Studies toward the Discovery of the Next Generation of Antidepressants. 3. Dual 5-HT$_{1A}$ and Serotonin Transporter Affinity within a Class of *N*-Aryloxyethylindolylalkylamines

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N-Aryloxylethylindolealkylamines (**5**) having dual 5-HT transporter and 5-HT$_{1A}$ affinity are described. These compounds represent truncated analogues of our previously reported piperidinyl derivatives (**3**). Compounds in this investigation were found to have more similar affinities and functional activities for the 5-HT$_{1A}$ receptor and 5-HT transporter. Though 5-HT$_{1A}$ antagonism is not consistently observed throughout series **5**, several molecular features were found to be essential to obtain high and balanced activities. The proper placement of a heteroatom in the aryl ring and the length of the linkage used to tether the indole moiety had significant influence on 5-HT$_{1A}$ and 5-HT transporter affinities. Introduction of a halogen into the aryl ring usually lowered intrinsic activity and in some cases led to full 5-HT$_{1A}$ antagonists. Compounds **33** and **34** were observed to be full 5-HT$_{1A}$ antagonists with K_i values of approximately 30 nM for the 5-HT$_{1A}$ receptor and K_i values of 5 and 0.5 nM for the 5-HT transporter, respectively. Unfortunately, similar to our previous series (**3**), compounds in this report also had high affinity for the α_1 receptor.

Over the past 50 years the psychopharmacology of depression[1,2] has evolved from medications discovered through serendipity to drugs rationally designed to target a single protein[3] (selective serotonin reuptake site inhibitors; SSRIs) or more recently to multiple sites associated with depression[4] (i.e., venlafaxine[5]). The monoamine theory, which postulates that depression arises as a result of reduced availability of serotonin (5-HT) and noradrenaline in the brain, has remained the prevailing basis for the design of new antidepressant drugs. First-generation antidepressants are associated with serious side effects and toxicity in overdose.[6] Though the second-generation antidepressant SSRIs are devoid of anticholinergic and cardiovascular side effects observed in their prototypes, they do not represent an improvement over older antidepressants in terms of broader efficacy or time to clinical efficacy (i.e., 2−6 weeks). The ability of SSRIs to increase serotonergic neurotransmission is believed to be an important component of their clinical antidepressant activity. However, therapeutic efficacy of SSRIs is thought to be compromised acutely by the stimulation of the somatodendritic 5-HT$_{1A}$ autoreceptors that inhibit 5-HT cell firing. Consequently reduction of the concentration of synaptic 5-HT occurs, and hence, suppression of the antidepressant effect is observed.[7,8] Nevertheless, upon sustained 5-HT reuptake site blockade antidepressant activity is manifested, presumably because of a desensitization of the somatodendritic 5-HT$_{1A}$ autoreceptors, allowing a progressive adaptation of serotonergic neurons to resume their normal firing.[9]

Strategies have been investigated by several groups that could potentially accelerate the antidepressant effect in current therapy.[10,11] Designing a 5-HT reuptake site inhibitor that can antagonize 5-HT$_{1A}$ autoreceptors should result in an advanced therapeutic action of the SSRI, allowing a more rapid onset of efficacy.[12] This accelerated effect was first observed in clinical trials performed by Artigas[13−16] and Blier[17,18] who reported that pindolol, the mixed 5-HT$_{1A}$/β-adrenoceptor antagonist, accelerates the antidepressant effects when coadministered with SSRIs. Numerous subsequent studies have been done since the observations of Artigas and Blier with mixed results, some showing either enhanced efficacy in refractory patients and/or faster onset of action or no difference from SSRIs alone.[19] Unfortunately pindolol is not the ideal agent because it must be given three times a day, is not a selective full 5-HT$_{1A}$ antagonist, and shows only minimal occupancy of 5-HT$_{1A}$ receptors in human PET studies.[20] For these reasons, final clinical confirmation of a desirable profile awaits the availability of optimized compounds with both properties. Further preclinical support of this hypothesis was later observed when the 5-HT$_{1A}$ antagonist WAY 100635 (**1**) was found to potentiate the antidepressant effects of several SSRIs[21,22] More recently, vilazodone (EMD 68843), having combined high affinity and selectivity for the 5-HT reuptake site transporter and 5-HT$_{1A}$ receptor (partial agonist), was found to increase extracellular 5-HT levels higher than those produced by conventional SSRIs.[23] It is possible that the 5-HT partial agonist component of vilazodone desensitizes the 5-HT$_{1A}$ autoreceptor's ability to inhibit 5-HT transmission. Therefore, incorporating both 5-HT$_{1A}$ antagonism and 5-HT reuptake site inhibition within a

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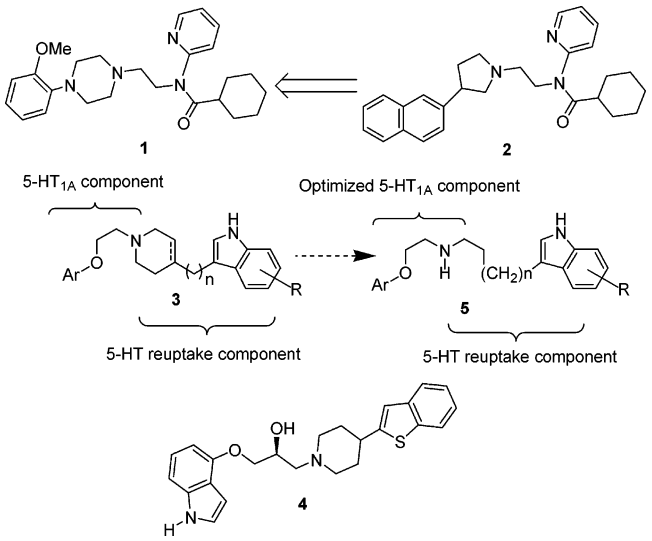


Figure 1. Design strategy.

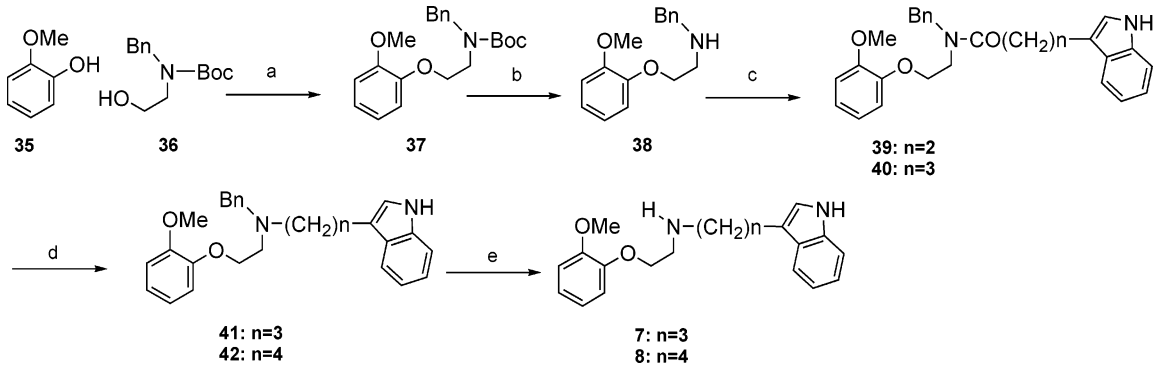
single molecule could lead to the next generation of antidepressant agents.

Recently several groups have reported their initial efforts and design strategies toward constructing hybrid 5-HT_{1A} antagonists and 5-HT reuptake site inhibitors.[24−29] Their general approaches were based on modifying the 3-aryloxy-2-propanol framework (i.e., pindolol-like derivatives) or the ubiquitous arylpiperzine moiety, commonly employed in the 5-HT_{1A} pharmacophore. Essentially this strategy entailed beginning with a 5-HT_{1A} ligand followed by the modification and incorporation of fragments reported to have 5-HT reuptake site activity through a common nitrogen. Initially, attempts at exploring this strategy mostly produced only new classes of 5-HT_{1A} derivatives with modest 5-HT reuptake site affinity at best. However, a series of arylcycloalkylamines where the side chain of WAY 100635 (**1**) was attached to a naphthylcyclopentylamine (i.e., **2**, Figure 1) represented one of the first compounds reported to have 5-HT reuptake site inhibition (IC_{50} = 20 nM) and 5-HT_{1A} antagonism (IC_{50} = 3 nM).[27] On the basis of our experience in both the 5-HT_{1A}[30,31] and 5-HT reuptake site areas,[32] we recognized that the 5-HT_{1A} pharmacophore[33−36] was well defined and that this activity could be achieved using a slightly different design strategy. Therefore, a modification of the above-mentioned design strategy has been to identify 5-HT reuptake site ligands with robust reuptake site activity, which could be modified with little or no loss of 5-HT reuptake site activity. In part 1,[37] we began with a less recognized series of indolylcyclohexylamines having 5-HT reuptake site activity that was systematically modified to understand how both 5-HT_{1A} and 5-HT reuptake site affinities were affected. In part 2,[38] we reported the discovery of a new class of molecules (**3**) having affinity for the 5-HT reuptake site and 5-HT_{1A} receptor. Surprisingly, 5-HT_{1A} antagonist activity was consistently observed within this series, though the structural features that influence 5-HT_{1A} antagonism were not understood. Again, our modified strategy was to identify a known class of robust 5-HT reuptake site inhibitors and subsequently append an appropriate side chain (e.g., the aryloxyethy group) toward fulfilling the 5-HT_{1A} receptor pharmacophore requirements.[33−36] Soon after our work was published, another class of aryloxylpropylpiperidines (**4**) was reported to have dual 5-HT_{1A} antagonism and SSRI activities.[28,29] By use of a common basic nitrogen, the 5-HT_{1A} and 5-HT reuptake site pharmacophore components were amalgamated. This generic strategy had been previously termed "the overlapping type approach".[24] Though the approach in part 2 led to a series of molecules having both 5-HT reuptake site inhibition and 5-HT_{1A} antagonism, one of the shortcomings was an unbalanced activity profile, whereby the series was more potent for the 5-HT reuptake site than for the 5-HT_{1A} receptor. From our previous findings[39] we observed that an aryloxyethy group was most effective as a 5-HT_{1A} pharmacophoric subunit when tethered by a secondary amine. With this knowledge, we hoped to optimize the 5-HT_{1A} pharmacophoric requirements by modifying series **3** into secondary amines by removing the piperidinyl moiety. In this report we will discuss the synthesis and structure−activity relationships (SAR) of a new series of aryloxyethylaminoindoles (**5**) with more similar affinity and functional activity at the 5-HT reuptake site and 5-HT_{1A} receptor.

Chemistry

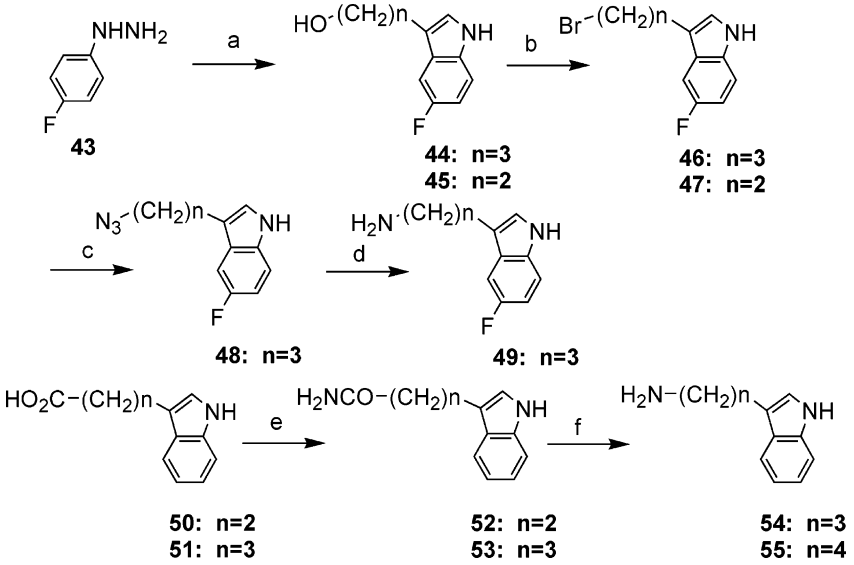
The synthesis of target molecules **6**−**34** is shown in Schemes 1−12. In Scheme 1 is shown the synthesis of compounds **7** and **8**. Briefly, phenol **35** was reacted with alcohol **36** using Mitsunobu conditions, followed by deprotection and coupling to the appropriate 3-indole alkanoic acid. Reduction with lithium aluminum hydride (LAH) followed by hydrogenolysis afforded the secondary amines **7** and **8**. The preparation of several requisite 3-indole alkyl side chain derivatives was carried out by initial Fisher indole chemistry followed by subsequent conversion of the alcohol to the amine moiety or by conversion of the appropriate carboxylic acid to the amine group as shown in Scheme 2. In Scheme 3 is shown the preparation of compounds **9**−**12**. The known fluorophenol **57** was converted to the chloroethoxy group, followed by treatment with sodium azide and reduction to give amine **61**. Coupling **59** and **61** to the appropriate 3-indole side chains afforded **10**−**12**. Shown in Scheme 4 is the synthesis of naphthalene **13** and quinolines **14** and **15**. Compounds **13** and **15** were prepared according to a similar strategy previously depicted in Scheme 3. However, quinoline **14** was prepared by attaching the hydroxyethyl group onto the 3-indole alkylamine **54**, followed by coupling to 8-hydroxyquinoline using Mitsunobu conditions. Target indoles **17**−**19** (Scheme 5) were prepared using a strategy similar to that depicted in Scheme 3. Benzimidazoles **20**−**22** were prepared starting from phenol **71** followed by coupling and chlorination to afford **73** as one product. Treatment of **72** and **73** with the appropriate 3-indolepropylamine followed by reduction led to diamines **77**−**79**. Heating with formic acid produced the corresponding benzimidazoles **20**−**22**. Intermediate **75** was protected and reduced to diamine **81** (Scheme 6), which was treated with glyoxal and deprotected to afford quinazoline **16**. Shown in Scheme 7 are the four- and five-step routes used to prepared benzofuran **23** and dihydrobenzofuran **24**, respectively. Briefly, commercially available **83** was decarboxylated, demethylated, and coupled to afford **86**. Hydrogenation to the dihydrobenzofuran **87**

Scheme 1[a]



[a] Reagents: (a) PPh_3, DIAD; (b) TFA; (c) 3-indolylalkanoic acid, DMAPC; (d) LAH; (e) H_2, Pd/C.

Scheme 2[a]



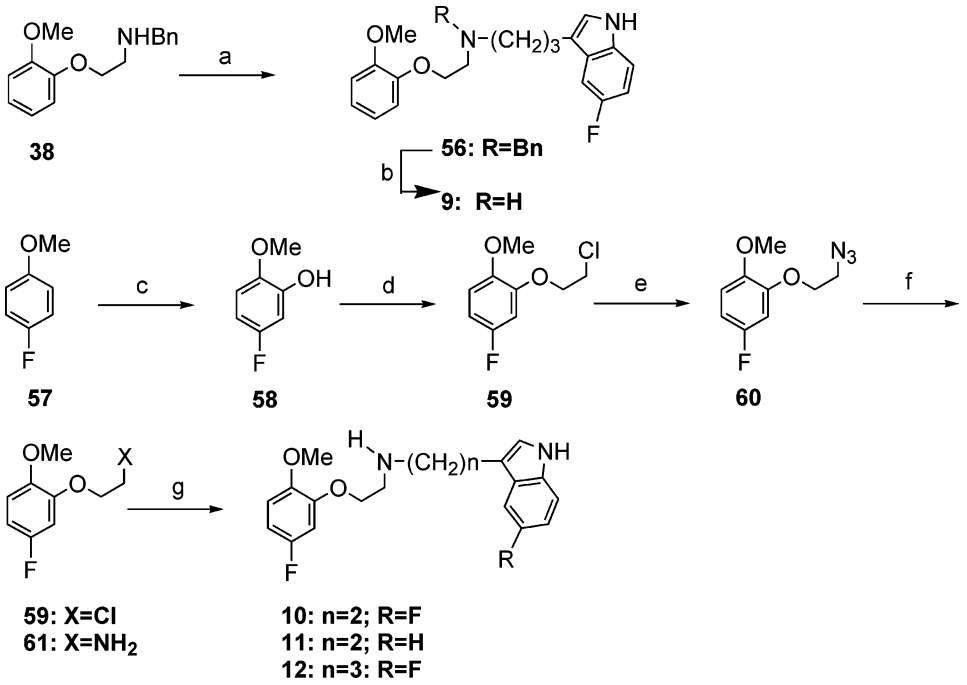
[a] Reagents: (a) reference 50; (b) CBr_4, PPh_3; (c) NaN_3; (d) H_2, Pd/C; (e) CDI, NH_3; (f) LAH.

followed by coupling of chloro derivatives **86** and **87** with 5-fluoro-3-indole-propyamine afforded the desired products **23** and **24**, respectively. The fluoro derivative **25** was prepared in seven steps beginning with commercially available **88** (Scheme 8). Methylation of **88** followed by the Bayer−Villiger reaction afforded **90**. Treatment of **90** with bromoacetaldehyde acetal and cyclization using PPA and demethylation produced 5-fluoro-7-hydroxybenzofuran (**93**), which was subsequently converted to the desired product **25**. Further hydrogenation of **25** produced **26**. Scheme 9 shows the synthesis for 5-fluorodihydrobenzofuran **27**. Beginning with commercially available **95**, a three-step sequence led to 5-fluorodihydrobenzofuran (**98**). Formylation followed by Bayer−Villiger reaction gave phenol **100** that was converted into **27** using chemistry described previously. Scheme 10 depicts the preparation of compounds **28**−**30** using a similar strategy as described previously in Scheme 3. 7-Fluorodihydrobenzodioxan **31** was prepared in seven steps (Scheme 11) from commercially available 5-fluoro-2-hydroxyacetophenone (**111**). Briefly, acetylation followed by Fries rearrangement provided **113**. Alkylation of **113** and the subsequent Bayer−Villiger reaction led to the diacetate **115**. Exposure of **115** to basic conditions resulted in cyclization to the 7-fluorodihydrodioxan **116**, which was further converted in two steps to **31**. 6-Fluorochromans **32**−**34** (Scheme 12) were prepared in either five or seven steps using similar strategy described beginning with commercially available 6-fluroro-4-chromanone (**118**).

