±0.8) | |
| haloperidol | 0.5 | 10 | 6.8 (±0.7) | −35[d] | 6.2 (±0.9) | −30[e] |

[a] Duration was 21 days. [b] Number of units/12 tracks (±SEM). [c] Distilled $H_2O$. [d] Significantly lower or greater than control at $p < 0.01$. [e] Significantly lower of greater than control at $p < 0.05$.

**Table 6.** In Vitro Profile of **45**

| receptor | tissue | radioligand | inhibitn of ligand binding: $IC_{50}$ (nM) |
|---|---|---|---|
| $\alpha_1$ adrenergic | whole brain | [$^3$H]WB4101 | 0.4 |
| 5-$HT_2$ | cortex | [$^3$H]spiperone | 9.0 |
| 5-$HT_{1A}$ | cortex | [$^3$H]-8-OH-DPAT | 210 |
| $D_2$ | striatum | [$^3$H]spiperone | 110 |
| $D_1$ | striatum | [$^3$H]SCH23390 | 750 |
| $\sigma$ | sections—hippocampus | [$^3$H]-(+)-SKF10,047 | 64 |
| muscarinic | whole brain | [$^3$H]quinuclidinyl benzilate | >1000 |

**45** does not cause a decrease in the number of DA neurons in the A9 area. This finding, along with the other in vivo results, strongly suggests that compound **45** should be a clinically effective antipsychotic with low EPS liability.[29]

Table 6 shows a more detailed receptor binding profile of compound **45**. When evaluated at the $\alpha_1$ noradrenergic receptor, **45** showed a very high affinity, presumably acting as an antagonist. Recent studies have suggested that the $\alpha_1$ antagonist properties of antipsychotics may contribute to their efficacy.[30]

Binding to the serotonergic receptors is highlighted by the compound's high affinity for the 5-$HT_2$ site ($K_i$ = 3.1 nM),[26] but it additionally showed a moderate affinity for the 5-$HT_{1A}$ receptor ($K_i$ = 168 nM). Also, coupled with its moderate affinity for the $D_2$ receptor ($K_i$ = 54 nM), **45** also showed some affinity for the $D_1$ site ($K_i$ = 546 nM), albeit weak. Recent evidence suggests that positive activity in the social interaction paradigm and thus potential efficacy against negative symptoms is best correlated with a $D_1$/5-$HT_{1A}$ $K_i$ ratio of 1 or greater.[26] Compound **45** manifests such a characteristic as does clozapine and risperidone. Additionally, **45** binds with moderately high affinity for the $\sigma$ receptor. Whether or not such a characteristic contributes to the antipsychotic activity remains speculative. $\sigma$ receptor

antagonists have shown potential antipsychotic activity in some animal models; however, they have yet to prove their efficacy in a clinical setting.[31] The compound shows no muscarinic cholinergic binding, in contrast to the marked affinity displayed by clozapine.[5]

Compound **45** was also tested in ex vivo experiments to determine its magnitude of inhibition of binding and duration of occupancy at 5-$HT_2$ and $D_2$ receptors. When tested at doses of 2.5–20 mg/kg ip, in cortical and subcortical areas of the rat, **45** showed an inhibition of 5-$HT_2$ receptors of 50–94% and a duration of greater than 4 h. On the other hand, $D_2$ receptors were inhibited to an extent of only 10–20% with the peak effect at 1 h.[32] Clozapine showed a similar, greater inhibition of 5-$HT_2$ receptors coupled with a weaker effect on $D_2$ receptors, a property not shared by the typical antipsychotics like haloperidol.[33] In further ex vivo experiments, **45** was studied at a dose of 10 mg/kg ip for 19 days for its ability to affect the number of $D_2$ receptors in the nucleus accumbens and six regions of the striatum.[32] Similar to clozapine and unlike haloperidol,[34] **45** did not increase the number of $D_2$ receptors in these regions of the rat brain. It has been suggested that up regulation of $D_2$ receptors may be responsible for tardive dyskinesia, which is a troubling side effect of typical antipsychotics.[35] However, in the same chronic study, it was found that **45** reduced the number of cortical 5-$HT_2$ receptors by 41% ($B_{max}$). This result is also consistent with the cortical serotonin receptor effects shown with clozapine.[36] The results of these ex vivo studies suggest binding characteristics for **45** that are similar to the atypical antipsychotic clozapine. To what extent such characteristics contribute to clozapine's efficacy and lack of neurological side effects is uncertain. Nonetheless, if a cause and effect relationship does exist, then **45** could show a clinical profile similar to that of clozapine; however, as it is structurally distinct from clozapine, compound **45** might not be expected to cause the agranulocytosis that is associated with clozapine.

In summary, the pharmacological and biochemical profile of compound **45**, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone, would suggest that the compound should be an effective antipsychotic drug in the clinic. Additionally, it should have a low propensity to cause extrapyramidal side effects or tardive dyskinesia, along with the potential to be effective against the negative symptoms of schizophrenia. Compound **45** is currently in advanced clinical trials.

## Experimental Section

The structures of all compounds were supported by their IR (Perkin-Elmer 547), $H^1$ NMR (Varian XL-200), and MS spectra. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were determined on a Finnegan 4500 spectrometer equipped with an INCOS data system or a VG Trio 2 GC-MS spectrometer equipped with a Lab-Base data system. Preparative HPLC was performed on a Waters Associates Prep LC System 500. Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY, or Roberston Microlit Laboratories, Inc., Madison, NJ.