Results and Discussion

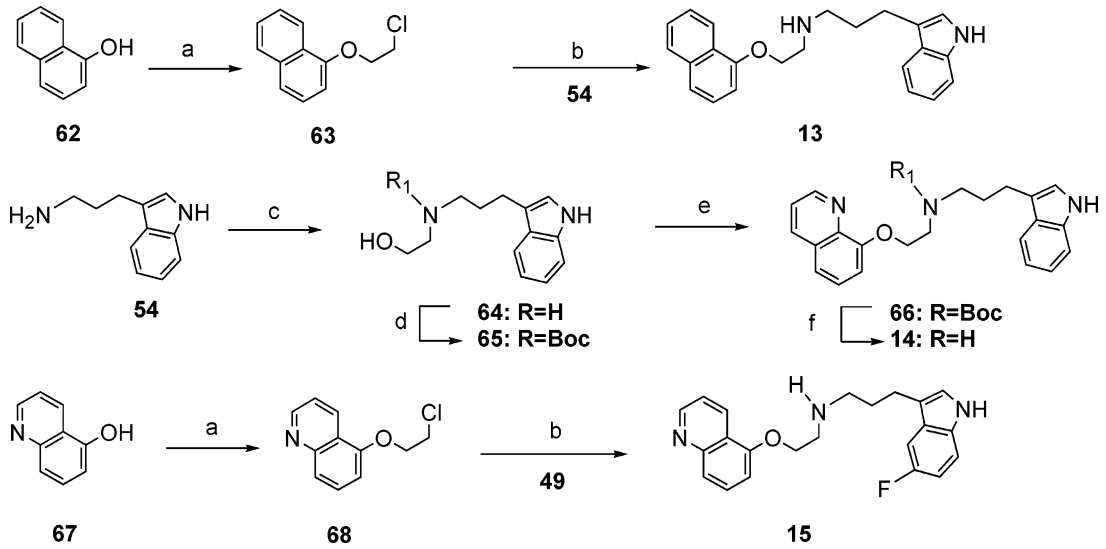
Compounds were evaluated in vitro to determine their affinity for the 5-HT transporter and 5-HT$_{1A}$ and α_1 receptors. A protocol similar to that for Cheetham et al.[40] was used to determine the affinity for the serotonin transporter employing [^{3}H]-paroxetine. Activity for the human 5-HT transporter was determined by incubating test compound with a human carcinoma cell line (JAR cells) previously treated with staurosporine to enhance the expression of endogenous 5-HT transporters and measuring specific [^{3}H]-HT uptake.[41] Affinity for human 5-HT$_{1A}$ receptors was determined by incubating Chinese hamster ovary (CHO) cells transfected with human 5-HT$_{1A}$ receptors with [^{3}H]-8-OH-DPAT and test compound.[42] Affinity for the α_1 receptor was determined by incubating rat cortical membranes with [^{3}H]-prazosin.[43] All K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[44] Antagonism at the 5-HT$_{1A}$ receptor was determined using a [^{35}S]-GTPγS binding assay similar to that of Larenzo[45] and a cAMP assay reported by Dunlop.[46] E_{max} refers to the maximum agonist effect observed. Since 5-HT$_{1A}$ antagonism is of interest in this study, IC_{50} values were calculated for

Scheme 3[a]



[a] Reagents: (a) **46**, DMSO, NEt_3; (b) Pd/C, H_2; (c) ref 51; (d) $Br(CH_2)Cl$, K_2CO_3, MEK; (e) NaN_3, DMF; (f) PPh_3, THF, H_2O; (g) 3-(bromoalkyl)indole, DMSO or 3-(aminoalkyl)indole, DMSO.

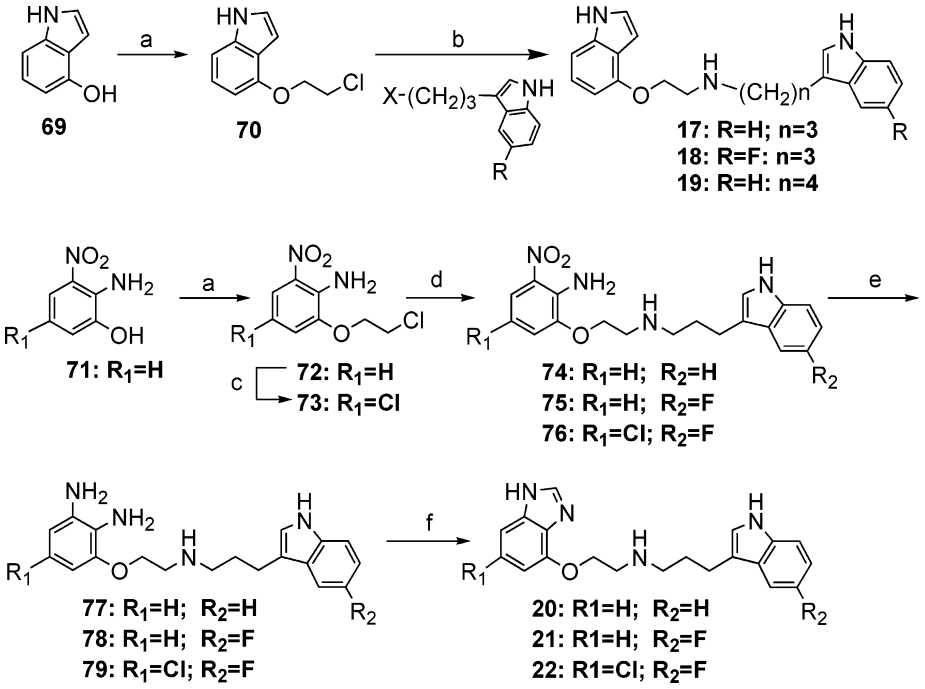
Scheme 4[a]



[a] Reagents: (a) PPh_3, DIAD, $Cl(CH_2)OH$; (b) Et_3N, DMSO; (c) $Cl(CH_2)OH$, DMSO; (d) $(Boc)_2O$; (e) 8-OH-quinoline, PhP_3, DIAD; (f) TFA, DCM.

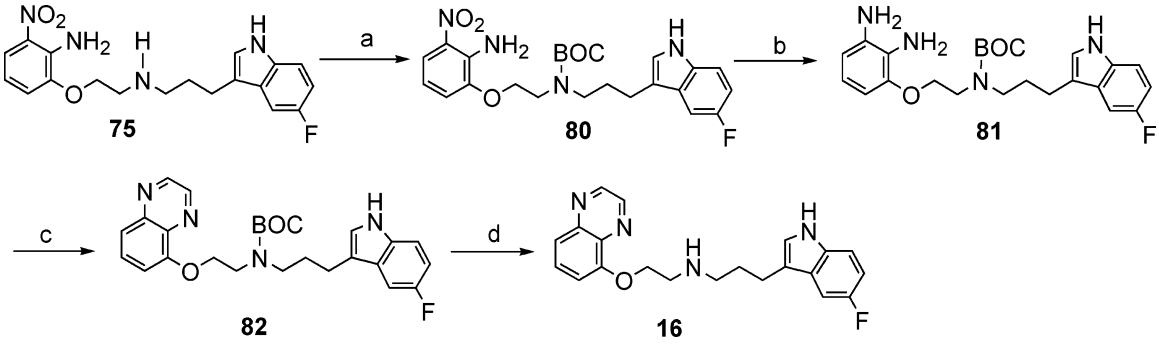
those compounds displaying significant antagonism. WAY 100635 (5-HT_{1A} antagonist) and fluoxetine (5-HT transporter inhibitor) are shown as reference standards in Table 1. Our objective in this investigation was to understand how to design and to identify molecules that had similar affinity and functional activity at both the 5-HT_{1A} receptor and 5-HT transporter site. Compounds with these properties demonstrated positive effects on rat cortical 5-HT levels and activity in various animal models such as the rat resident intruder model, the mouse four plate, and rat schedule-induced poldypsia (unpublished results). Paroxetine binding to 5-HT transporters in rat cortical membranes was performed to predict subsequent activity in rat microdialysis studies. Paroxetine binding in rat cortical membranes is very sensitive to SSRIs, and in-house results have shown that compounds with K_i values less than 10 nM are most likely to have significant activity in the functional human 5-HT transporter assay and to show effects in microdialysis. Since SSRIs can show different affinities at the rat versus human transporter,[47] determination of functional activity and potency at human 5-HT transporters was done to confirm activity at both rat and human 5-HT transporters. An indirect measure of in vivo 5-HT_{1A} antagonism, when combined with sufficient 5-HT transporter activity, is the ability to acutely increase rat cortical 5-HT levels. SSRIs alone have no immediate effect on 5-HT levels in the mediolateral prefrontal cortex in our labs.

Scheme 5[a]



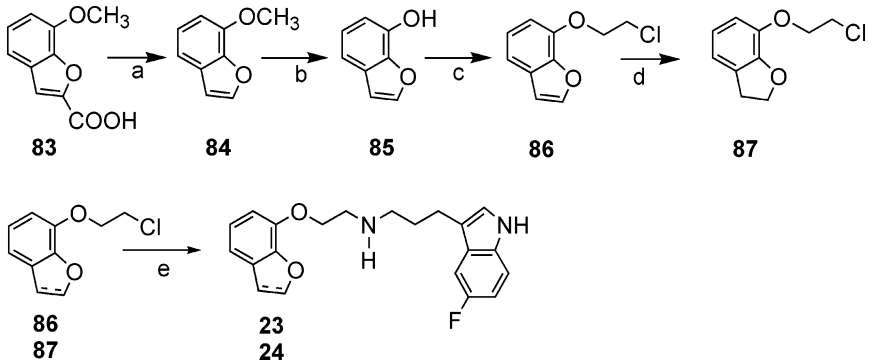
[a] Reagents: (a) $ClCH_2CH_2Cl$, K_2CO_3, MEK; (b) Et_3N, DMSO; (c) NCS, CH_3CN; (d) **49** or **54**, Et_3N, DMSO; (e) Pd/C, H_4N_2 or PtS_2, H_2; (f) HCO_2H.

Scheme 6[a]



[a] Reagents: (a) $(Boc)_2O$, THF; (b) Pd/C, H_2NNH_2; (c) glyoxal; (d) TFA, DCM.

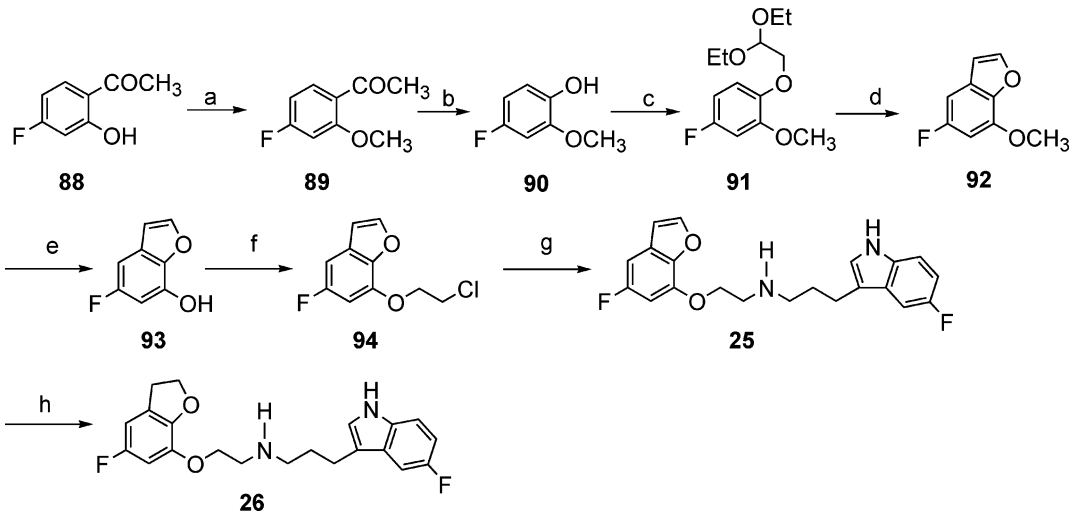
Scheme 7[a]



[a] Reagents: (a) Cu, quinoline; (b) BBr_3, DCM; (c) $ClCH_2CH_2OH$, PPh_3, DIAD; (d) H_2, Pd/C, AcOH; (e) Et_3N/DMSO, fluoroindolylpropylamine.

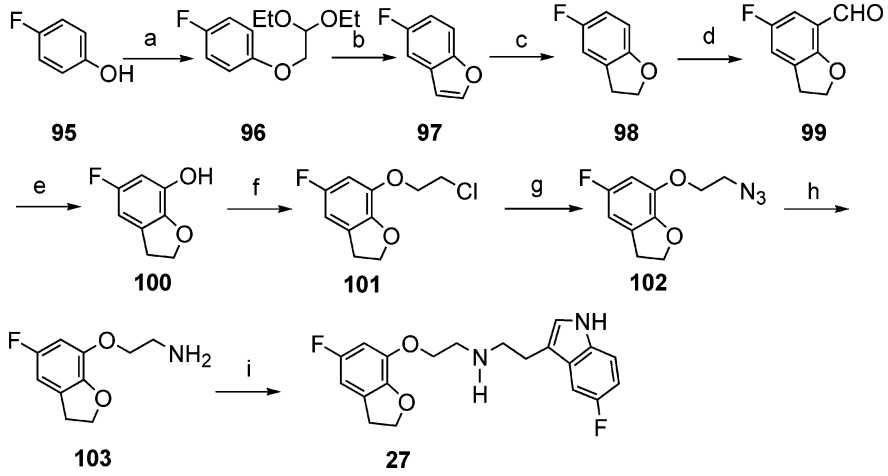
In contrast to our previous paper (part 2) where the tertiary amine and indole groups were embedded within a piperidinyl moiety, compounds in this study were all secondary amines attached to more flexible alkyl chains in order to increase the chances of binding to the 5-HT$_{1A}$ receptor. As shown in Table 1, comparing phenoxy analogues **6** and **9** revealed an increase in both affinity and function at the 5-HT transporter and 5-HT$_{1A}$ receptor by attaching the *o*-methoxy group. The 3-carbon tether (i.e., **7**) resulted in slightly higher 5-HT$_{1A}$ affinity when compared to the four-carbon tether (i.e., **7** vs **8**) or to the two-carbon tether (i.e., **10** vs **12**). Attaching the 5-fluoro substituent to the indole had little effect on affinity when tethered by a two-carbon

Scheme 8[a]



[a] Reagents: (a) MeI, K_2CO_3, DMSO; (b) (i) mCPBA, DCM, (ii) NaOH−EtOH−H_2O; (c) NaH, bromoacetaldehyde, DMF; (d) PPA, xylene; (e) BBr_3, DCM; (f) PPh_3, DIAD, $ClCH_2CH_2OH$, THF; (g) **49**, Et_3N, DMSO; (h) Pt_2O, H_2.