**Method A. 1-[4-(3-Chloropropoxy)-3-(methylamino)phenyl]ethanone (15).** To a stirred suspension of NaH (0.87 g, 18 mmol of a 50% oil dispersion) in DMF (25 mL) under $N_2$ and cooled to 0 °C in an ice–salt bath was added, dropwise, a solution of 1-[4-hydroxy-3-(methylamino)phenyl]ethanone (3.0 g, 18 mmol) dissolved in DMF (55 mL) so that the temperature did not rise above 3 °C. After the addition was complete, the reaction mixture was stirred for 80 min at ambient temperature. The reaction mixture was cooled to 5 °C, and a solution of 1-bromo-3-chloropropane (3.1 g, 12 mmol) in DMF (20 mL) was added dropwise. After this addition was complete, the ice bath was removed and the reaction mixture was stirred at ambient temperature for 2.5 h. $H_2O$ (75 mL) was carefully added, and after stirring vigorously for 5 min, the reaction mixture was left to stand overnight. The aqueous mixture was extracted with EtOAc, and the EtOAc extract was washed with $H_2O$, dried with $MgSO_4$, and concentrated to yield 3.9 g of a dark solid. The compound was purified by preparative HPLC on silica gel (dichloromethane/MeOH, 99:1) to yield 2.0 g of a solid. This was combined with an additional sample (3.8 g total) and recrystallized twice from EtOH to afford 2.1 g (31%) of **15**: mp 115–117 °C; NMR ($CDCl_3$) $\delta$ 2.31 (quintet, 2H), 2.56 (s, 3H), 2.93 (s, 3H), 3.75 (t, 2H), 4.23–4.26 (m, 3H), 6.78 (d, 1H), 7.20–7.36 (m, 2H); MS *m/e* 241. Anal. ($C_{12}H_{16}ClNO_2$) C, H, N.

**Method B. 1-[4-(3-Bromopropoxy)-3-(methylthio)phenyl]ethanone (14).** A mixture of 1-[4-hydroxy-3-(methylthio)-phenyl]ethanone (5.4 g, 30 mmol), $K_2CO_3$ (4.2 g), and 1,3-dibromopropane (8 g, 39 mmol) in acetonitrile (150 mL) was heated at reflux for 3 h and stirred at room temperature overnight. Acetonitrile was removed at reduced pressure, and the residue was extracted into dichloromethane (250 mL). The insolubles were filtered off, and the dichloromethane solution was concentrated. The crude product was purified on a silica gel column (100 g; eluted with 3:2 hexane:dichloromethane, 1.6 L). The compound crystallized upon concentration, and the product (3.5 g) was recrystallized from ethanol (40 mL) to yield 2.0 g (22%) of **14**: mp 120–122 °C; NMR ($CDCl_3$) $\delta$ 2.40 (quintet, 2H), 2.47 (s, 3H), 2.59 (s, 3H), 3.67 (t, 2H), 4.26 (t, 2H), 7.12 (d, 1H), 7.44 (s, 1H), 7.57 (d, 1H); MS *m/e* 302, 304. Anal. ($C_{12}H_{15}BrOS$) C, H, N.

**Method C. 1-[3-(Acetylamino)-4-(3-chloropropoxy)-phenyl]ethanone (31).** A stirred mixture of 1-[3-(acetylamino)-4-hydroxyphenyl]ethanone (7.7 g, 40 mmol), $K_2CO_3$ (5.7 g), 3-chloro-1-bromopropane (8.9 g, 56 mmol), and acetone (100 mL) was refluxed for 16 h. The reaction mixture was allowed to cool to ambient temperature and filtered. Concentration of the filtrate yielded 8.5 g of a white solid. The solid was recrystallized from toluene and then from EtOH to afford 6.5 g of an off-white solid. A 3.3 g sample of this material was flash chromatographed on silica gel with EtOAc as eluent, to afford 2.8 g of a solid. Recrystallization from toluene and then from EtOH–$H_2O$ yielded 2.2 g (51%) of **31**: mp 124–126 °C; NMR ($CDCl_3$) $\delta$ 2.23 (s, 3H), 2.35 (quintet, 2H), 2.58 (s, 3H), 3.76 (t, 2H), 4.30 (t, 2H), 6.95 (d, 1H), 7.71–7.76 (m, 2H), 8.99 (s, 1H); MS *m/e* 269. Anal. ($C_{13}H_{16}ClNO_3$) C, H, N.

**Method D. 1-[4-[2-[4-(1,2-Benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone Fumarate (37).** A mixture of 3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (4.8 g, 20 mmol), $K_2CO_3$ (5.2 g, 40 mmol), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (5.0 g, 22 mmol), and DMF (90 mL) was heated at 90 °C for 16 h. The reaction mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The EtOAc was washed ($H_2O$) and dried ($MgSO_4$), and the solvent was concentrated to afford an oil. Upon standing, the oil solidified to a beige solid. The crude solid was recrystallized twice from EtOH to afford 5.9 g of an off-white solid. The solid was dissolved in EtOAc, and fumaric acid (1.2 g, 1.1 equiv) was added. The mixture was heated briefly on a steam bath and then stirred at ambient temperature for 2 h. An initial green oil settled out, and the supernatant solution was decanted. Ether was added to the decantant, and 4.0 g of a white fumarate salt was collected. The salt was recrystallized twice from ethanol–ether to yield 1.7 g (17%) of **37**: mp 127–129 °C; NMR (DMSO-$d_6$) $\delta$ 1.98–2.08 (m, 4H), 2.52 (m, 5H), 2.98 (t, 2H), 3.18–3.24 (m, 3H), 3.84 (s, 3H), 4.28 (t, 2H), 6.61 (s, 2H), 7.14 (d, 1H), 7.38–7.46 (m, 2H), 7.61–7.71 (m, 3H), 7.98 (d, 1H); MS *m/e* 394. Anal. ($C_{23}H_{26}N_2O_4 \cdot C_4H_4O_4$) C, H, N.

**Method E. 1-[4-[3-[4-(5-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (43).** A mixture of 5-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10 mmol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (2.4 g, 10 mmol), $K_2CO_3$ (1.4 g), a few crystals of KI, and acetonitrile (100 mL) was stirred and refluxed for 8 h. The reaction mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The EtOAc extract was washed (brine), dried ($MgSO_4$), and concentrated to afford 4.0 g of a white solid. The solid was chromatographed on a preparative HPLC column on silica gel (dichloromethane/MeOH, 95:5). Concentration of the appropriate fractions afforded 2.0 g (47%) of **43**: mp 103–105 °C; NMR ($CDCl_3$) $\delta$ 2.04–2.22 (m, 8H), 2.61 (m, 5H), 2.64–3.13 (m, 3H), 3.93 (s, 3H), 4.20 (t, 2H), 6.95 (d, 1H), 7.24–7.41 (m, 2H), 7.48–7.60 (m, 3H); MS *m/e* 426. Anal. ($C_{24}H_{27}FN_2O_4$) C, H, N.

**Method F. 1-[2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-5-methylphenyl]ethanone (73).** A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (2.87 g, 11.23 mmol), $K_2CO_3$ (2.5 g), 1-[2-(3-bromopropoxy)-5-methylphenyl]ethanone (3.74 g, 13.8 mmol) in DMF (10 mL), and acetonitrile (50 mL) was heated at 95 °C for 6 h. At the end of the reaction, the solvent was concentrated and the mixture was extracted into dichloromethane (300 mL). The organic solution was washed with water and brine, dried over $MgSO_4$, and then concentrated to a crude oil. The purification was done by flash chromatography over a silica gel column (60 g; eluted with 1% MeOH:dichloromethane, 1.2 L, and 3% MeOH:dichloromethane, 600 mL). The resulting material was crystallized from a small volume of $Et_2O$ and hexane to provide 2.13 g (46%) of **73**: mp 92–93 °C; NMR ($CDCl_3$) $\delta$ 2.04–2.18 (m, 8H), 2.3 (s, 3H), 2.62 (m, 5), 3.06–3.12 (m, 3H), 4.13 (t, 2H), 6.88 (d, 1H), 7.05–7.11 (m, 1H), 7.22–7.28 (m, 2H), 7.55 (s, 1H), 7.66–7.73 (m, 1H); MS *m/e* 410. Anal. ($C_{24}H_{27}FN_2O_3$) C, H, N.

***N*-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl]-6-acetyl-2-benzoxazolinone (9).** To a stirred suspension of NaH (7.8 g, 160 mmol, $Et_2O$-washed) in DMF (75 mL) was added dropwise, under nitrogen, 2-benzoxazolinone (20.0 g, 150 mmol) dissolved in DMF (150 mL). After complete addition, the reaction mixture was stirred at ambient temperature for 30 min and then it was cooled to −5 °C with an ice–acetone bath. A solution of 3-chloro-1-bromopropane (46.6 g, 300 mmol) in DMF (50 mL) was then added dropwise (temperature never exceeded 0 °C). The reaction mixture was allowed to reach ambient temperature and stirred for 16 h. The reaction mixture was poured into water, and the aqueous mixture was extracted with EtOAc. The EtOAc was washed with $H_2O$ and dried ($MgSO_4$) and the extract concentrated to afford 21.9 g of a brown solid. The solid was recrystallized from toluene–hexane to afford *N*-(3-chloropropyl)-2-benzoxazolinone (**7**) as large needles, 15.6 g (49%): mp 264–266 °C; NMR ($CDCl_3$) $\delta$ 2.30 (m, 2H), 3.61 (t, 2H), 4.02 (t, 2H), 7.03–7.32 (m, 3H); MS *m/e* 211.

A mixture of *N*-(3-chloropropyl)-2-benzoxazolinone (8.5 g, 40 mmol), poly(phosphoric acid) (100 g), and HOAc (2.4 g, 2.3 mL, 40 mmol) was stirred and heated at 100 °C for 2 h. The hot solution was poured into ice–water to deposit a yellow gum. The mixture was extracted with dichloromethane, and the insolubles were filtered. The dichloromethane extract was washed with water, dried ($K_2CO_3$), and concentrated to afford 6.4 g of a slightly green solid. This was recrystallized from EtOH (95%) to yield *N*-(3-chloropropyl)-6-acetyl-2-benzoxazolinone (**8**) as a brown solid, 3.5 g (35%): mp 100–103 °C; NMR ($CDCl_3$) $\delta$ 2.30 (m, 2H), 2.60 (s, 3H), 3.60 (t, 2H), 4.08 (t, 2H), 7.16 (d, 1H), 7.90 (m, 2H); MS *m/e* 237.

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.0 g, 9 mmol), *N*-(3-chloropropyl)-6-acetyl-2-benzoxazolinone (2.4 g, 9 mmol), $K_2CO_3$ (3.6 g), a few crystals of KI, and acetonitrile (50 mL) was stirred and refluxed for 13 h. The reaction mixture was poured into water, and a dark brown solid that separated was collected to afford 3.3 g of crude product. The solid was chromatographed on silica gel on a preparative HPLC column (dichloromethane/MeOH, 96:4), to afford 2.3 g of a yellow solid. Recrystallization from EtOAc yielded 1.2 g (31%) of **9**: mp 152–154 °C; NMR ($CDCl_3$) $\delta$ 1.95 (m, 8H), 2.46 (t, 2H), 2.61 (s, 3H), 2.92–3.04 (m, 3H), 4.00 (t, 2H), 7.03–7.27 (m, 3H), 7.67 (m, 1H), 7.82–7.91 (m, 2H); MS *m/e* 347. Anal. ($C_{24}H_{24}FN_3O_4$) C, H, N.