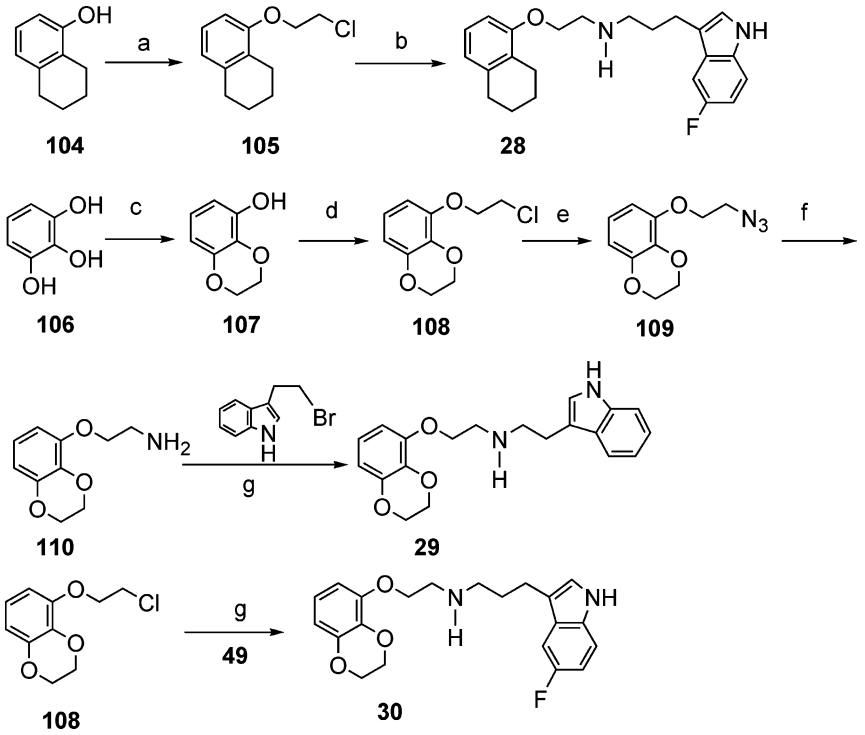
Scheme 9[a]



[a] Reagents: (a) $BrCH_2CH(OEt)_2$, NaH/DMF; (b) PPA; (c) Pd/C, H_2; (d) Cl_2CHOCH_3, $TiCl_4$; (e) mCPBA; (f) $BrCH_2CH_2Cl$, K_2CO_3, MEK; (g) NaN_3; (h) PPh_3, THF, H_2O; (i) 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide, Et_3N, DMSO.

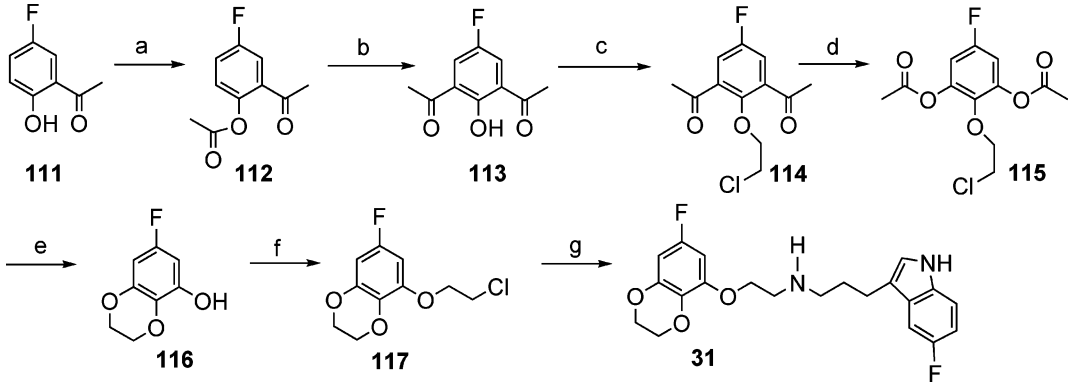
side chain (**10** vs **11**). However, the 5-fluoro-3-indolyl group led to a dramatic increase in 5-HT transporter affinity when attached to the three-carbon tether (**7** vs **9**). Compound **11** in Table 1 was observed to be a 5-HT_{1A} antagonist in the GTPγS binding assay with near-equal affinity and activity for the 5-HT transporter. Table 2 shows that the heteroaryl groups play a beneficial role in 5-HT transporter affinity when compared to the naphthenly group (**13** vs **14**−**16**). Having the aryl nitrogen atom adjacent to the oxyethyl linkage also increased affinity for the 5-HT_{1A} receptor (**13** vs **14**; **15** vs **16**). However, all compounds in Table 2 were observed to be 5-HT_{1A} partial agonists. Tetralin **13** and quinoline **15** were also noted to be the least potent members in this class for the α_1 receptor. Similar affinities were observed for indoles **17**−**19** and benzimidazoles **20**−**22** for the 5-HT transporter and 5-HT_{1A} receptor, in particular compounds **18** and **21** (Table 3). Interestingly, attaching the 6-chloro substituent to the benzimidazole (i.e., **22** vs **21**) resulted in a full 5-HT_{1A} antagonist as confirmed by both 5-HT_{1A} functional assays. A comparison of the benzofurans and dihydrobenzofurans in Table 4 shows similar affinities and functional activities at both the 5-HT reuptake site and 5-HT_{1A} receptor. The combination of the 5-fluoro substituent on the indole ring with the propyl tether again resulted in a significant improvement in 5-HT transporter affinity and function (**26** vs **27**). Dihydrobenzofuran **27** was observed to be a 5-HT_{1A} antagonist in the cAMP assay and a partial agonist in the GTPγS assay. Table 5 reveals that the benzodioxan and chroman moieties were also effective aryl groups that maintained good to excellent 5-HT transporter and 5-HT_{1A} affinities. A significant deterioration of both affinities was observed when there was no heteroatom in the aryloxy moiety (i.e., **28**). Again, tethering the indole moiety with a three-carbon spacer resulted in a marked improvement over the two-carbon spacer in both 5-HT transporter and 5-HT_{1A} affinities and function (**29** vs **30**). In fact, benzodioxan **30** was observed to be overall the most potent compound found in this investigation, though it was not a 5-HT_{1A} antagonist. However, benzodioxan **30** could be converted into a 5-HT_{1A} antagonist upon introduction of a fluorine atom into the 7 position of the benzodioxan ring, (i.e., **31**). Unfortunately, introduction of a halogen at this corresponding position led to a

Scheme 10[a]



[a] Reagents: (a) $BrCH_2CH_2Cl$, K_2CO_3, MEK; (b) **49**/NEt_3/DMSO; (c) $BrCH_2CH_2Br$, K_2CO_3, MEK; (d) PPh_3, DIAD, $ClCH_2CH_2OH$, THF; (e) NaN_3; (f) PPh_3, THF, H_2O; (g) Et_3N, DMSO.

Scheme 11[a]



[a] Reagents: (a) Ac_2O, H_2SO_4; (b) $AlCl_3$; (c) $ClCH_2CH_2Br$, K_2CO_3, MEK; (d) 30% H_2O_2, $(CF_3CO)_2O$, DCM; (e) NaOH, EtOH−H_2O; (f) $ClCH_2CH_2OH$, PPh_3, DIAD, THF; (g) **49**/NEt_3/DMSO.

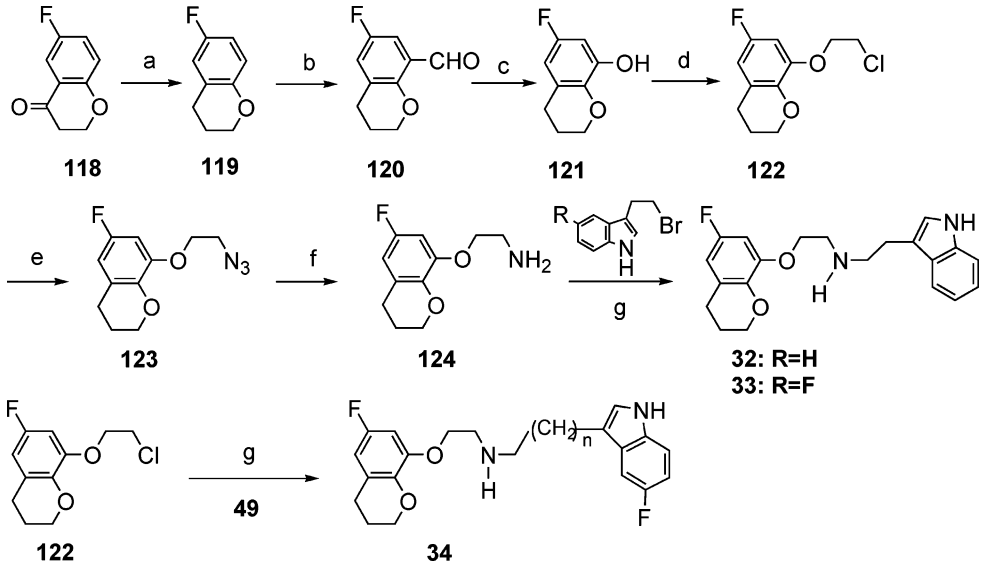
significant decrease in 5-HT$_{1A}$ affinity, which was a consistent trend observed in this class of molecules (e.g., **7** vs **12**; **21** vs **22**; **30** vs **31**). The 6-fluorochroman **34** was found to be a full 5-HT$_{1A}$ antagonist in both the cAMP and GTPγS assays. Attaching a halogen to this particular position of the chroman moiety had been previously reported by Yasunaga[48] and resulted in lowering 5-HT$_{1A}$ intrinsic activity in our study as well, although not always predictable. In contrast to series **3** in part 2, where nearly every compound was observed to have a higher affinity for α_1 receptors than 5-HT$_{1A}$ receptors, several of the aryloxyethylamine derivatives (i.e., **13**−**16**, **23**, and **30**) in this study had modest 5-HT$_{1A}$ selectivity (3- to 17-fold).

Conclusion

The compounds in this investigation demonstrated that similar affinity and functional activities for the 5-HT transporter and 5-HT$_{1A}$ receptor could be achieved within this series of *N*-aryloxyethylindolealkylamines (**5**). Modifying the original series of molecules (i.e., **3**), by incorporating the more flexible secondary amine moiety, enabled series **5** to achieve higher affinity for the 5-HT$_{1A}$ receptor. However, an increase in 5-HT$_{1A}$ affinity was observed at the loss of consistent of 5-HT$_{1A}$ antagonism, whereby the rigid piperidinyl moiety in series **3** was found to be playing a major role in achieving 5-HT$_{1A}$ antagonism. However, attaching a halogen substituent to the appropriate position of the aryl group of the 5-HT$_{1A}$ pharmacophoric component in series **5** can in some cases regain 5-HT$_{1A}$ antagonism.

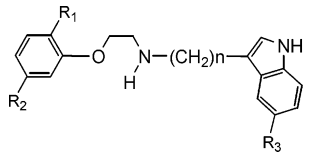
To optimize 5-HT transporter and 5-HT$_{1A}$ activities within this series of aryloxyethylamines (**5**), it was beneficial to have (1) at least one heteroatom in the aryloxy group (**6**, **13**, **28** were the least potent), where a heteroatom in the aryl group needs to be ortho to the

Scheme 12[a]



[a] Reagents: (a) Pd/C, H_2; (b) Cl_2CHOCH_3, $TiCl_4$; (c) mCPBA; (d) $Br(CH_2)_2Cl$, K_2CO_3, MEK; (e) NaN_3; (f) PPh_3, THF, H_2O; (g) NEt_3, DMSO.

Table 1. Phenoxethylamine Analogues[a]



					5-HT transporter		5-HT$_{1A}$ receptor			
compd	R_1	R_2	n	R_3	affinity K_i (nM)[b]	function IC_{50} (nM)[c]	affinity K_i (nM)[d]	GTPγS E_{max} (EC_{50} (nM))[e]	cAMP E_{max} (EC_{50} (nM))[f]	α_1 receptor K_i [g]
1					>10000	>4500	0.96 ± 0.22	0 (7.1 ± 2.1)	0 (7.1 ± 1.6)	89 ± 31 nM
fluoxetine					2.72 ± 0.34	32.4 ± 3.0	nd	nd	nd	605 nM
6	H	H	3	F	120	3790	9.2 ± 1.1	97.4 (84.3)	nd	3.4 nM
7	OMe	H	3	H	29.5 ± 5.3	nd	2.0 ± 0.1	79.6 ± 0.4 (13.0)	93.5 ± 0.4 (1.3)	27% (0.1 μM)
8	OMe	H	4	H	31.5 ± 4.6	nd	7.7 ± 1.4	60 (44)	nd	99% (0.1 μM)
9	OMe	H	3	F	0.48 ± 0.06	20.0 ± 0.6	1.3 ± 0.2	76.7 ± 0.2 (41.6)	97.0 ± 2.1 (4.3)	95% (0.1 μM)
10	OMe	F	2	F	23.5 ± 3.2	nd	91.4 ± 4.0	nd	nd	4.8 ± 1.1
11	OMe	F	2	H	43.0 ± 7.8	249	48.0 ± 7.4	3 (IC_{50} = 208)	141 ± 7.0	3.3
12	OMe	F	3	F	1.36 ± 0.27	20.5 ± 3.8	35.0 ± 0.2	28.5 (0.34)	98.5 ± 1.1 (4.7)	2.5

[a] K_i, IC_{50}, and EC_{50} values are the mean of at least two experiments ± SEM (performed in triplicate, determined from nine concentrations). Values without SEM are for a single determination only. Percentages represent inhibition of binding at the micromolar concentration shown in parentheses. nd: not determined. [b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]-paroxetine.[40] [c] Inhibition of [^{3}H]5-HT uptake by human 5-HT transporters in JAR cells.[41d] Binding affinity at human 5-HT$_{1A}$ receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[42] [e] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT$_{1A}$ receptors.[45] E_{max} refers to maximal agonist effect relative to 5-HT. [f] Maximal agonist effect (E_{max}) relative to 5-HT in inhibiting forskolin-stimulated adenylate cyclase activity.[46] [g] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]-prazosin.[43]

oxyethylamine linkage to be the most influential for 5-HT$_{1A}$ affinity, (2) a 5-fluoro-3-indolylpropyl group to increase 5-HT transporter affinity, and (3) a halogen meta to the oxyethylamine to lower 5-HT$_{1A}$ intrinsic activity.

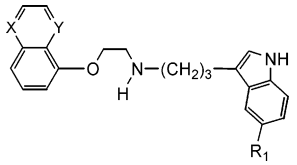
Though several molecules from this study showed modest 5-HT$_{1A}$ selectivity versus the α_1 receptor, one continual shortcoming observed in both series **3** and **5** was their ability to bind with high affinity to the α_1 receptor. Efforts are in progress to understand how to design molecules that selectively bind with similar affinities to the 5-HT reuptake site and 5-HT$_{1A}$ receptor using this dual pharmacophore design strategy.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400, Varian VXR-300, or Varian XL-200 instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6. Microanalyses were obtained on a Perkin-Elmer 2400 elemental analyzer. The mass spectra were determined on an LKB-9000S, Kratos MS 50, or Finnigan 8230 mass spectrometer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light and stained with either an alcohol solution of phosphomolybdic acid or in an iodine chamber. Where analyses in the tables are indicated by symbols of the elements, analytical results obtained for those elements were ±0.4% of the theoretical values. Solvents and reagents were used as purchased.