**1-[4-[[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]amino]-3-hydroxyphenyl]ethanone (10).** A mixture of *N*-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-6-acetyl-2-benzoxazolinone (6.0 g, 14 mmol) and 10% aqueous sodium hydroxide (50 mL) was stirred and refluxed for 40 min. Water was added, the reaction mixture was made acidic with 5% hydrochloric acid, and then saturated $Na_2CO_3$ was added until effervescence ceased. The resultant dark brown solid (4.2 g) was collected and treated with saturated sodium bicarbonate solution and the mixture extracted with dichloromethane. The filtrate from above was extracted with dichloromethane, and after washing with $H_2O$ and brine, drying ($MgSO_4$), and concentrating the extracts, a total of 5.0 g of the crude phenol was realized. The compound was flash chromatographed on silica gel (dichloromethane/MeOH, 9:1) to afford 3.5 g (61%) of a solid. The compound was recrystallized from toluene to afford **10**: mp 150–152 °C; NMR (DMSO-$d_6$) $\delta$ 1.69–2.20 (m, 8H), 2.37–2.60 (m, 5H), 2.93–3.33 (m, 5H), 6.10 (t, 1H), 6.50 (d, 1H), 7.30 (m, 2H), 7.45 (dd, 1H), 7.70 (dd, 1H), 8.00 (m, 1H), 9.65 (br s, 1H); MS *m/e* 411. Anal. ($C_{23}H_{26}FN_3O_3$) C, H, N.

**1-[4-(3-Chloropropoxy)-3-hydroxyphenyl]ethanone (11).** A mixture of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (10.0 g, 41.2 mmol) and concentrated $H_2SO_4$ (50 mL) was stirred at 65 °C for 23 h. The cooled reaction mixture was poured into 250 g of ice and stirred vigorously for 10 min. The aqueous mixture was extracted with dichloromethane, and the resultant dichloromethane extract was washed well with 5% NaOH. The basic phases were then combined and washed with dichloromethane. The aqueous mixture was cooled in an ice bath, and concentrated HCl was added until a precipitate formed. The product was isolated by filtration and dired to yield 3.1 g of a light brown solid. This was combined with an additional sample (5.0 g total), and two consecutive recrystallizations from toluene provided 3.4 g (22%) of 11: mp 101–103 °C; NMR ($CDCl_3$) $\delta$ 2.30–2.39 (quintet, 2H), 2.55 (s, 3H), 3.75 (t, 2H), 4.30 (t, 2H), 5.77 (t, 1H), 6.92 (d, 1H), 7.55 (m, 2H); MS *m/e* 228. Anal. ($C_{11}H_{13}ClO_3$) C, H, N.

**4-(3-Chloropropoxy)-3-hydroxy-α-methylbenzenemethanol (18).** To a flask charged with $NaBH_4$ (1.5 g, 39.4 mmol) under nitrogen and chilled to 10 °C was added, slowly, a solution of 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone (11) (6.0 g, 26.2 mmol) dissolved in EtOH–THF (120 mL, 2:1). After total addition, the ice bath was removed and the reaction was stirred at ambient temperature for 3 h. An additional amount of $NaBH_4$ (0.2 g, 5.3 mmol) was carefully added, and after stirring at ambient temperature for 1 h, the solvent was removed *in vacuo*. The resultant solid residue was diluted with water (100 mL) and left for 16 h. The product was isolated by vacuum filtration yielding 3.8 g. Two consecutive recrystallizations from toluene provided 3.3 g (55%) of **18**: mp 107–109 °C; NMR ($CDCl_3$) $\delta$ 1.46 (d, 3H), 1.81 (s, 1H), 2.82 (quintet, 2H), 3.74 (t, 2H), 4.21 (t, 2H), 4.81 (m, 1H), 5.63 (s, 1H), 6.85 (s, 2H), 6.97 (s, 1H); MS *m/e* 230. Anal. ($C_{11}H_{15}ClO_3$) C, H, N.

**1-[4-(3-Chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone (22).** To a stirred suspension, under nitrogen, of NaH (6.4 g, 130 mmol of a 50% oil dispersion, ether-washed) in THF (220 mL) was added pyrazole (4.4 g, 60 mmol) in THF (60 mL), dropwise. After complete addition, the reaction mixture was stirred for about 15 min and then 4-(3-chloropropoxy)-3-methoxybenzaldehyde (24.5 g, 107 mmol) was added. The nitrogen was stopped, and air was sparged into the reactor for about 3 h. The reaction mixture was then allowed to stir at ambient temperature open to the atmosphere for 16 h. Water was added, the reaction mixture was cooled in an ice bath, and concentrated HCl (25 mL) was added dropwise. More water was added, the yellow solid that separated was collected to afford 16.2 g of product, and subsequent extraction of the filtrate afforded an additional 9.3 g. The samples were combined and recrystallized from acetonitrile to yield 12.6 g of a light yellow solid of 4-(3-chloropropoxy)-3-methoxybenzoic acid: mp 154–156 °C; NMR ($CDCl_3$)

δ 2.30 (m, 2H), 3.80 (t, 2H), 3.90 (s, 3H), 4.23 (t, 2H), 6.93 (d, 1H), 7.59 (s, 1H), 7.70 (dd, 1H), 9.20 (br s, 1H); MS *m/e* 244.

To a mixture of 4-(3-chloropropoxy)-3-methoxybenzoic acid (2.4 g, 10 mmol) in dichloromethane (5 mL) was added thionyl chloride (0.9 mL, 12 mmol) dissolved in dichloromethane (5 mL). The reaction mixture was stirred and refluxed for 1 h, and then the dichloromethane was removed *in vacuo* to leave a dark oil. The oil was triturated with hexane, and the solid that formed while scratching with a glass rod was collected to afford 1.6 g of 4-(3-chloropropoxy)-3-methoxybenzoyl chloride: mp 60–63 °C; NMR ($CDCl_3$) δ 2.30 (m, 2H), 3.80 (t, 2H), 3.90 (s, 3H), 4.27 (t, 2H), 6.95 (d, 1H), 7.54 (s, 1H), 7.83 (dd, 1H); MS *m/e* 262.

To a stirred mixture of 4-(3-chloroproxy)-3-methoxybenzoyl chloride (10.0 g, 38 mmol) in dichloromethane (55 mL) cooled to −70 °C was condensed bromotrifluoromethane (70 g, 47 mmol) followed by the addition of hexamethylphosphoramide (9.4 g, 41 mmol) dissolved in dichloromethane (7 mL). The first 90% was added quite rapidly and the remainder at a slower rate.[37] After complete addition, the reaction mixture was stirred at −70 to −65 °C for an additional hour. The reaction mixture was allowed to come to room temperature, an equal volume of hexane was added, and the layers were separated. The lower layer was extracted with hexane and then with $Et_2O$. The extracts were combined and concentrated to yield 5.6 g of a thick, colorless oil. The oil was chromatographed on silica gel on a preparative HPLC column (EtOAc/hexane, 8:2) to afford 2.7 g of oil, which upon being evacuated solidified to 2.4 g (21%) of **22**: mp 45–47 °C; NMR ($CDCl_3$) δ 2.30 (m, 2H), 3.80 (t, 2H), 3.95 (s, 3H), 4.28 (t, 2H), 6.95 (d, 1H), 7.56 (s, 1H), 7.70 (d, 1H); MS *m/e* 296. Anal. ($C_{12}H_{12}ClF_3O_3$) C, H, N.

**1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-ethoxyphenyl]ethanone (54).** A suspension of NaH (0.28 g of a 50% oil dispersion, 5.9 mmol) in DMF (20 mL) was cooled to 5 °C in an ice bath. To this was added, dropwise, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone (**47**) (2.3 g, 5.6 mmol) dissolved in DMF (40 mL). After total addition, the mixture was stirred under nitrogen for 1 h, keeping the temperature below 10 °C. A solution of bromoethane (1.3 g, 11.8 mmol) dissolved in DMF (15 mL) was then added, dropwise, to the reaction mixture, and stirring under nitrogen was continued for 3 h, allowing the temperature to slowly rise to ambient temperature. The reaction mixture was cooled in an ice bath, $H_2O$ was added, and the aqueous mixture was extracted with EtOAc. The EtOAc extract was washed with $H_2O$, dried with $MgSO_4$, and concentrated to yield 3.9 g of a damp, beige solid. The solid was triturated with $Et_2O$ and filtered to yield 1.5 g. This was combined with an additional sample (3.5 g total), and recrystallization from ethanol provided 3.0 g (57%) of **54**: mp 121–114 °C; NMR ($CDCl_3$) δ 1.49 (t, 3H), 2.04–2.22 (m, 8H), 2.58–2.65 (m, 5H), 3.07–3.12 (m, 3H), 4.10–4.21 (m, 4H), 6.93 (d, 1H), 6.95–7.11 (m, 1H), 7.25 (dd, 1H), 7.52–7.59 (m, 2H), 7.66–7.73 (m, 1H); MS *m/e* 440. Anal. ($C_{25}H_{29}FN_2O_4$) C, H, N.

**4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxy-α-methylbenzenemethanol (56).** To a stirred mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (**45**) (4.0 g, 9.4 mmol) in MeOH/THF (60 mL, 1:1) was added $NaBH_4$ (0.4 g, 10 mmol). After an initial evolution of gas, all insolubles went into solution. The reaction mixture was stirred at ambient temperature for 3 h, and TLC at this time showed a slight amount of starting ketone. Therefore, another 0.1 g of $NaBH_4$ was added, and stirring was continued for an additional 0.5 h. TLC then showed complete disappearance of starting material. The reaction mixture was concentrated to an off-white residue, which was diluted with water and collected to yield 3.4 g of alcohol. This was recystallized from toluene (twice, with a charcoal treatment) to yield 2.7 g (67%) of **56**: mp 136–138 °C; NMR ($CDCl_3$) δ 1.49 (d, 3H), 2.01–2.23 (m, 9H), 2.57 (t, 2H), 3.04–3.11 (m, 3H), 3.88 (s, 3H), 4.08 (t, 2H), 4.84 (q, 1H), 6.89 (s, 2H), 6.96–7.68 (m, 3H), 7.70–7.75 (m, 1H); MS *m/e* 428. Anal. ($C_{24}H_{29}FN_2O_4$) C, H, N.