[2-(2-Methoxyphenoxyethyl]benzylcarbamic Acid *tert*-Butyl Ester (37).[49] To a solution of (2-hydroxyethyl)benzylcarbamic acid *tert*-butyl ester (3.2 g, 12.6 mmol) and 2-methoxyphenol (1.0 g, 8.4 mmol) containing triphenylphosphine (3.3

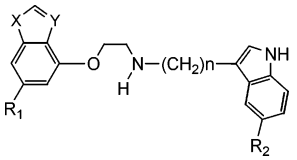
Table 2. Aryloxyethylamine Analogues[a]



				5-HT transporter		5-HT$_{1A}$ receptor			
compd	X	Y	R_1	affinity K_i (nM)[b]	function IC_{50} (nM)[c]	affinity K_i (nM)[d]	GTPγS E_{max} (EC_{50} (nM))[e]	cAMP E_{max} (EC_{50} (nM))[f]	α_1 receptor K_i (nM)[g]
13	C	C	H	123	2170	16.8 ± 1.5	71.9 (60.8)	nd	204
14	C	N	H	18.0 ± 4.2	nd	0.54 ± 0.04	76 (3.0)	nd	7.4
15	N	C	F	1.10 ± 0.02	73	35.5 ± 1.64	43 (35)	91.5 ± 1.8 (9.06)	122
16	N	N	F	1.20 ± 0.08	20	9.8 ± 0.2	55.0 (46)	95.5 ± 1.1 (13.7)	52

[a] K_i, IC_{50}, and EC_{50} values are the mean of at least two experiments ± SEM (performed in triplicate, determined from nine concentrations). Values without SEM are for a single determination only. Percentages represent inhibition of binding at the micromolar concentration shown in parentheses. nd: not determined. [b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]-paroxetine.[40] [c] Inhibition of [^{3}H]5-HT uptake by human 5-HT transporters in JAR cells.[41d] Binding affinity at human 5-HT$_{1A}$ receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[42] [e] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT$_{1A}$ receptors.[45] E_{max} refers to maximal agonist effect relative to 5-HT. [f] Maximal agonist effect (E_{max}) relative to 5-HT in inhibiting forskolin-stimulated adenylate cyclase activity.[46] [g] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]-prazosin.[43]

Table 3. Aryloxyethylamine Analogues[a]



						5-HT transporter		5-HT$_{1A}$ receptor			
compd	X	Y	R_1	*n*	R_2	affinity K_i (nM)[b]	function IC_{50} (nM)[c]	affinity K_i (nM)[d]	GTPγS E_{max} (EC_{50} (nM))[e]	cAMP E_{max} (EC_{50} (nM))[f]	α_1 receptor K_i [g]
17	NH	C	H	3	H	20.0 ± 4.2	154 ± 22	2.5 ± 0.2	66.0 (4.0)	nd	89% (0.1 μM)
18	NH	C	H	3	F	2.0 ± 1.0	24.4 ± 1.1	1.5 ± 0.1	90.0 (2)	nd	5.6 nM
19	NH	C	H	4	H	19.5 ± 1.1	862	4.2 ± 0.1	59.2 (25.8)	nd	nd
20	NH	N	H	3	H	15.5 ± 1.8	nd	0.87 ± 0.10	76.8 (1.6)	97 ± 1.4 (8.7)	nd
21	NH	N	H	3	F	0.39 ± 0.03	nd	0.69 ± 0.02	80.4 ± 2.9 (1.4)	87.0 ± 0.1 (7.2)	93% (0.1 μM)
22	NH	N	Cl	3	F	0.39 ± 0.6	4.5	10.7 ± 1.3	0.0 (IC_{50} = 66.5)	0.0 (IC_{50} = 238)	4.6 nM

[a] K_i, IC_{50}, and EC_{50} values are the mean of at least two experiments ± SEM (performed in triplicate, determined from nine concentrations). Values without SEM are for a single determination only. Percentages represent inhibition of binding at the micromolar concentration shown in parentheses. nd: not determined. [b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]-paroxetine.[40] [c] Inhibition of [^{3}H]5-HT uptake by human 5-HT transporters in JAR cells.[41d] Binding affinity at human 5-HT$_{1A}$ receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[42] [e] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT$_{1A}$ receptors.[45] E_{max} refers to maximal agonist effect relative to 5-HT. [f] Maximal agonist effect (E_{max}) relative to 5-HT in inhibiting forskolin-stimulated adenylate cyclase activity.[46] [g] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]-prazosin.[43]

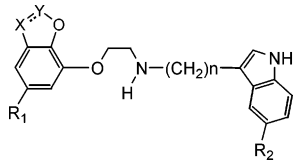
g, 12.6 mmol) in anhydrous THF (40 mL) was slowly added DIAD (2.5 g, 12.6 mmol). The reaction mixture was allowed to stir for 18 h and then was poured into CH_2Cl_2 (250 mL) and washed with 1 N NaOH (3 × 80 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to a clear oil. The oil was dissolved in ether (70 mL), and hexanes were slowly added until the triphenylphosphine oxide precipitated. The solid was filtered and the solvent was removed to afford a thick oil that was then purified by column chromatography (15% EtOAc−hexanes) to afford 2.57 g (57.0%) of a clear oil: MS (EI) 358 *m/e* (M^+); ^{1}H NMR ($CDCl_3$) δ1.46, 1.51 (rotamers, s, 9H), 3.54−3.63 (2H, m), 3.86 (3H, s), 4.10−4.19 (2H, m), 4.62 (2H, s), 6.85−6.94 (4H, m), 7.23−7.35 (5H, m). Anal. ($C_{21}H_{27}NO_4$) C, H, N.

[2-(2-Methoxyphenoxy)ethyl]benzylamine (38). To a solution of **37** (18.0 g, 50.4 mmol) in CH_2Cl_2 (350 mL) was slowly added trifluoroacetic acid (60 mL). The reaction mixture was stirred at room temperature for 12 h and then poured into 1 N NaOH (200 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with 1 N NaOH (2 × 150 mL) followed by water (2 × 100 mL), then dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2) afforded 12.4 g (96%) of a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.06 (t, J = 5.5 Hz, 2H), 3.84 (s, 3H), 3.88 (s, 2H), 4.15 (t, J = 5.52 Hz, 2H), 6.87−6.94 (m, 4H), 7.26−7.37 (m, 5H). Anal. ($C_{16}H_{19}NO_2$) C, H, N. The fumarate salt was prepared in ethanol: mp 121.5−122 °C. Anal. ($C_{16}H_{19}NO_2 \cdot C_4H_4O_4$) C, H, N.

***N*-Benzyl-3-(1*H*-indol-3-yl)-*N*-[2-(2-methoxyphenoxy)-ethyl]propionamide (39).** To a solution of 3-indole-propionic acid (4.1 g, 21.7 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (4.4 g, 23 mmol) in CH_2Cl_2 (80 mL) was added a solution of **38** (3 g, 11.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 2 h the reaction mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with 1 N NaOH (50 mL), followed by water (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2) provided 3.3 g (66.0%) of product as a white solid: mp 46.5−47.5 °C; MS EI *m/e* 428 (M^+).

***N*-Benzyl-3-(1*H*-indol-3-yl)-*N*-[2-(2-methoxyphenoxy)-ethyl]butyramide (40).** Replacing 3-(1*H*-indol-3-yl)propionic acid acid with 3-(1*H*-indol-3-yl)butyric acid (1.8 g, 8.9 mmol) as described in the previous experiment for the preparation of **39** afforded 1.3 g (78%) of the titled compound as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.85−1.97 (m, 2H), 2.63−2.74 (m, 2H), 3.58−3.61 (m, 2H), 3.72 (s, 3H), 4.00−4.07

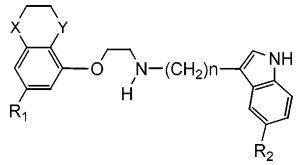
Table 4. Benzofuranoxyethylamine Analogues[a]



					5-HT transporter		5-HT$_{1A}$ receptor			
compd	X−Y	R_1	*n*	R_2	affinity K_i (nM)[b]	function IC_{50} (nM)[c]	affinity K_i (nM)[d]	GTPγS E_{max} (EC_{50} (nM))[e]	cAMP E_{max} (EC_{50} (nM))[f]	α_1 receptor K_i[g]
23	CH=CH	H	3	F	5.8 ± 1.4	28.1 ± 8.5	1.6 ± 0.1	99.9 (2.9)	nd	27.7 nM
24	CH_2CH_2	H	3	F	1.67 ± 0.66	9.7 ± 0.4	1.6 ± 0.04	80.0 ± 9.9 (4.7)	nd	74% (0.1 μM)
25	CH=CH	F	3	F	2.2	104 ± 7.3	12.9 ± 05	50 (IC_{50} = 107)	77.5 (56)	34.3 ± 2.4 nM
26	CH_2CH_2	F	2	F	10.5 ± 1.1	254 ± 56	35.1 ± 3.6	36 (IC_{50} = 138)	nd	85% (0.1 μM)
27	CH_2CH_2	F	3	F	1.17 ± 0.06	61.5	17.1 ± 1.3	34.5 ± 4.6 (nd)	0 (IC_{50} = 445)	9.2 nM

[a] K_i, IC_{50}, and EC_{50} values are the mean of at least two experiments ± SEM (performed in triplicate, determined from nine concentrations). Values without SEM are for a single determination only. Percentages represent inhibition of binding at the micromolar concentration shown in parentheses. nd: not determined. [b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]-paroxetine.[40] [c] Inhibition of [^{3}H]5-HT uptake by human 5-HT transporters in JAR cells.[41d] Binding affinity at human 5-HT$_{1A}$ receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[42] [e] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT$_{1A}$ receptors.[45] E_{max} refers to maximal agonist effect relative to 5-HT. [f] Maximal agonist effect (E_{max}) relative to 5-HT in inhibiting forskolin-stimulated adenylate cyclase activity.[46] [g] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]-prazosin.[43]

Table 5. Aryloxyethylamine Analogues[a]



						5-HT transporter		5-HT$_{1A}$ receptor			
compd	X	Y	*n*	R_1	R_2	affinity K_i (nM)[b]	function IC_{50} (nM)[c]	affinity K_i (nM)[d]	GTPγS E_{max} (EC_{50} (nM))[e]	cAMP E_{max} (EC_{50} (nM))[f]	α_1 receptor K_i (nM)[g]
28	CH_2	CH_2	3	H	F	33.5 ± 4.6	305 ± 20	170 ± 24	nd	nd	nd
29	O	O	2	H	F	13.5 ± 1.1	84.7 ± 24	5.8 ± 1.4	99.8	nd	80% (0.1 μM)
30	O	O	3	H′	F	0.08	6.3 ± 1.1	0.7 ± 0.2	75.4 (15.7)	90 (1.1)	9.6
31	O	O	3	F	F	0.49 ± 0.06	24.6 ± 12	22.4 ± 0.4	20 (IC_{50} = 156)	0 (IC_{50} = 198)	13.3
32	CH_2	O	2	F	H	6.8 ± 1.6	42.2 ± 2.2	8.5 ± 0.8	49 (36)	nd	4.4
33	CH_2	O	2	F	F	5.0 ± 0.4	86.4 ± 7.8	29.2 ± 1.1	0 (IC_{50} = 79)	0 (IC_{50} = 235)	11.9
34	CH_2	O	3	F	F	0.47 ± 0.3	7.0 ± 0.9	26.6 ± 6.5	0 (IC_{50} = 121)	0 (IC_{50} = 49)	79% (0.1 μM)

[a] K_i, IC_{50}, and EC_{50} values are the mean of at least two experiments ± SEM (performed in triplicate, determined from nine concentrations). Values without SEM are for a single determination only. Percentages represent inhibition of binding at the micromolar concentration shown in parentheses. nd: not determined. [b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]-paroxetine.[40] [c] Inhibition of [^{3}H]5-HT uptake by human 5-HT transporters in JAR cells.[41d] Binding affinity at human 5-HT$_{1A}$ receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[42] [e] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT$_{1A}$ receptors.[45] E_{max} refers to maximal agonist effect relative to 5-HT. [f] Maximal agonist effect (E_{max}) relative to 5-HT in inhibiting forskolin-stimulated adenylate cyclase activity.[46] [g] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]-prazosin.[43]

(m, 2H), 4.64−4.67 (m, 2H), 6.83−7.51 (m, 14H); MS FAB *m/e* 443 $(M + H)^+$; MS FAB *m/e* 465 $(M + Na)^+$.

Benzyl-[3-(1*H*-indol-3-yl)propyl]-[2-(2-methoxyphenoxy)ethyl]amine (41). To a solution of **39** in THF (50 mL) at room temperature was added $LiAlH_4$ (1.8 g). The reaction mixture was heated to reflux for 12 h and then allowed to cool to room temperature. The reaction was quenched with saturated ammonium chloride, and the solid precipitates were filtered through Celite. The solvent was concentrated under vacuum and the product was purified by chromatography (5% MeOH−CH_2Cl_2) to afford 2.0 g (86%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m 2H), 2.59 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.4 Hz, 2H), 2.79 (t, J = 6.2 Hz, 2H), 3.60 (s, 2H), 3.69 (s, 3H), 3.98 (t, J = 6.2 Hz, 2H), 6.81−7.06 (m, 7H), 7.21−7.46 (m, 7H), 10.7 (s, 1H), 10.7 (br, 1H); MS EI *m/e* 414 (M^+). Anal. ($C_{27}H_{30}N_2O$) C, H. N: calcd, 78.23; found, 77.53.

Benzyl-[4-(1*H*-indol-3-yl)butyl]-[2-(2-methoxyphenoxy)-ethyl]amine (42). *N*-Benzyl-3-(1*H*-indol-3-yl)-*N*-[2-(2-methoxyphenoxy)ethyl]butylamide (**40**) (1.2 g, 2.7 mmol) was reduced with $LiAlH_4$ as described above for **41** to afford 1.06 g (91%) of desired product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53 (m, 2H), 1.62 (m, 2H), 2.63 (t, J = 7.2 Hz, 2H), 3.63 (s, 3H), 3.70 (s, 3H), 3.98 (t, J = 6.2 Hz, 2H), 6.81−6.94 (m, 5H), 7.21−7.33 (m, 5H), 7.44 (d, J = 7.9 Hz, 2H), 10.69 (br, 1H); MS EI *m/e* 428 (M^+).

[3-(1*H*-Indol-3-yl)propyl]-[2-(2-methoxyphenoxy)ethyl]-amine (7). A mixture of **41** (2 g, 4.7 mmol) and 5% palladium on carbon in ethanol was hydrogenated for 20 h. The catalyst was filtered off, and the solvent was removed under vacuum. Chromatography (EtOAc−hexanes−MeOH−NH_4OH, 4:4:1:1) afforded 0.79 g (52%) of product as a white solid: mp 101−102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78 (m, 2H), 2.68 (m, 4H), 2.90 (t, J = 5.7 Hz, 2H), 3.73 (s, 3H), 4.00 (t, J = 5.7 Hz, 2H), 6.83−7.09 (m, 7H), 7.30 (m, 1H), 7.49 (m, 1H), 10.73 (s, 1H). The fumarate salt was prepared in ethanol: mp 130−130.5 °C. Anal. ($C_{20}H_{24}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25\ H_2O$) C, H, N.

[4-(1*H*-Indol-3-yl)butyl]-[2-(2-methoxyphenoxy)ethyl]-amine (8). Hydrogenation of **42** as described above for **7** afforded 0.79 g (100%) of product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68 (m, 4H), 2.48−2.49 (m, 2H), 3.03−3.07 (m, 2H), 3.28−3.30 (m, 2H), 3.74 (s, 3H), 4.18 (t, J = 5.1 Hz, 2H), 6.86−7.06 (m, 7H), 7.33 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 10.7 (br, 1H). The oxalate salt was prepared from 2-propanol: mp 167−168 °C. Anal. ($C_{21}H_{24}N_2O_2 \cdot C_4H_4O_4$) C, H, N.

2-(5-Fluoro-1*H*-indol-3-yl)ethanol (45). To a solution of 5-fluoroindol-3-acetic acid (4.3 g, 22 mmol) in anhydrous THF (35 mL) was added $LiAlH_4$ (1.0 M, 33 mL, 33 mmol) at 0 °C. The mixture was allowed to stir for 0.5 h, and then the reaction was quenched with a saturated NH_4Cl solution. The mixture was then filtered through Celite, and the filtrate was washed with 1 N NaOH (3 × 100 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2) afforded 4.04 g (100%) of product as an off-white solid: mp 59−61 °C. Anal. ($C_{10}H_{10}$FNO) C, H, N.

5-Fluoroindolyl-3-propyl Bromide (46). A solution of 3-(5-fluoro-1*H*-indol-3-yl)propan-1-ol (**44**)[50] (25.4 g, 0.13 mol), CBr_4 (65.5 g, 0.2 mol), and triphenylphosphine (52 g, 0.2 mol) in CH_2Cl_2 (156 mL) was allowed to stir for 2 h. The solvent was evaporated, and the product was chromatographed (30% EtOAc−hexanes) to afford 33.5 g (99%) of product: ^{1}H NMR (400 MHZ, DMSO-d_6) δ 2.07 (m, 2H), 2.76 (t, J = 6.8 Hz, 2H), 3.52 (t, J = 6.7 Hz, 2H), 6.88 (td, J = 9.2, 2.5 Hz, 1H), 7.22 (m, 1H), 7.27 (m, 1H), 7.31 (m, 1H), 10.9 (br, 1H).

3-(5-Fluoro-1*H*-indol-3-yl)ethyl Bromide (47). To a solution of **45** (4 g, 22.5 mmol) in CH_2Cl_2 (50 mL) at room temperature was added CBr_4 (11.2 g, 34 mmol) followed by triphenylphosphine (8.8 g, 33 mmol). The reaction mixture was allowed to stir for 2.5 h, and the solvent was removed under vacuum. Chromatography (30% EtOAc−hexanes) afforded 5.91 g (98%) of product as an off -white solid: mp: 58−59 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.2 (t, J = 7.4 Hz, 2H), 3.71 (t, J = 7.4 Hz, 2H), 6.89 (m, 1H), 7.31−7.34 (m, 3H), 11.0 (br, 1H). Anal. ($C_{10}H_9$FBrN) C, H, N.