**6-Fluoro-3-[1-[3-[2-methoxy-4-(1-methylethenyl)-phenoxy]propyl]-4-piperidinyl]-1,2-benzisoxazole Hydrochloride (64).** A solution of butyllithium (4.7 mL of a 2.3 M solution in hexanes, 10.7 mmol) in tetrahydrofuran (65 mL) was stirred under nitrogen and cooled to −70 °C in an isopropyl alcohol–dry ice bath. Methyltriphenylphosphonium bromide (3.8 g, 10.6 mmol) was added portionwise over the course of 10 min. After complete addition, the reaction mixture was stirred at −65 °C for 1 h and then allowed to gradually warm to ambient temperature, where it was stirred for an additional 3.5 h. The reaction mixture was cooled to 0 °C, and a solution of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (**45**) (4.7 g, 11.0 mmol) dissolved in tetrahydrofuran (50 mL) was added, dropwise, over the course of 0.5 h. After the addition was complete, the reaction mixture was stirred at ambient temperature for 19 h. The reaction mixture was poured into $H_2O$, and the aqueous mixture was extracted with $Et_2O$. The $Et_2O$ extract was washed several times with $H_2O$, dried with $MgSO_4$, and concentrated to yield 7.0 g of a light orange solid. Recrystallization from toluene–hexane provided 1.4 g of triphenylphosphine oxide, and concentration of the filtrate afforded 5.5 g of a glassy solid. The latter was combined with an additional sample (6.5 g total), and purification by preparative HPLC gave 5.2 g of a beige solid, which remained contaminated by triphenylphosphine oxide. A salt was prepared by dissolving the compound in anhydrous $Et_2O$ (300 mL) and methanol (5 drops) and adding ethereal HCl to precipitate 4.0 g of the salt. Recrystallization (twice) from EtOH gave 2.5 g (49%) of **64**: mp 192–194 °C; NMR (DMSO-$d_6$) δ 2.10–2.61 (m, 8H), 3.14–3.86 (m, 11H), 9.11–9.23 (m, 2H), 5.07 (s, 1H), 5.39 (s, 1H), 6.90–7.15 (m, 2H), 7.35 (dt, 1H), 7.62–7.76 (m, 2H), 8.31 (m, 1H), 11.38 (brs, 1H); MS *m/e* 424. Anal. ($C_{25}H_{29}FN_2O_3$·HCl) C, H, N.

**1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone Oxime (65).** A mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone (**45**) (4.3 g, 10 mmol), hydroxylamine hydrochloride (1.3 g, 18 mmol), ammonium acetate (1.7 g, 22 mmol), and EtOH (85 mL)–$H_2O$ (25 mL) was stirred and refluxed for 16 h. The reaction mixture was poured into water, and the mixture was cooled in an ice bath for 2 h. The resultant white solid was collected, washed with water, and dried to yield 4.6 g of hydrochloride salt of the oxime. The compound was dispersed in water, and $NH_4OH$ was added until the suspension was decidedly basic. The basic suspension was then extracted with dichloromethane, and after washing with $H_2O$, drying ($MgSO_4$), and concentrating the extract, 3.0 g of white solid was harvested. The compound was recrystallized from DMF to yield 2.3 g (52%) of **65**: mp 168–170 °C; NMR (DMSO-$d_6$) δ 1.81–2.16 (m, 11H), 2.45–2.52 (m, 2H), 2.96–3.38 (m, 3H), 3.79 (s, 3H), 4.04 (t, 2H), 6.96 (d, 1H), 7.13–7.23 (m, 3H), 7.68 (dd, 1H), 7.96–8.03 (m, 1H), 11.05 (s, 1H); MS *m/e* 441. Anal. ($C_{24}H_{28}FN_3O_4$) C, H, N.

**1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone Hydrazone (66).** A stirred mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (**45**) (4.3 g, 10 mmol), hydrazine (0.8 g, 2.5 mmol), and EtOH (40 mL) was refluxed for 16 h. The cooled solution was concentrated to yield an oily residue. The residue was triturated with water, and the resultant solid was collected to afford 4.2 g of the hydrazone as a yellow solid. The compound was recrystallized from 2-propanol and then from toluene to afford 1.7 g (39%) of **66**: mp 106–108 °C; NMR ($CDCl_3$) δ 2.03–2.70 (m, 11H), 2.60 (t, 2H), 3.05–3.11 (m, 3H), 3.91 (s, 3H), 4.13 (t, 2H), 5.28 (s, 2H), 6.89 (d, 1H), 7.02–7.13 (m, 2H), 7.24 (dd, 1H), 7.36 (s, 1H), 7.67–7.73 (m, 1H); MS *m/e* 440. Anal. ($C_{24}H_{29}FN_4O_3$) C, H, N.

**3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyaniline (75).** A mixture of 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenylacetamide (**74**) (4.2 g, 9.5 mmol), in 15% HCl (60 mL), was heated at reflux (110 °C) for 2 h. At the end of the reaction, the solution was cooled to 0 °C and then basified with 25% NaOH to pH 10. The aqueous suspension was extracted

with EtOAc, and the EtOAc solution was washed with $H_2O$ and brine and then dried over $Na_2SO_4$. The solvent was removed at reduced pressure to afford an oil which was purified by flash chromatography on a silica gel column (dichloromethane/MeOH/$Et_2NH$, 98.7:1.0:0.3) to yield 2.6 g of an oil . Upon treatment with EtOH–petroleum ether (8 mL, 5:3), the oil crystallized to yield 1.2 g of **75**: mp 94–95 °C; NMR ($CDCl_3$) $\delta$ 2.03–2.21 (m, 8H), 2.60 (t, 2H), 3.03–3.11 (m, 3H), 3.43 (br s, 2H), 3.80 (s, 3H), 4.06 (t, 2H), 6.24 (dd, 1H), 6.36 (d, 1H), 6.72 (d, 1H), 7.05 (m, 1H), 7.24 (dd, 1H), 7.67–7.74 (m, 1H); MS *m/e* 399. Anal. ($C_{22}H_{26}FN_3O_3$) C, H, N.

**1-[4-[[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]amino]-3-methoxyphenyl]ethanone (81).** To a stirred suspension of NaH (0.37 g, 7 mmol of a 50% oil dispersion) in DMF (20 mL) was added, dropwise, 1-[4-[[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]amino]-3-hydroxyphenyl]ethanone (**10**) (2.9 g, 7 mmol) dissolved in dimethylformamide (25 mL). The reaction mixture was stirred at ambient temperature for 15 min, and then it was cooled with an ice bath to about 5 °C, whereupon methyl iodide (1.0 g, 7 mmol) in DMF (1 mL) was added dropwise. The reaction mixture was stirred at ambient temperature for 0.5 h, and then $H_2O$ was added. The resulting aqueous mixture was extracted with EtOAc, the extract washed with water and dried ($MgSO_4$), and the solvent was concentrated to afford 4.9 g of a brown oil, which solidified on standing. The solid was flash chromatographed on silica gel (EtOAc/$Et_2NH$, 95:5), and the appropriate fractions were concentrated to yield 2.7 g of product as a yellow solid. Recrystallization from toluene–hexane yielded 2.0 g (67%) of **81**: mp 96–98 °C; NMR ($CDCl_3$) $\delta$ 1.81–1.93 (m, 2H), 2.12–2.19 (m, 6H), 2.52–2.61 (m, 5H), 3.14 (m, 3H), 3.32 (q, 2H), 3.91 (s, 3H), 6.50 (d, 1H), 7.08 (dt, 1H), 7.23–7.29 (m, 1H), 7.41 (s, 1H), 7.54 (dd, 1H), 7.64–7.71 (m, 2H); MS *m/e* 424. Anal. ($C_{24}H_{28}FN_3O_3$) C, H, N.

**6-Aceto-2-[[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl]-1,4-benzodioxan (82).** To a stirred solution of 6-aceto-2-(hydroxymethyl)-1,4-benzodioxan (3.4 g, 16.3 mmol) and triethylamine (2.5 g) in $CHCl_3$ (100 mL), at 0 °C, was added dropwise methanesulfonyl chloride (2.5 g, 22 mmol). After stirring at ambient temperature for 2 h, more $CHCl_3$ was added and the organic phase was washed with an ice–dilute HCl mixture, $NaHCO_3$ solution, and brine. The organic layer was then dried ($MgSO_4$) and concentrated to yield 5.6 g of an oil. The oil was flash chromatographed on silica gel (dichloromethane) to afford 3.6 g (78%) of 6-aceto-2-[(mesyloxy)methyl]-1,4-benzodioxan as an oil: NMR ($CDCl_3$) $\delta$ 2.52 (s, 3H), 3.10 (s, 3H), 4.08–4.63 (m, 5H), 6.90 (d, 1H), 7.52 (m, 2H); MS *m/e* 286.

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 mmol), $K_2CO_3$ (2 g, 14.5 mmol), and 6-aceto-2-[(mesyloxy)methyl]-1,4-benzodioxan (3.5 g, 12 mmol) in acetonitrile (100 mL) was heated at reflux for 3 h. At the end of the reaction, the solvent was removed under reduced pressure and the residue was extracted into dichloromethane (350 mL). The insolubles were filtered off, and the dichloromethane solution was concentrated to an oil. The oil was purified by flash chromatography on silica gel (dichloromethane/MeOH, 99:1) to afford 3.4 g of a yellow solid. Recrystallization from EtOH gave 3.2 g of **82**: mp 122–123 °C; NMR ($CDCl_3$) $\delta$ 2.04–2.12 (m, 4H), 2.34–2.46 (m, 2H), 2.54 (s, 3H), 2.68–2.76 (m, 2H), 3.02–3.18 (m, 3H), 4.01–4.11 (m, 1H), 4.35–4.42 (m, 2H), 6.93 (d, 1H), 7.07 (d, t, 1H), 7.25 (m, 1H), 7.52 (m, 2H), 7.65–7.72 (m, 1H); MS *m/e* 410. Anal. ($C_{23}H_{23}FN_2O_4$) C, H, N.

**In Vitro Studies.** Receptor binding assays were performed according to previously reported procedures.[26,38]

**In Vivo Studies. Apomorphine-Induced Climbing in Mice.** This method is a modification of Protais et al.[39] and Costall et al.[40] Male CD-1 mice (18–30 g) were individually placed in wire-mesh stick cages (4 × 4 × 10 in.) and allowed 1 h for adaptation. Animals (8/dose group) received either distilled water or test drugs ip 30 or 60 min prior to apomorphine challenge (1.5 mg/kg sc). Animals were then observed for climbing behavior for 30 min. $ED_{50}$ values were calculated by linear regression analysis.

**Apomorphine-Induced Stereotypy in Rats.** The procedure is a modification of Janssen et al.[41] Male Wistar rats (150–250 g) were dosed ip with distilled water or test compounds (6–10/dose group). After 50 min, apomorphine (1.5 mg/kg sc) was administered and the rats were placed in individual opaque plastic cages (40 × 22 × 18 cm). After 10 min, the rats were observed for the presence of continuous stereotyped licking or sniffing behavior. The percent inhibition of a drug was determined by the number of animals protected in each group as compared to the control group. The $ED_{50}$ value for antagonism of stereotypy was calculated by means of probit analysis.

**Catalepsy in Rats.** The procedure is a modification of Costall and Naylor.[42] Male Wistar rats (150–250 g) were dosed ip with distilled water or test compounds (6–10/dose group). Every hour for 6 h after dosing, each rats' forepaws were placed on an elevated wooden bar mounted in an opaque plastic cage. If the forepaws remained on the bar for 60 s, the animal was considered to be cataleptic at that time.

**Pole Climbing Avoidance in Rats.** The procedure is similar to that described by Cook and Weidley.[43] Male Long Evans rats were trained in a discrete trial, signaled avoidance paradigm. A tone and light (CS) signaled the onset (4 s) of foot shock delivered through the grid floor of a test cage. A jump onto a steel pole suspended in the center of the test cage during the CS prevented the onset of shock, and an avoidance response was recorded. Pole climbing after the onset of shock terminated the shock, and an escape response was recorded. Rats failing to pole climb after the onset of shock could receive a maximum of 26 s of shock per trial. There were 25 trials per 50 min test session. Rats were trained to 80% avoidance prior to use. Distilled water or test compounds were administered ip to rats (6/dose group) at the pretreatment times listed in Table 4. Individual rat avoidance responses and escape failures were compared with those of the corresponding distilled water controls. $ED_{50}$ values were calculated by linear regression analysis.