5-Fluoroindolyl-3-propylazide (48). A solution of **46** (10.67 g, 41 mmol) and sodium azide (3.9 g, 60 mmol) in anhydrous DMF (60 mL) was allowed to stir at 60 °C for 18 h. The mixture was poured into water (150 mL), extracted with CH_2Cl_2 (3 × 150 mL), and washed with water (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (30% EtOAc−hexanes) afforded 8.1 g (89%) of product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.87 (m, 2H), 2.70 (t, 7.7 Hz, 2H), 3.35 (t, J = 6.8 Hz, 2H), 6.89 (td, J = 9.2, 2.6 Hz, 1H), 7.20 (m, 1H), 7.25 (dd, J = 10.1, 2.6 Hz, 1H), 7.31 (m, 1H), 10.8 (br, 1H). Anal. ($C_{11}H_{11}FN_3$) C, H, N.

5-Fluoroindolyl-3-propylamine (49). A solution of **48** (8 g, 37 mmol) and 10% palladium on carbon in ethanol was hydrogenated at 50 psi for 16 h. The catalyst was filtered, and the solvent was removed under vacuum. The Celite was washed with MeOH (300 mL), and the solvent was removed under vacuum. Chromatography (15% MeOH−CH_2Cl_2 plus NH_4OH) afforded 4.33 g (61%) of product as a yellow solid: mp 82−84.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.67 (m, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 3.25 (br, 2H), 6.86 (dd, J = 9.2, 2.4 Hz, 1H), 7.16 (m, 1H), 7.22 (dd, J = 10.1, 2.4 Hz, 1H), 7.29 (dd, J = 8.8, 4.6 Hz, 1H), 10.82 (br, 1H). Anal. ($C_{11}H_{13}FN_2$) C, H, N.

3-Indolylpropionamide (52). A solution of 3-(1*H*-indol-3-yl)propionic acid (15 g, 79 mmol) and 1,1′-carbonyldimidazole (16.7 g, 100 mmol) in anhydrous THF (150 mL) was allowed to stir for 1.5 h at room temperature. Then ammonia was bubbled through the solution for 2.5 h at room temperature. The solvent was removed under vacuum, and the residue was dissolved in EtOAc (500 mL). The organic solution was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. The white solid was collected and dried under vacuum to afford 10.4 g (96%): mp 124−125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (t, J = 8.0 Hz, 2H), 2.87 (t, J = 8.0 Hz, 2H), 6.72 (br, 1H), 6.92−6.96 (m, 1H), 7.01−7.06 (m, 2H), 7.29 (m, 2H), 7.49 (d, J = 8.0 Hz, 1H), 10.72 (br, 1H); HRMS (ESI) *m/e* 189.1015 (M + H$^+$), $C_{11}H_{12}N_2O$ requires 189.1022.

3-Indolylbutyramide (53). This compound was prepared in the manner described above for **52**, using 3-(1*H*-indol-3-yl)-butyric acid (**51**) and 1,1′-carbonyldimidazole to afford the title compound in 96% yield as an off-white solid: mp 86−87 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 2.08 (t, J = 7.3 Hz, 2H), 2.64 (t, J = 7.4 Hz, 2H), 6.68 (br, 1H), 6.93 (m, 1H), 7.00−7.07 (m, 2H), 7.22 (br, 1H), 7.29 (m, 1H), 7.47 (m 1H), 10.72 (br, 1H); HRMS (ESI) *m/e* 203.1172 (M + H$^+$), $C_{12}H_{14}N_2O$ requires 203.1179.

3-Indolylpropylamine (54). To a solution of **52** (5 g, 24.7 mmol) in THF anhydrous (150 mL) was slowly added $LiAlH_4$ (1.0 M solution in THF; 100 mL). The reaction mixture was heated to reflux for 3 h, then was quenched by adding water (4 mL), 15% NaOH (4 mL), and water (12 mL) at 0 °C. The mixture was filtered through Celite and concentrated under vacuum. Chromatography (10% MeOH−CH_2Cl_2 plus NH_4OH) afforded 4.0 g (86%) of product as a white solid: mp 58−60.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.66−1.78 (m, 2H), 2.58 (t, J = 8.0 Hz, 2H), 2.67 (t, J = 8.0 Hz, 2H), 6.91−7.02 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 10.77 (br, 1H); HRMS (ESI) *m/e* 175.1226 (M + H$^+$), $C_{11}H_{14}N_2$ requires 175.1230.

3-Indolylbutylamine (55). This compound was prepared in the manner described above for **54** using **53** and $LiAlH_4$ to afford the title compound in 75% yield as a yellow solid: mp 51−53 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38−1.44 (m, 2H), 1.59−1.66 (m, 2H), 2.55 (t, J = 8 Hz, 2H), 2.64 (t, J = 8 Hz, 2H), 6.93 (m, 1H), 7.0−7.06 (m, 2H), 7.29 (d, J = 8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 10.71 (br, 1H).

[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-[2-(2-methoxyphenoxy)ethyl]benzylamine (56). A solution of **38** (1.0 g, 3.9 mmol), **46** (1.4 g, 5.8 mmol), and triethylamine (0.79 g, 7.8 mmol) in anhydrous DMSO (40 mL) was allowed to stir for 16 h at 100 °C. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 100 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (30% EtOAc−hexanes) afforded 940 mg (58%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 2H), 2.66 (t, J = 7.3 Hz, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.95 (t, J = 6.6 Hz, 2H), 4.06 (t, J = 6.6 Hz, 2H), 6.77 (m, 1H), 6.83−6.95 (m, 5H), 7.19−7.32 (m, 5H), 7.36−7.38 (m, 2H), 7.87 (br, 1H). HRMS (ESI) *m/e* 433.2271 (M + H$^+$), $C_{27}H_{29}FN_2O_2$ requires 433.2286.

[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-[2-(2-methoxyphenoxy)ethyl]amine (9). A mixture of **56** (0.94 g, 2.2 mol) and 10% palladium on carbon (250 mg) in ethanol was hydrogenated for 20 h. The catalyst was filtered off, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2) afforded 0.63 g (85%) of product as an off-white solid: mp 125−126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (m, 2H), 2.62 (t, J = 7.0 Hz, 2H), 3.67 (t, J = 7.5 Hz, 2H), 2.86 (t, J = 7.5 Hz, 2H), 3.73 (m, 3H), 3.98 (t, J = 5.7 Hz, 2H), 6.83−6.90 (m, 3H), 6.93−6.96 (m, 2H), 7.17−7.18 (m, 1H), 7.23 (dd, J = 10.1, 2.6 Hz, 1H), 7.31 (dd, J = 8.8, 4.6 Hz, 1H), 10.86 (br, 1H). The oxalate salt was prepared in 2-propanol: mp 146−149 °C. Anal. ($C_{20}H_{23}FN_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

2-(5-Fluoro-2-methoxyphenoxy)ethyl Chloride (59). A solution of **58**[51] (4.34 g, 31 mmol), 1-bromo-2-chloroethane (8.9 mL, 107 mmol), and K_2CO_4 (14.8 g, 106 mmol) in 2-butanone (60 mL) was allowed to reflux for 24 h. The mixture was poured into water (150 mL), extracted with CH_2Cl_2 (3 × 150 mL), and washed with brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 4.77 g (76%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (t, J = 6.2 Hz, 2H), 3.84 (s, 3H), 4.25 (t, J = 6.2 Hz, 2H), 6.62−6.69 (m, 2H), 6.82−6.84 (m, 1H). Anal. ($C_9H_{10}FClO_2$) C, H, N.

2-(5-Fluoro-2-methoxyphenoxy)ethylazide (60). A solution of **59** (3.97 g, 19 mmol) and sodium azide (2.6 g, 39 mmol) in anhydrous DMF (60 mL) was allowed to stir at 60 °C for 18 h. The mixture was poured into water (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was washed with water (3 × 100 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 3.75 g (92%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (t, J = 5.2 Hz, 2H),

3.83 (s, 3H), 4.15 (t, J = 5.1 Hz, 2H), 6.62−6.68 (m, 2H), 6.8−6.84 (m, 1H). Anal. ($C_9H_{10}FN_3O_2$) C, H, N.

2-(5-Fluoro-2-methoxyphenoxy)ethylamine (61). A solution of **60** (3.97 g, 19 mmol) and triphenylphosphine (5.95 g, 23 mmol) in THF (80 mL) and water (1.5 mL) was allowed to stir for 18 h at room temperature. The solvent was removed under vacuum, and the product was purified by chromatography (EtOAc) to remove excess triphenylphosphine and triphenylphosphine oxide and (25−50% MeOH−EtOAc plus NH_4OH) afforded 3.14 g (90%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (t, J = 5.2 Hz, 2H), 3.83 (s, 3H), 4.00 (t, J = 5.2 Hz, 2H), 6.58−6.62 (m, 1H), 6.65 (dd, J = 10.1, 3.1 Hz, 1H), 6.78 (dd, J = 9.0, 5.5 Hz, 1H). HRMS (ESI) m/z 186.0922 (M + H^+), $C_9H_{12}FNO_2$ requires 186.0925.

[2-(5-Fluoro-1*H*-indol-3-yl)ethyl]-[2-(5-fluoro-2-methoxyphenoxy)ethyl]amine (10). A solution of **61** (0.51 g, 2.8 mmol), 2-(5-fluoro-1*H*-indol-3-yl)ethyl chloride (0.44 g, 1.8 mmol), and triethylamine (0.29 g, 3 mmol) in DMSO (20 mL) was allowed to stir for 8 h at 90 °C. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2) afforded 0.27 g (43%) of product as a brown oil. The oxalate salt was prepared in ethanol: mp 185−188 °C. Anal. ($C_{19}H_{20}F_2N_2O_2\cdot C_2H_2O_4$) C, H, N.

[2-(5-Fluoro-1*H*-indol-3-yl)ethyl]-[2-(5-fluoro-2-methoxyphenoxy)ethyl]amine (11). A solution of **61** (0.41 g, 2.2 mmol) and 3-(2-bromoethyl)indole (0.25 g, 1.1 mmol) in DMSO (20 mL) was allowed to stir for 12 h at 90 °C. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2) afforded 0.15 g (34%) of product as a brown oil: ^{1} H NMR (400 MHz, DMSO-d_6) δ 2.70 (m, 4H), 2.91 (t, J = 5.7 Hz, 2H), 3.67 (s, 3H), 4.01 (t, J = 5.7 Hz, 2H), 6.66 (m, 1H), 6.90−6.96 (m, 3H), 7.31 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 10.77 (br, 1H). The oxalate salt was prepared in ethanol: mp 188−189 °C. Anal. ($C_{19}H_{21}FN_2O_2\cdot C_2H_2O_4\cdot 0.25H_2O$) C, H, N.

[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-[2-(5-fluoro-2-methoxyphenoxy)ethyl]amine (12). A solution of **59** (0.3 g, 1.5 mmol) and 3-(5-fluoro-1*H*-indol-3-yl)propylamine (0.56 g, 2.9 mmol) in DMSO (20 mL) was allowed to stir for 12 h at 90 °C. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2) afforded 0.39 g (77%) of product as a white solid: mp 119−122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (m, 2H), 2.66−2.73 (m, 4H), 2.97 (t, J = 5.5 Hz, 2H), 3.71 (s, 3H), 4.05 (t, J = 5.7 Hz, 2H), 6.67−6.72 (m, 1H), 6.85−6.95 (m, 3H), 7.18−7.31 (m, 3H), 10.86 (br, 1H). The oxalate salt was prepared in ethanol: mp 175−177 °C. Anal. ($C_{20}H_{22}F_2N_2O_2\cdot C_2H_2O_4$) C, H, N.

2-(Naphthalen-1-yloxy)ethyl Chloride (63). To a solution of 1-naphthol (5 g, 35 mmol), triphenylphosphine (13.6 g, 52 mmol), and 2-chloroethanol (4.2 g, 5.2 mmol) in THF (50 mL) was slowly added DIAD (10.5 g, 52 mmol). The reaction mixture was stirred at room temperature for 2 h. THF was removed under vacuum, and chromatography (25% EtOAc−hexanes) afforded 6.34 g (82%) of product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (m, 2H), 2.66−2.73 (m, 4H), 2.97 (t, J = 5.5 Hz, 2H), 3.71 (s, 3H), 4.05 (t, J = 5.7 Hz, 2H), 6.67−6.72 (m, 1H), 6.85−6.95 (m, 3H), 7.18−7.31 (m, 3H), 10.86 (br, 1H). Anal. ($C_{12}H_{11}ClO$) C, H, N.

[3-(1*H*-indol-3-yl)propyl]-[2-(naphthalen-1-yloxy)ethyl]amine (13). This compound was prepared in the manner described above for **12** by reacting 2-(naphthalen-1-yloxy)ethyl chloride (0.6 g, 2.8 mmol) with 3-(1*H*-indol-3-yl)propylamine (1.35 g, 7.2 mmol) to afford the title compound in 85% yield (1.42 g) as a yellow solid: mp 119−120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (m,2H), 2.1 (br s, 1H), 2.68−2.74 (m, 4H), 3.02 (t, J = 5.5 Hz, 2H), 5.48 (t, J = 5.5 Hz, 2H), 6.91−6.96 (m, 2H), 7.01−7.05 (m, 1H), 7.08 (d, J = 2.2 Hz, 1H), 7.29−7.52 (m, 6H), 7.83−7.86 (m, 1H), 8.18−8.21 (m, 1H), 10.72 (br s, 1H). The fumarate salt was prepared in ethanol: mp 203−205 °C. Anal. ($C_{23}H_{24}N_2O\cdot 0.5C_4H_4O_4\cdot 0.25H_2O$) C, H, N.

[3-(1*H*-Indol-3-yl)propyl]-(2-hydroxyethyl)amine (64). A solution of 3-(1*H*-indol-3-yl)propylamine (3.5 g, 18.6 mmol) and 2-chloroethanol (1 g, 12.4 mmol) in anhydrous DMSO (20 mL) was allowed to stir at 80 °C for 12 h. The mixture was poured into water (100 mL), extracted with CH_2Cl_2 (3 × 150 mL), and washed with water (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (15% MeOH−CH_2Cl_2) afforded 1.04 g (38%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 2H), 2.57−2.61 (m, 4H), 2.69 (t, J = 7.4 Hz, 2H), 3.48 (t, J = 5.3 Hz, 2H), 6.86−7.00 (m 3H), 7.25 (dd, J = 7.8, 0.9 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 10.44 (br s, 1H). HRMS (ESI) m/e 219.1487 (M + H^+), $C_{13}H_{18}N_2O$ requires 219.1492.

(2-Hydroxyethyl)-[3-(1*H*-indol-3-yl)propyl]carbamic Acid-*tert*-Butyl Ester (65). A solution of **64** (1.05 g, 4.5 mmol), di-*tert*-dicarbonate (5 g, 24 mmol) in anhydrous THF (20 mL) was heated at 80 °C for 2 h. The mixture was poured into water (100 mL), extracted with CH_2Cl_2 (3 × 150 mL), and washed with water (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2) afforded 0.86 g (56%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30−1.37 (m, 9H), 1.83 (m, 2H), 2.62 (t, J = 5.7 Hz, 2H), 3.18−3.25 (m, 4H), 3.42−3.44 (m, 2H), 4.62 (br s, 1H), 6.94 (tm, J = 8.1 Hz, 1H), 7.04 (tm, J = 6.1 Hz, 1H), 7.11 (br s, 1H), 7.30 (d, J = 6.1 Hz, 1H), 7.45 (d, J = 5.7 Hz, 1H), 10.73 (br s, 1H); HRMS (ESI) m/e 319.2015 (M + H^+), $C_{18}H_{26}N_3O_3$ requires 319.2016.

[3-(1*H*-Indol-3-yl)propyl]-[2-(quinolin-8-yloxy)ethyl]-amine (14). To a solution of **65** (0.86 g, 2.7 mmol), triphenylphosphine (0.71 g, 2.7 mmol), and 8-hydroxyquinoline (0.26 g, 2.7 mmol) in THF (50 mL) was slowly added DIAD (0.55 g, 2.7 mmol), and the reaction was stirred at room temperature for 3 h. THF was removed under vacuum, and chromatography (5% MeOH−CH_2Cl_2) afforded a yellow solid that was dissolved in CH_2Cl_2 (30 mL). To this solution was added a trifluoroacetic acid solution (4 mL in 10 mL of CH_2Cl_2). The reaction mixture was allowed to stir for 2 h at room temperature. The mixture was then quenched with saturated Na_2CO_4 and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum, and purification by chromatography (10−15% MeOH−CH_2Cl_2 plus NH_4OH) afforded 170 mg (18%) of product as a light-yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (m, 3H), 2.62−2.73 (m, 4H), 2.99−3.01 (m, 2H), 4.22 (t, J = 4.3 Hz, 2H), 6.90 (t, J = 5.25 Hz, 1H), 7.03 (t, J = 5.27 Hz, 1H), 7.1 (m, 1H), 7.19−7.22 (m, 1H), 7.30 (d, J = 6.12 Hz, 1H), 7.48−7.54 (m, 4H), 8.29 (dd, J = 6.27, 1.32 Hz, 1H), 8.84 (dd, J = 3.15, 1.32 Hz, 1H), 10.72 (br, 1H). The HCl salt was prepared in EtOAc: mp 83−86 °C. Anal. ($C_{22}H_{23}N_3O\cdot HCl\cdot 1.25H_2O$) C, H, N.

5-(2-Chloroethyoxy)quinoline (68). To a solution of 5-hydroxyquinoline (1.0 g, 6.9 mmol), 2-chloroethanol (0.92 mL, 13.8 mmol), and triphenylphosphine (3.6 g, 13.8 mmol) in anhydrous THF (40 mL) was slowly added DIAD (2.7 mL, 13.8 mmol). The reaction mixture was allowed to stir overnight at room temperature, and the solvent was removed under vacuum. Purification by chromatography (50% hexanes−EtOAc) afforded 1.37 g (89%) of product as a white solid: mp 69.5−72 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.09 (t, J = 5.0 Hz, 2H), 4.67 (t, J = 5.0 Hz, 2H), 7.09 (d, J = 7.4 Hz, 1H), 7.52 (dd, J = 8.6, 4.2 Hz, 1H), 7.59−7.68 (m, 2H), 8.52−8.55 (m, 1H), 8.89−8.9 (m, 1H). HRMS (ESI) m/e 208.0519 (M + H^+), $C_{11}H_{10}ClNO$ requires 208.0524.

[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-[2-(quinolin-5-yloxy)-ethyl]amine (15). A solution of **68** (0.5 g, 2.23 mmol) and 3-(5-fluoro-1*H*-indol-3-yl)propylamine (0.65 g, 3.3 mmol) in DMSO (20 mL) was allowed to stir for 12 h at 90 °C. The reaction

mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (7% MeOH−CH_2Cl_2) afforded 0.3 g (34%) of product as a yellow oil. The oxalate salt was prepared in ethanol: mp 244−246 °C; ^{1}H NMR (400 MHz, DMSO- d_6) δ 2.0 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 3.50 (t, J = 4.4 Hz, 2H), 3.55 (m, 2H), 4.41 (t, J = 4.6 Hz, 2H), 6.89 (m, 1H), 7.07 (d, J = 7.2 Hz, 1H), 7.23 (m, 1H), 7.28−7.34 (m, 2H), 7.50 (dd, J = 8.6, 4.2 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 8.4 Hz, 1H), 8.70−8.78 (m, 1H), 8.88−8.93 (m, 1H), 10.95 (br s, 1H). Anal. ($C_{22}H_{22}FN_3O\cdot C_2H_2O_4\cdot H_2O$) C, H, N.

2-(1*H*-Indol-4-yloxy)ethyl Chloride (70). To a solution of 4-hydroxyindole (4.0 g, 30 mmol), 2-chloroethanol (6.03 mL, 90 mmol), and triphenylphosphine (23.6 g, 90 mmol) in THF (90 mL) was added DEAD (14.1 mL, 90 mmol) under nitrogen at room temperature. After the reaction mixture was stirred for 2 h at room temperature, the solvent was removed under vacuum. To the cooled residue was added Et_2O, the precipitated triphenylphosphine oxide was filtered, and the filtrate was concentrated. The crude product was purified by chromatography (silica gel, EtOAc−hexanes, 1.5:8.5) to give an oil, which was triturated with Et_2O−hexanes (1:10) to afford 4.8 g of the title compound (82%) as a white solid: mp 60 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.99 (t, J = 5.1 Hz, 2H), 4.34 (t, J = 5.1 Hz, 2H), 6.42−6.43 (m, 1H), 6.49 (d, J = 7.5 Hz, 1H), 6.95−7.03 (m, 2H), 7.21 (t, J = 2.6, 1H), 11.08 (s, 1H); MS (+) APCI m/e 196 (M + H)$^+$.

[3-(1*H*-Indol-3-yl)-propyl]-[2-(1*H*-indol-4-yloxy)ethyl]-amine (17). A solution of **70** (0.7 g, 3.6 mmol), 5-fluoroindolyl-3-propylamine (1.0 g, 5.4 mmol) in DMSO (20 mL) was allowed to stir for 12 h at 90 °C. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (5−10% MeOH−CH_2Cl_2) afforded 0.54 g (43%) of product as a white solid: mp 70−73 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (m, 2H), 2.48−2.74 (m, 4H), 2.95 (t, J = 5.7 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 6.41−6.43 (m, 1H), 6.46 (dd, J = 6.6, 2.2 Hz, 1H), 6.92−6.99 (m, 3H), 7.01−7.05 (m, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.30−7.32 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 10.7 (br, 1H), 11.0 (br, 1H). The oxalate salt was prepared in ethanol: mp 183.5−185 °C. Anal. ($C_{21}H_{23}N_3O\cdot C_2H_2O_4$) C, H, N.

[2-(1*H*-Indol-4-yloxy)ethyl]-[3-(5-fiuoro-1*H*-indol-3-yl)-propyl]amine (18). This compound was prepared in the manner described above for compound **17** using 2-(1*H*-indol-4-yloxy)ethyl chloride and 3-(5-fluoro-1*H*-indolyl)propylamine to afford the title compound in 43% yield as a white solid: mp 70−73 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 1.79 (m, 2H), 2.67−2.70 (m, 4H), 2.97 (t, J = 5.72 Hz, 2H), 4.12 (t, J = 5.72 Hz, 2H), 6.41−6.42 (m, 1H), 6.46 (dd, J = 6.6, 1.96 Hz, 1H), 6.87 (td, J = 9.0, 2.64 Hz, 1H), 6.93−6.99 (m, 2H), 7.16−7.18 (m, 2H), 7.24 (dd, J = 9.3, 2.64 Hz, 1H), 7.29 (dd, J = 9.0, 4.6 Hz, 1H), 10.8 (br, 1H), 11.0 (br s, 1H). The oxalate salt was prepared in 2-propanol: mp 183.5−185 °C. Anal. ($C_{21}H_{22}FN_3O\cdot C_2H_2O_4$) C, H, N.

[3-(1*H*-Indol-3-yl)butyl]-[2-(1*H*-indol-4-yloxy)ethyl]-amine (19). This compound was prepared in the manner described above for **17** using 2-(1*H*-indol-4-yloxy)ethyl chloride and 3-indolylbutylamine in 43% yield as an off-white solid: mp 70−73 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.48−1.55 (m, 2H), 1.64−1.72 (m, 2H), 2.64−2.70 (m, 4H), 2.94 (t, J = 5.7 Hz, 2H), 4.10 (t, J = 5.7 Hz, 2H), 6.39 (d, J = 2.9 Hz, 1H), 6.45 (dd, J = 7.0, 1.1 Hz, 1H), 6.91−7.05 (m, 5H), 7.16 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 10.71 (br s, 1H), 11.0 (br s, 1H). The oxalate salt was prepared in ethanol: mp 183.5−185 °C. Anal. ($C_{22}H_{25}N_3O\cdot C_2H_2O_4$) C, H, N.

2-(2-Chloroethoxy)-6-nitrophenylamine (72). A slurry containing 2-amino-3-nitrophenol (32.0 g, 0.208 mol), 1,2-dichloroethane (260.0 g, 2.65 mol), K_2CO_4 (35.0 g, 0.252 mol), and 2-butanone (750 mL) was heated to reflux for 24 h. The mixture was cooled and filtered, and the solid was washed with EtOAc. The filtrate was concentrated to an oily residue that was dissolved in EtOAc (500 mL). The organic layer was washed with 1 N NaOH (250 mL), water (500 mL), and brine (2 × 500 mL) and then dried over anhydrous $MgSO_4$. Concentration of the filtered solution and trituration of the residue with hexanes afforded 37.8 g (84.6%) of product as an orange solid: mp 71−73 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.03 (appt, J = 5.2 Hz, 2 H), 4.34 (appt, J = 5.1 Hz, 2 H), 6.60 (appt, J = 8.2 Hz, 2H), 6.98 (bs, 2H), 7.16 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 7.63 (dd, J = 8.9, 1.2 Hz, 1H); MS EI m/e 216 (M$^+$). Anal. ($C_8H_9ClN_2O_3$) C, H. N.

2-(2-Chloroethoxy)-4-chloro-6-nitrophenylamine (73). A solution of **72** (30.0 g, 0.14 mol), *N*-chlorosuccinimide and acetonitrile (1.3 L) was allowed to reflux for 4 h. The mixture was concentrated under vacuum, and the residue was diluted with EtOAc (500 mL). The organic layer was washed with water (2 × 250 mL) and brine (250 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under vacuum to give an orange solid residue. Crystallization from EtOAc−hexanes gave 33.5 g (95.3%) of product as an orange solid: mp 109−110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 (appt, J = 5.1 Hz, 2 H), 4.34 (t, J = 5.1 Hz, 2 H), 7.16 (bs, 2H), 7.23 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 2.2 Hz, 1H); MS (EI) 250/252/254 m/e (M$^+$). Anal. ($C_8H_8Cl_2N_2O_3$) C, H, N.

2-{2-[3-(1*H*-Indol-3-yl)propylamino]ethoxy}-6-nitrophenylamine (74). A solution containing **72** (4.1 g, 19 mmol) and 3-(1*H*-indol-3-yl)propylamine (7.1 g, 40.8 mmol) in anhydrous DMSO (50 mL) was heated at 60 °C for 12 h. EtOAc (200 mL) was added, and the mixture was washed with saturated $NaHCO_3$ (3 × 200 mL) and brine (200 mL). The organic layer wad dried over anhydrous $MgSO_4$, filtered, and concentrated to give crude product. Purification by chromatography (EtOAc−hexanes−2 N ammonia in MeOH, 25:25:1) afforded 4.6 g (68.9%) of product as a yellowish red viscous oil; MS EI m/e 354 (M$^+$). Anal. ($C_{19}H_{22}N_4O_3\cdot 0.4H_2O\cdot 0.1C_4H_8O_2\cdot 0.05CH_2Cl_2$) C, H, N.

2-{2-[3-(5-Fluoro-1*H*-indol-3-yl)propylamino]ethoxy}-6-nitrophenylamine (75). A solution of **72** (0.5 g, 2.3 mmol), 3-(5-fluoro-1*H*-3-yl)propylamine (1.1 g, 5.7 mmol), and triethylamine (0.58 g, 5.7 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 12 h at 90 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.67 g (78%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78 (m, 2H), 2.63 (t, J = 7.3 Hz, 2H), 2.69 (t, J = 7.4 Hz, 2H), 2.92 (t, J = 5.0 Hz, 2H), 4.06 (t, J = 5.0 Hz, 2H), 6.56 (m, 1H), 6.87 (m, 1H), 7.06 (m, 1H), 7.17−7.28 (m, 4H), 7.30 (m, 1H), 7.57 (m, 1H), 10.8 (br s, 1H); HRMS (ESI) m/e 373.1666 (M + H$^+$), $C_{19}H_{21}FN_4O_3$ requires 373.1670.

2-{2-[3-(5-Fluoro-1*H*-indol-3-yl)propylamino]ethoxy}-4-chloro-6-nitrophenylamine (76). This compound was prepared in the manner described above for compound **75** using 2-(2-chloroethoxy)-4-chloro-6-nitrophenylamine and 3-(5-fluoro-1*H*-indolyl)propylamine in 50% yield as a red solid: mp 47−50 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76 (m, 2H), 2.61 (t, J = 7.0 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 2.90 (t, J = 5.0 Hz, 2H), 4.10 (t, J = 5.0 Hz, 2H), 6.86 (td, J = 9.4, 2.6 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.22 (dd, J = 10, 2.4 Hz, 1H), 7.29 (dd, J = 8.8, 4.6 Hz, 1H), 7.36 (br, 2H), 7.56 (d, J = 2.2 Hz, 1H), 10.83 (br s, 1H); HRMS (ESI) m/e 407.1272 (M + H$^+$), $C_{19}H_{20}FClN_4O_3$ requires 407.1281.

3-{2-[3-(1*H*-Indol-3-yl)propylamino]ethoxy}benzene-1,2-diamine (77). To a solution of the **74** (1.9 g, 5.39 mmol) in ethanol (40 mL) was added 5% palladium on carbon (0.5 g) under nitrogen. The slurry was hydrogenated under 40 psi for 4 h. The catalyst was removed by filtration and the ethanol was evaporated to afford the crude product. Purification by chromatography (3−10% 2 N solution of ammonia in MeOH

in CH_2Cl_2) gave 1.57 g (90.6%) of product as a brown oil that was immediately used to prepare compound **20**.

3-{2-[3-(5-Fluoro-1*H*-indol-3-yl)propylamino]ethoxy}-benzene-1,2-diamine (78). A mixture **75** (0.65 g, 1.7 mmol) and 10% palladium on carbon in ethanol was hydrogenated for 3 h. The catalyst was filtered off, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2) afforded 0.49 g (82%) of product as a light-brown oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79 (m, 2H), 2.66 (m, 4H), 2.88 (t, J = 5.28 Hz, 2H), 3.92 (t, J = 5.28 Hz, 2H), 4.44 (br, 1H), 6.7−6.20 (m, 2H), 6.33 (t, J = 7.92 Hz, 1H), 6.88 (m, 1H), 7.18 (m, 1H), 7.25 (dd, J = 10.1, 2.64 Hz, 1H), 7.30 (dd, J = 8.8, 4.64 Hz, 1H), 10.8 (br s, 1H); HRMS (ESI) *m/e* 365.1770 (M + Na^+), $C_{19}H_{23}FN_4O$ requires 365.1748.

3-{2-[3-(5-Fluoro-1*H*-indol-3-yl)propylamino]ethoxy}-benzene-5-chloro-1,2-diamine (79). A mixture **76** (0.65 g, 1.7 mmol) and 5% platinum on sulfide carbon in ethanol was hydrogenated for 1 h. The catalyst was filtered off, and the solvent was removed under vacuum. Chromatography (15% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.59 g (80%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.91 (m, 2H), 3.15 (m, 2H), 4.06 (t, J = 4.6 Hz, 2H), 4.80 (br 2H), 6.23 (d, 2.2 Hz, 1H), 6.27 (d, J = 2.2 Hz, 1H), 6.89 (dd, J = 9.4, 2.4 Hz, 1H), 7.22 (m, 1H), 7.28−7.34 (m,2H), 10.9 (br s, 1H); HRMS (ESI) *m/e* 377.1535 (M + H^+), $C_{19}H_{22}ClFN_4O$ requires 377.1539.

[2-(3*H*-Benzoimidazol-4-yloxy)ethyl]-[3-(1*H*-indol-3-yl)-propyl]amine (20). A solution of **77** (0.75 g, 2.3 mmol) dissolved in 15 mL of formic acid (98%) was heated to 104 °C for 6 h. The excess formic acid was removed by vacuum distillation, and water (100 mL) and EtOAc (100 mL) were added. The EtOAc layer was separated, washed with water (50 mL) and brine (75 mL), and dried over anhydrous $MgSO_4$. Concentration of the solvent gave 0.7 g of product as a brown solid. Purification by chromatography (2 N ammonia in MeOH−CH_2Cl_2, 20:1.5) and crystallization from EtOAc−ethanol) afforded 0.34 g (45%) of product as a white solid: mp 121−124 °C (dec). The HCl salt was prepared in ethanol: mp 256−258 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.17 (m, 2 H), 2.80 (t, J = 7.4 Hz, 2 H), 3.11 (m, 2H), 3.37 (m, 2H), 4.51 (t, J = 5.1 Hz, 2H), 6.96 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 7.06 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 9.39 (bs, 2H), 9.56 (s, 1H), 10.85 (s, 1H). Anal. ($C_{20}H_{22}N_4O\cdot 2HCl\cdot 0.25H_2O$) C, H, N.

[2-(3*H*-Benzoimidazol-4-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)]propyl]amine (21). A solution of **78** (0.49 g) in formic acid (30 mL) was allowed to reflux for 4 h. The mixture was poured into NaOH (1 N, 150 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. Chromatography (10% MeOH−CH_2Cl_2) afforded 0.25 g (50%) of product as a off-white solid: mp 93−95 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77 (m, 2H), 2.61−2.89 (m, 4H), 2.93 (t, J = 5.68 Hz, 2H), 4.22 (t, J = 5.5 Hz, 2H), 6.70 (d, J = 7.8 Hz, 1H), 6.86 (m, 1H), 7.06 (t, J = 7.92 Hz, 1H), 7.16 (m, 2H), 7.23 (dd, J = 10.12, 2.64 Hz, 1H), 7.29 (dd, J = 9.0, 4.84 Hz, 1H), 8.08 (s, 1H), 10.8 (br s, 1H). The oxalate salt was prepared in ethanol: mp 185−187 °C. Anal. ($C_{20}H_{21}FN_4O\cdot 2C_2H_2O_4$) C, H, N.