**Intracranial Self-Stimulation in Rats.** Male Wistar rats (300–400 g) were stereotaxically implanted with chronic electrodes aimed at the medial forebrain bundle at the level of the preoptic nucleus as described by Ornstein.[44] Following a 2 week surgical recovery period, they were trained to lever press for a train of biphasic square wave pulses. Afater stable base line responding for electrical stimulation was established, drugs were administered ip (3–6/dose group) and compared to nondrug controls. $ED_{50}$ values were calculated by linear regression analysis by using percent change from controls.

**Social Interaction in Rats.** The procedure is a modification of that used by File[45] and Gardner and Guy.[46] Pairs of male Wistar rats (200–275 g) were placed in an arena (45 × 45 × 40 cm) and allowed to acclimate for 8 min on two consecutive days. On the third day, rats naive to one another were assigned to treatment groups, six pairs per treatment group, and the rats received test drug or vehicle. After 30 or 60 min, the appropriate rats were paired and placed in the test arena for observation of social interaction behavior (time spent sniffing partner, climbing over partner, following partner, mutual grooming, etc.) for 5 min. Social interaction time (in seconds) and total activity (counts/body length of movement) for the test groups were compared to those of the control, and statistical significance was determined by a one-way ANOVA and Duncan's multiple range test.

**Dopamine Neuron Sampling.** Male Wistar rats (280–360 g) were used in this procedure. They were housed for at least 48 h in a climate-controlled vivarium with food and water continuously available. Each rat was initially anesthetized with chloral hydrate (400 mg/kg ip) and maintained with additional injections as needed throughout the experiment. The animal was mounted in a stereotaxic apparatus (Kopf, model 900). The cranium was exposed, cleaned of connective tissue, and dried. The skull overlying both the substantia nigra [A9: anterior (A) 3000–3400 $\mu$m, lateral (L) 1800–2400 $\mu$m from lambda] and the ventral tegmental area (A10: A 3000–3400 $\mu$m, L 400–1000 $\mu$m from lambda][47] was removed. Using the dura as a point of reference, a micropipette driven by a hydraulic microdrive was lowered through the opening

in the skull at vertical 6000–8500 μm. Spontaneously firing dopamine neurons within both the substantia nigra and the ventral tegmental areas were counted by lowering the electrode into 12 separate tracks (each track separated from the other by 200 μm) in each region. The sequence of the tracks were kept constant, forming a block of tissue which could be reproducibly located from animal to animal.

Extracellular neuronal signals were sampled using a single barrel micropipette approximately 1 μm at its tip and filled with 2 M NaCl saturated with 1% pontamine sky blue dye. The in vitro impedance of this pipet (measured with a Winston Electronics Co. BL-1000 Micro Electrode Tester) was between 5 and 10 mΩ. Electrical potentials were passed through a high-impedance preamplifier, and the signal was sent to a window discriminator (WPI model 121) which converted potentials above background noise levels to discrete pulses of fixed amplitude and duration. Only cells whose electrophysiological characteristics matched those previously established for midbrain dopamine neurons were counted. In an anesthetized rat, a neuron was considered to be dopaminergic if it displayed a triphasic positive–negative–positive spike profile of 0.4–1.5 μV amplitude and 2.5 ms duration, firing in an irregular pattern of 3–9 Hz with occasional bursts characterized by progressively decreasing spike amplitude and increasing spike duration.

At the end of each experiment, the location of the last recorded track tip was marked by passing a 25 μA cathodal current through the recording micropipette barrel for 15 min in order to deposit a spot of dye. The rat was sacrificed; the brain was then removed, dissected, and frozen on a bed of dry ice. Frozen serial sections (20 μm in width) were cut, mounted, stained with cresyl violet, and examined using a light microscope.

Animals pretreated with vehicle prior to neuronal sampling served as controls. Compounds were prepared as percent base. Each compound was suspended in distilled water and 1 drop of Tween 80 and kept constantly agitated during dosing. All compounds were delivered at a dosage volume of 1 mg/kg by the intraperitoneal route. For animals used in the chronic single-unit dopamine neuron sampling assay, the compounds were administered once a day for 21 days and dopamine neuron sampling was begun 2 h after the last dose on the 21st day. Drug treatment groups were compared to vehicle groups with a one-way ANOVA with a post hoc Neuman–Keuls analysis for significance.

**Antagonism of L-5-Hydroxytryptophan-Induced Head Twitch Behavior.** Groups of eight male Wistar rats (180–280 g) were used in this test procedure. Sixty minutes prior to scoring head twitch behavior, L-5-hydroxytryptophan (5-HTP) was administered intraperitoneally (ip) at a dosage volume of 10 mg/kg. Thirty minutes following the injection, compounds were administered ip at a dosage volume of 10 mg/kg.

Suitable amounts of 5-HTP were prepared separately using 240 mg/10 mL of distilled $H_2O$ with the addition of 1 drop of Tween 80. Control groups were administered the appropriate vehicle. Sixty minutes post-5-HTP-administration, each animal was individually placed in a clear plastic cage and observed for the head twitch response in the presence of white noise. The number of head twitches per animal was recorded over a 10 min interval and the total summed for each group. The percent change from control for each group was then calculated. A dose response was tested in the same manner as a primary screen, except three to four dose groups and one vehicle group were tested. $ED_{50}$ and 95% confidence limits for active compounds were calculated by means of linear regression analysis.

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