[2-(6-Chloro-1*H*-benzoimidazol-4-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)]propyl]amine (22). This compound was prepared in a similar fashion described for **21** by replacing 3-{2-[3-(5-fluoro-1*H*-indol-3-yl)propylamino]ethoxy}benzene-1,2-diamine (**78**) with 3-{2-[3-(5-fluoro-1*H*-indol-3-yl)propylamino]-ethoxy}benzene-5-chloro-1,2-diamine (**79**) to give the product in 76% yield (0.22 g) as a white solid: mp 96−99 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (m, 2H), 2.67−2.74 (m, 4H), 3.00 (t, J = 5.3 Hz, 2H), 4.29 (t, J = 5.3 Hz, 2H), 6.78 (d, J = 1.3 Hz, 1H), 6.84 (td, J = 9.4, 2.6 Hz, 1H), 7.19 (m, 1H), 7.23−7.26 (m, 2H), 7.29 (dd, J = 8.8, 4.6 Hz, 1H), 8.16 (s, 1H), 10.8 (br s, 1H). The oxalate salt was prepared in ethanol: mp 185−187 °C. Anal. ($C_{20}H_{20}FN_4O\cdot 2C_2H_2O_4\cdot 2H_2O$) C, H, N.

***N*-[2-(2-Amino-3-nitrophenoxy)ethyl]-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-2,2-dimethylpropionamide (80).** A solution of **75** (0.56 g, 1.5 mmol) and di-*tert*-butyl dicarbonate (0.5 g, 2.25 mmol) in THF (30 mL) was stirred at room temperature for 1.5 h. The mixture was poured into the water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (2% MeOH−CH_2Cl_2) afforded 0.94 g (100%) of product as a red oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (br, 9H), 1.82 (m, 2H), 2.59 (t, J = 7.7 Hz, 2H), 3.60 (m, 2H), 4.10 (m, 2H), 6.55 (t, J = 8.6 Hz, 1H), 6.82−6.88 (m, 3H), 7.15−7.18 (m, 2H), 7.27 (dd, J = 8.8, 4.4 Hz, 1H), 7.5 (d, J = 8.8 Hz, 1H), 10.82 (br s, 1H); HRMS (ESI) *m/e* 473.2189 (M + H^+), $C_{24}H_{29}FN_4O_5$ requires 473.2195.

***N*-[2-(2,3-Diaminophenoxy)ethyl]-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-2,2-dimethylpropionamide (81).** A solution of **80** (0.94 g, 2.0 mmol) and 10% palladium on carbon in ethanol was heated at 50 °C for 10 min, then hydrazine monohydrate (3 g) in ethanol (10 mL) was slowly added to above mixture. The resulting mixture was stirred for 1 h, followed by filtration of the catalyst through Celite that was washed with ethanol (100 mL). The organic solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2) afforded 0.83 g (88%) of product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30−1.37 (m, 9H), 1.83 (m, 2H), 2.59 (t, J = 7.5 Hz, 2H), 3.13 (d, J = 5.3 Hz, 2H), 3.52 (m, 2H), 3.90 (br, 2H), 6.16 (m, 1H), 6.19 (d, J = 7.0 Hz, 1H), 6.32 (t, J = 7.9 hz,1H), 6.85 (td, J = 8.7, 2.6 Hz, 1H), 7.16−7.20 (m, 2H), 7.27 (dd, J = 8.8, 4.6 Hz, 1H), 10.81 (br s, 1H); HRMS (ESI) *m/e* 443.2440 (M + H^+), $C_{24}H_{31}FN_4O_3$ requires 443.2453.

***N*-[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-2,2-dimethyl-*N*-[2-(quinoxalin-5-yloxy)-ethyl]propionamide (82).** A solution of **81** (0.5 g, 1.12 mmol) and glyoxal (40% in water, 0.4 mL) in ethanol (20 mL) was heated to reflux for 1 h. The reaction was quenched with water and extracted with CH_2Cl_2. The organic portion was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2) afforded 0.38 g (72%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 9H), 1.88 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 3.40 (m, 2H), 3.66 (t, J = 5.7 Hz, 2H), 4.28 (m, 2H), 6.86 (td, J = 9.2, 2.4 Hz, 1H), 7.13−7.20 (m, 2H), 7.27 (t, J = 4.2 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 10.83 (br s, 1H); HRMS (ESI) *m/e* 465.2297 (M + H^+), $C_{26}H_{29}FN_4O_3$ requires 465.2296.

[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-[2-(quinoxalin-5-yloxy)ethyl]amine (16). To a solution of **82** (0.27 g, 0.58 mmol) and anisole (0.5 mL, 4.6 mmol) in CH_2Cl_2 (20 mL) was added TFA (1 mL) slowly at 0 °C. The resulting mixture was slowly warmed to room temperature and stirred for 4 h. The mixture was quenched with saturated Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed with water and dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2) afforded 47 mg (23%) of product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79 (m, 2H), 2.69 (m, 4H), 3.04 (t, J = 5.5 Hz, 2H), 4.26 (t, J = 5.7 Hz, 2H), 6.86 (td, J = 9.2, 2.6 Hz, 1H), 7.18 (m, 1H), 7.23 (dd, J = 10.1, 2.4 Hz, 1H), 7.28 (t, J = 4.2 Hz, 1H), 7.31 (d, J = 7.0 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 8.87 (m, 1H), 8.92 (M, 1H), 10.83 (br, 1H); MS ESI *m/e* 365 (M + 1)$^+$.

7-Methoxybezofuran (84). A solution of 7-methoxy-2-benzofuran-2-carboxylic acid (5 g, 0.026 mol) and copper (0.2 g) in quinoline (30 mL) was heated at reflux for 2 h. The mixture was filtered through Celite and washed with EtOAc. The solvent was removed under vacuum followed by chromatography (25% EtOAc−hexanes) to afford 2.45 g (64%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H), 6.76 (d, J = 1.96 Hz, 1H), 6.80 (dd, J = 7.4, 1.3 Hz, 1H), 7.14−7.21 (m, 2H), 7.62 (d, J = 2.2 Hz, 1H); MS EI *m/e* 148 (M^+).

7-Hydroxybezofuran (85). To a solution of **84** (1 g, 6.7 mmol) in anhydrous CH_2Cl_2 (25 mL) was carefully added a

solution of boron tribromide in CH_2Cl_2 (1 M, 10 mL). The reaction mixture was kept at −78 °C for 6 h and then was allowed to stir at room temperature overnight. After quenching with water (20 mL), the reaction mixture was extracted with ethyl ether and the solvent was removed under vacuum. Chromatography (25% EtOAc−hexanes) afforded 0.47 g (52%) of product as a light-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 3H), 6.78 (d, J = 1.96 Hz, 1H), 6.83 (dd, J = 7.68, 1.32 Hz, 1H), 7.11 (t, J = 7.68 Hz, 1H), 7.61 (d, J = 1.96 Hz, 1H); MS EI *m/e* 134 (M^+).

2-(Benzofuran-7-yloxy)ethyl Chloride (86). To a solution of **85** (0.47 g, 3.5 mmol), triphenylphosphine (2.3 g, 8.7 mmol), and 2-chloroethanol (0.7 g, 8.7 mmol) in THF ((50 mL) was slowly added DIAD (1.8 g, 8.7 mmol). The reaction mixture was stirred at room temperature for 3 h, and the THF was removed under vacuum. Chromatography (25% EtOAc−hexanes) afforded 0.58 g (84%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (t, J = 6.12 Hz, 2H), 4.48 (t, J = 6.16 Hz, 2H), 6.77 (d, J = 1.96 Hz, 1H), 6.83 (dd, J = 7.92, 0.88 Hz, 1H), 7.15 (t, J = 7.92 Hz, 1H), 7.24 (dd, J = 7.92, 0.88 Hz, 1H), 7.62 (d, J = 3.84 Hz, 1H); MS EI *m/e* 196 (M^+).

2-(2,3-Dihydrobenzofuran-7-yloxy)ethyl Chloride (87). A solution of **86** (0.64 g) and 10% palladium on carbon in acetic acid (20 mL) was hydrogenated under 40 psi for 20 h. The catalyst was filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 0.39 g (60%) of product as a white solid: mp 49−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (t, J = 8.76 Hz, 2H), 3.81 (t, J = 6.36 Hz, 2H), 4.31 (t, J = 6.36 Hz, 2H), 4.62 (t, J = 8.76 Hz, 2H), 6.75−6.79 (m, 2H), 6.88 (m, 2H); HRMS (ESI) *m/e* 199.0515 ($M + H^+$), $C_{10}H_{11}ClO_2$ requires 199.0520.

[2-(Benzofuran-7-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)propyl]amine (23). A solution of **86** (0.58 g, 2.9 mmol), 3-(5-fluoro-1*H*-indol-3-yl)propylamine (1.4 g, 7.4 mmol), and triethylamine (0.74 g, 7.4 mmol) in anhydrous DMSO (20 mL) was allowed to stir at 90 °C for 12 h. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (7% MeOH−CH_2Cl_2) afforded 0.31 g (30%) of product as a light-brown oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79 (m, 2H), 2.69 (m, 2H), 2.98 (t, J = 5.72 Hz, 2H), 4.22 (t, J = 5.72 Hz, 2H), 6.84−6.92 (m, 3H), 7.11−7.31 (m, 5H), 7.93 (d, J = 2.2 Hz, 1H), 10.8 (br, 1H). The oxalate salt was prepared in THF: mp 181−183 °C. Anal. ($C_{21}H_{21}FN_2O_2 \cdot C_2H_2O_4$) C, H, N.

[2-(2,3-Dihydrobenzofuran-7-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)propyl]amine (24). This compound was prepared in a similar fashion described for **23** by replacing **86** with **87** (0.38 g, 19 mmol) to give the title compound in 77% yield (0.52 g) as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78 (m, 2H), 2.66 (m, 4H), 2.89 (t, J = 5.72 Hz, 2H), 3.15 (t, J = 8.76 Hz, 2H), 4.04 (t, J = 5.72 Hz, 2H), 4.49 (t, J = 8.8 Hz, 2H), 6.71−6.90 (m, 4H), 7.16−7.31 (m, 3H), 10.8 (br, 1H). The fumarate salt was prepared in ethanol: mp 158−160 °C. Anal. ($C_{21}H_{23}FN_2O_2 \cdot C_4H_4O_4$) C, H, N.

1-(4-Fluoro-2-methoxyphenyl)ethanone (89). A solution of 4-fluoro-2-hydroxyacetophenone (**88**) (1.0 g, 6.5 mmol), K_2CO_3 (1.34 g, 9.7 mmol), and methyl iodide (0.44 mL, 7 mmol) in anhydrous DMSO (20 mL) was stirred at room temperature for 2 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum to afford 1.1 g (100%) of product as a white solid: mp 50−51.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 3.91 (s, 3H), 6.68−6.72 (m, 2H), 7.78−7.83 (m, 1H); MS EI *m/e* 135 (M^+). Anal. ($C_9H_9FO_2$) C, H, N.

4-Fluoro-2-methyoxyphenol (90). A solution of **89** (16.8 g, 0.1 mol), 3-*tert*-butyl-4-hydroxy-5-methylenyl sulfide (0.2 g), and mCPBA (37 g) in CH_2Cl_2 (100 mL) was heated to reflux overnight. The white solid was filtered off, and the solution was concentrated under vacuum. The crude material was hydrolyzed with NaOH (12 g) in 100 mL of ethanol−water (1:1) for 2 h and neutralized with HCl (12 N) until the pH is 7. The mixture was extracted with CH_2Cl_2 and was washed with water, and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the product was chromatographed (25% EtOAc−hexane) to afford 10.0 g (71%) of product as a light-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.54−6.64 (m, 2H), 6.83 (dd, J = 8.8, 5.4 Hz, 1H); MS EI *m/e* 142 (M^+).

1-(2,2-Diethoxyethoxy)-4-fluoro-2-methyoxybenzene (91). To a suspension of sodium hydride (60%, 5.7 g, 0.14 mol) in anhydrous DMF (20 mL) was added **90** (13.5 g, 0.09 mol) at 0 °C. After hydrogen evolution had ceased, bromoacetaldehyde diethyl acetal (17 mL, 0.11 mol) was added to the solution. The reaction mixture was heated at 160−170 °C overnight and poured into ice/water. The mixture was extracted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered and the product was purified by chromatography (25% EtOAc−hexane) to afford 12.4 g (51%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.28 (m, 6H), 3.59−3.67 (m, 2H), 3.72−3.79 (m, 2H), 3.83 (s, 3H), 4.01 (d, J = 5.3 Hz, 2H), 4.84 (t, J = 5.3 Hz, 1H), 6.53−6.58 (m, 1H), 6.62 (dd, J = 10.1, 2.8 Hz, 1H), 6.88 (dd, J = 8.8, 5.52 Hz, 1H); HRMS (ESI) *m/e* 281.1154 ($M + Na^+$), $C_{13}H_{19}FO_4$ requires 281.1160.

5-Fluoro-7-methoxybenzofuran (92). A solution of **91** (0.5 g, 3.5 mmol) and polyphosphoric acid (1.2 g, 3.5 mmol) in xylene (40 mL) was heated at reflux for 0.5 h. The reaction mixture was cooled to room temperature and decanted from the polyphosphoric acid. The solvent was removed under vacuum followed by chromatography (25% EtOAc−hexanes) to afford 88 mg (15%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 6.57 (dd, J = 11, 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.85 (dd, J = 8.4, 2.2 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H); MS EI *m/e* 166 (M^+).

5-Fluorobenzofuran-7-ol (93). To a solution of **92** (2.16 g, 0.013 mol) in anhydrous CH_2Cl_2 (25 mL) was added boron tribromide (19.5 mL, 19.5 mmol) at −78 °C. The mixture was stirred at −78 °C for 6 h and at room temperature overnight. The mixture was poured into ice/water and extracted with CH_2Cl_2. The organic layer was washed with brine (3 × 100 mL) and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the product was chromatographed (25% EtOAc−hexanes) to afford 1.4 g (71%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H, 5.70 (s, 1H), 6.62 (dd, J = 10.3, 2.2 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H, 6.83 (dd, J = 8.4, 2.4 Hz, 1H), 7.62 (d, J = 2.2 Hz, 1H); MS EI *m/e* 152 (M^+).

7-(2-Chloroethoxy)-5-fluorobenzofuran (94). To a solution of **93** (1.4 g, 9.2 mmol), triphenylphosphine (6 g, 23 mmol), and 2-chloroethanol (1.53 mL, 23 mmol) in THF (50 mL) was slowly added DIAD (4.5 mL, 23 mmol). The reaction mixture was stirred at room temperature for 2 h, and the THF was removed under vacuum. Chromatography (25% EtOAc−hexanes) afforded 1.76 g (89%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (t, J = 5.9 Hz, 2H), 4.45 (t, J = 5.9 Hz, 2H), 6.59 (dd, J = 10.7, 2.2 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.89 (dd, J = 8.1, 2.4 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H); MS EI *m/e* 214 (M^+).

[2-(5-Fluorobenzofuran-7-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)propyl]amine (25). This compound was prepared in a similar fashion described for **23** by replacing **86** with **94** (0.55 g, 2.6 mmol) to give 0.6 g of desired product (63%) as a yellow solid: mp 118−120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77 (m, 2H), 2.62−2.67 (m, 4H), 2.93 (t, J = 5.5 Hz, 2H), 4.20 (t, J = 5.7 Hz, 2H), 6.84−6.89 (m, 3H), 6.91 (d, J = 2.2 Hz, 1H), 6.99 (dd, J = 8.6, 2.3 Hz, 1H), 7.16 (m, 1H), 7.22 (dd, J = 10.1, 2.4 Hz, 1H), 7.28 (dd, J = 8.8, 4.6 Hz, 1H), 7.99 (d, J = 2.0 Hz, 1H), 10.83 (br, 1H). The oxalate salt was prepared in ethanol: mp 210−211 °C. Anal. ($C_{21}H_{20}F_2N_2O_2$) C, H, N.

[2-(5-Fluoro-2,3-Dihydrobenzofuran-7-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)propyl]amine (26). A solution of **25** (0.3 g) and platinium oxide (0.14 g) in ethanol (70 mL) was hydrogenated under 50 psi for 36 h. The catalyst was filtered, and the solvent was removed under vacuum. Chromatography (2−3% MeOH−CH_2Cl_2) afforded 0.14 g (46%) of product as a

clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76 (m, 2H), 2.62−2.68 (m, 4H), 2.87 (t, J = 5.7 Hz, 2H), 3.14 (t, = 8.6 Hz, 2H), 4.04 (t, J = 5.8 Hz, 2H), 4.49 (t, J = 8.6 Hz, 2H), 6.66−6.73 (m, 2H), 6.87 (dd, J = 9.2, 2.64 Hz, 1H), 7.16 (m, 1H), 7.22 (dd, J = 10.1, 2.6 Hz, 1H), 7.30 (dd, J = 8.8, 4.6 Hz, 1H), 10.6 (br s, 1H). The oxalate salt was prepared: mp 193−195 °C. Anal. ($C_{21}H_{22}F_2N_2O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N

2-(4-Fluorophenoxy)acetaldehyde Diethyl Acetal (96). To a suspension of NaH (5.4 g, 0.134 mol) in anhydrous DMF (100 mL) was added 4-fluorophenol (10 g, 0.089 mol) at 0 °C. After hydrogen evolution had ceased, bromoacetaldehyde diethyl acetal (16 mL, 0.11 mol) was added. The reaction mixture was heated at 160−170 °C for 18 h. The mixture was poured into ice/water, extracted with EtOAc (3 × 150 mL), and washed with 1 N NaOH (3 × 100 mL) and brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Purification by chromatography (25% EtOAc−hexanes) afforded 16.4 g (80%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 6H), 3.61−3.66 (m, 2H), 3.72−3.79 (m, 2H), 3.98 (d, J = 5.3 Hz, 2H), 4.81 (t, J = 5.3 Hz, 1H), 6.84−6.87 (m, 2H), 6.93−6.98 (m, 2H); HRMS (ESI) *m/e* 251.1049 (M + Na^+), $C_{12}H_{17}FO_3$ requires 251.1054.

5-Fluorobenzofuran (97). To a mixture of benzene (200 mL) containing polyphosphoric acid (7.9 g, 0.035 mol) was added **96** (8 g, 0.035 mol). The mixture was stirred vigorously while being heated at reflux for 2.5 h. The reaction mixture was cooled to room temperature and decanted from the polyphosphoric acid. The solvent was removed under vacuum and the product was chromatographed (5% EtOAc−hexanes) to afford 3.4 g (45%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd J = 2.2, 1.1 Hz, 1H), 7.01 (td, J = 9.0, 2.6 Hz, 1H), 7.25 (dd, J = 8.6, 2.6 Hz, 1H), 7.41−7.44 (m, 1H), 7.65 (d, J = 2.2 Hz, 1H).

5-Fluoro-2,3-dihydrobenzofuran (98). A solution of **97** and 10% palladium on carbon in acetic acid (25 mL) was hydrogenated under 50 psi for 12 h. The catalyst was filtered through Celite and washed with CH_2Cl_2 (200 mL). The organic layer was washed with 1 N NaOH (3 × 100 mL) and brine (3 × 100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to afford 2.59 g (85%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (t, J = 8.4 Hz, 2H), 4.57 (t, J = 8.7 Hz, 2H), 6.65−6.69 (m, 1H), 6.75−6.80 (m, 1H), 6.87−6.91 (m, 1H).

5-Fluoro-2,3-dihydrobenzofuran-7-carbaldehyde (99). To a solution of **98** (7 g, 0.051 mol) in anhydrous CH_2Cl_2 (40 mL) was added $TiCl_4$ (9.5 mL, 0.087 mol), followed by α,α′-dichloromethyl methyl ether (4.6 mL, 0.051 mol) at 0 °C. The reaction mixture was allowed to reach room temperature slowly and was stirred overnight. The reaction mixture was poured into ice/water slowly, extracted with CH_2Cl_2 (3 × 100 mL), and washed with saturated Na_2CO_4 (5 × 100 mL) and brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. Chromatography (25% EtOAc−hexanes) afforded 3.3 g (39%) of product as a white solid: mp 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 (t, J = 8.4 Hz, 2H), 4.75 (t, J = 8.6 Hz, 2H), 7.10−7.26 (m, 1H), 7.22−7.26 (m, 1H), 10.15 (s, 1H). Anal. ($C_9H_7FO_2$) C, H, N.

5-Fluoro-7-hydroxy-2,3-dihydrobenzofuran (100). To a solution of **99** (3.29 g, 20 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (100 mg) in anhydrous CH_2Cl_2 (40 mL) at 0 °C was added mCPBA (8.5 g, 30 mmol) portionwise. The reaction mixture was heated to reflux for 16 h, and the excess mCBPA was destroyed by adding 10% sodium sulfite. The benzoic acid was filtered off, and the filtrate was extracted with CH_2Cl_2 (3 × 100 mL) and washed with water (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. The crude product was dissolved in ethanol−water (100 mL, 1:1), and NaOH (2.11 g, 53 mmol) was added at 0 °C. After 30 min, the ice bath was removed and the reaction mixture was allowed to stir for 3 h at room temperature. Ethanol was evaporated, and the residue was neutralized with concentrated hydrochloric acid. This mixture was extracted with CH_2Cl_2 (3 × 100 mL) and washed with saturated Na_2CO_4 (2 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over sodium sulfate and filtered, and the solvent was removed under vacuum. Chromatography (30% EtOAc−hexanes) afforded 1.62 g (50%) of product as a white solid: mp 102.5−103.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (t, J = 8.4 Hz, 2H), 4.61 (t, J = 8.5 Hz, 2H), 5.0 (s, 1H), 6.46−6.55 (m, 2H). Anal. ($C_8H_7FO_2$) C, H, N.

2-(5-Fluoro-2,3-dihydrobenzofuran-7-yloxy)ethyl Chloride (101). A solution of **100** (1.6 g, 10 mmol), 1-bromo-2-chloroethane (7.8 g, 55 mmol), and K_2CO_3 (2.2 g, 16 mmol) in 2-butanone (40 mL) was heated to reflux for 24 h. The mixture was poured into water (150 mL), extracted with CH_2Cl_2 (3 × 150 mL), and washed with brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (25% EtOAc−hexanes) afforded 2.1 g (97%) of product as a white solid: mp 72.5−74.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (t, J = 8.7 Hz, 2H), 3.80 (t, J = 5.9 Hz, 2H), 4.28 (t, J = 5.9 Hz, 2H), 4.61 (t, J = 8.8 Hz, 2H), 6.48−6.51 (m, 1H), 6.57−6.60 (m, 1H). Anal. ($C_{10}H_{10}FClO_2$) C, H, N.

2-(5-Fluoro-2,3-dihydrobenzofuran-7-yloxy)ethylazide (102). A solution of **101** (2.05 g, 9.4 mmol) and sodium azide (1.23 g, 19 mol) in anhydrous DMF (30 mL) was allowed to stir at 60 °C for 24 h. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The organic layer washed with water (3 × 100 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 2.0 g (95%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (t, J = 8.7 Hz, 2H), 3.62 (t, J = 5.2 Hz, 2H), 4.19 (t, J = 5.2 z, 2H), 4.61 (t, J = 8.8 Hz, 2H), 6.48−6.51 (m, 1H), 6.57−6.60 (m, 1H); HRMS (ESI) *m/e* 224.0827 (M + H^+), $C_{10}H_{10}FN_3O_2$ requires 224.0830.

2-(5-Fluoro-2,3-dihydrofuran-7-yloxy)ethylamine (103). A solution of **102** (1.98 g, 89 mmol) and triphenylphosphine (2.8 g, 10.6 mmol) in THF (50 mL) and water (1.5 mL) was allowed to stir for 18 h at room temperature. The solvent was removed under vacuum and the product was chromatographed (EtOAc to first remove triphenylphosphine and triphenylphosphine oxide followed by 40% MeOH−CH_2Cl_2 plus NH_4OH) to afford 2.0 g (100%) of a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (t, J = 8.8 Hz, 2H), 3.20 (t, J = 5.3 Hz, 2H), 4.03 (t, J = 5.3 Hz, 2H), 4.61 (t, J = 8.8 Hz, 2H), 6.47−6.51 (m, 1H), 6.53−6.56 (m, 1H); MS ESI *m/e* 198 [M + 1].$^+$

[2-(5-Fluoro-2,3-dihydrobenzofuran-7-yloxy)ethyl]-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]amine (27). A solution of **103** (0.40 g, 2.1 mmol), 2-(5-fluoro-1*H*-indol-3-yl)ethyl bromide (0.25 g, 1.0 mmol), and triethylamine (0.29 mL, 2.1 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 14 h at 90 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 100 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.2 g (54%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.75 (m, 6H), 3.14 (t, J = 8.8 Hz, 2H), 4.01 (t, J = 5.7 Hz, 2H), 4.48 (t, J = 8.8 Hz, 2H), 6.64−6.67 (m, 2H), 6.84−6.90 (m, 1H), 7.20−7.31 (m, 3H), 10.87 (br s, 1H). The oxalate salt was prepared in ethanol: mp 209.5−210.5 °C. Anal. ($C_{20}H_{20}F_2N_2O_2 \cdot 1.5C_2H_2O_4 \cdot 0.25H_2O$) C. H, N.

2-(5,6,7,8-Tetrahydronaphthalen-1-yloxy)ethyl Chloride (105). This compound was prepared in the manner described for **59** above by replacing 5-fluoro-2-methoxyphenol with 5,6,7,8-tetrahydro-1-naphthol (4 g, 0.027 mol) in 46% yield (2.57 g) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73−1.80 (m, 4H), 2.69 (t, J = 5.9 Hz, 2H), 2.75 (t, J = 5.9 Hz, 2H), 3.82 (t, J = 5.9 Hz, 2H), 4.22 (t, J = 5.9 Hz, 2H), 6.61 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H). Anal. ($C_{12}H_{15}ClO$) C, H, N.

[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-[2-(5,6,7,8-tetrahydronaphthalen-1-yloxy)ethyl]amine (28). This compound was prepared in the manner described above for **23** by using compound **105** (0.6 g, 2.8 mmol) in 29% yield (0.3 g) as a yellow

oil. The fumarate salt was prepared in ethanol: mp 203−205 °C. Anal. ($C_{23}H_{27}FN_2O\cdot0.5C_4H_4O_4$) C, H, N.

5-Hydroxy-(2,3)-dihydrobenzo[1,4]dioxine (107). Pyrogallol (5 g, 0.04 mol) was dissolved in 2-butanone (600 mL) containing K_2CO_3 (1.82 g, 0.013 mol). The mixture was stirred at reflux while 1,2-dibromoethane (2.48 g, 1.14 mL, 0.013 mol) was slowly added dropwise. The reaction mixture was allowed to stir overnight and then was cooled to room temperature. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (5% MeOH−CH_2Cl_2) afforded 2.74 g (45%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26−4.32 (m, 4H), 6.44 (dd, J = 8.3, 1.3 Hz, 1H), 6.53 (dd, J = 8.3, 1.3 Hz, 1H), 7.22 (t, J = 8.3 Hz, 1H); HRMS (ESI) *m/e* 153.0537 (M + H^+), $C_8H_8O_3$ requires 153.0546.

5-(2-Chloroethoxy)-(2,3)-dihydrobenzo[1,4]dioxane (108). To solution of **107** (1.0 g, 6.5 mmol), 2-chloroethanol (0.79 g, 9.9 mmol), and triphenylphosphine (2.6 g, 9.9 mmol) in THF (50 mL) was slowly added DIAD (2.0 g, 9.8 mmol). After 2 h, another 1.5 equiv of triphenylphosphine, DIAD, and 2-chloroethanol was added and the mixture was stirred for another 2 h. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 1.7 g (76%) of product as a white solid: mp 70.5−72.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (t, J = 6.4 Hz, 2H), 4.24−4.32 (m, 6H), 6.50 (dd, J = 8.4, 1.3 Hz, 1H), 6.56 (m, 1H), 6.75 (t, J = 8.4 Hz, 1H). Anal. ($C_{10}H_{11}ClO_3$) C, H, N.

2-(2,3-Dihydrobenzo[1,4]dioxin-5-yloxy)ethylazide (109). A solution of **108** (4.6 g, 0.02 mol) and sodium azide (2.78 g, 0.043 mol) in anhydrous DMF (100 mL) was allowed to stir for 18 h at 60 °C. The mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 3.43 g (72%) of product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.62 (t, J = 4.8 Hz, 2H), 4.10 (t, J = 4.8 Hz, 2H), 4.20 (s, 4H), 6.50 (dd, J = 8.4,1.6 Hz, 1H), 6.55 (dd, J = 8.4, 1.5 Hz, 1H), 6.71 (t, J = 8.4 Hz, 1H); HRMS (ESI) *m/e* 222.0873 (M + H^+), $C_{10}H_{11}N_3O_3$ requires 222.0873.

2-(2,3-Dihydrobenzo[1,4]dioxin-5-yloxy)ethylamine (110). A solution of **110** (3.43 g, 0.016 mol), triphenylphosphine (6.3 g, 0.023 mol) in THF (50 mL), and water (2 mL) was allowed to stir for 18 h at room temperature. The solvent was removed under vacuum and the product was purified by chromatography (30% MeOH−CH_2Cl_2 plus NH_4OH) to afford 1.93 g (62%) of a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.85 (t, J = 5.7 Hz, 2H), 3.88 (t, J = 5.7 Hz, 2H), 4.20 (s, 4H), 6.44 (dd, J = 8.3, 1.5 Hz, 1H), 6.53 (dd, J = 8.3, 1.5 Hz, 1H), 6.70 (t, J = 8.3 Hz, 1H): HRMS (ESI) *m/e* 196.0963 (M + H^+), $C_{10}H_{13}NO_3$ requires 196.0968.

[2-(2,3-Dihydrobenzo[1,4]dioxin-5-yloxy)ethyl]-[2-(1*H*-indol-3-yl)ethyl]amine (29). A solution of **110** (0.38 g, 1.9 mmol), 3-(2-bromoethyl)indole (0.24 g, 1.1 mmol), and triethylamine (0.22 g, 2.2 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 14 h at 90 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.19 g (52%) of a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.81−2.88 (m, 4H), 2.91 (t, J = 5.5 Hz, 2H), 3.98 (t, J = 5.7 Hz, 2H), 4.18 (s, 4H), 6.44 (dd, J = 8.4, 1.3 Hz, 1H), 6.51 (dd, J = 8.3, 1.3 Hz, 1H), 6.68 (t, J = 8.3 Hz, 1H), 6.95 (m, 1H), 7.04 (m, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H). The oxalate salt was prepared in ethanol: mp 197.5−198.5 °C. Anal. ($C_{20}H_{22}N_2O_3\cdot C_2H_2O_4$) C, H, N.

[2-(2,3-Dihydrobenzo[1,4]dioxin-5-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)propyl]amine (30). A solution of **108** (0.75 g, 3.5 mmol), **49** (1.0 g, 5.2 mmol), and triethylamine (0.35 g, 3.5 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 14 h at 100 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (5−10% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.10 g (52%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77 (m, 2H), 2.66 (m, 4H), 2.88 (t, J = 5.7 Hz, 2H), 3.99 (t, J = 5.7 Hz, 2H), 4.18 (s, 3H), 6.45 (dd, J = 8.4, 1.5 Hz, 1H), 6.53 (dd, J = 8.4, 1,5 Hz, 1H), 6.70 (t, J = 8.4 Hz, 1H), 6.87 (td, J = 9.2, 2.4 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 10.1, 2.4 Hz, 1H), 7.30 (dd, J = 8.8, 4.6 Hz, 1H), 10.85 (br s, 1H). The fumarate salt was prepared in 2-propanol: mp 189.5−190.5 °C. Anal. ($C_{21}H_{23}FN_2O_3\cdot0.5C_4H_4O_4\cdot0.5H_2O$) C, H, N.

Acetic Acid 2-Acetyl-4-fluorophenyl Ester (112). To a suspension of 5-fluoro-2-hydroxyacetophenone (15 g, 0.097 mol) in acetic anhydride (20 mL) was added concentrated sulfuric acid (985, 0.4 mL). The reaction mixture was heated at 60 °C for 20 min. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and filtered and the solvent was removed under vacuum to afford 20.1 g of product as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.54 (s, 3H), 7.10 (dd, J = 8.8, 4.6 Hz, 1H), 7.20−7.25 (m, 1H), 7.48 (dd, J = 8.6, 3.1 Hz, 1H); HRMS (ESI) *m/e* 219.0425 (M + Na^+), $C_{10}H_9FO_3$ requires 219.0428.

1-(3-Acetyl-5-fluoro-2-hydroxyphenol)ethanone (113). Fresh aluminum chloride (37 g) was placed in three-neck round-bottom flask and heated at 140 °C for 20 min. To the above slurry was quickly added **112** (9.8 g). The resulting mixture was heated at 170−180 °C for 3 h. The hot mixture was quenched with concentrated HCl and filtered through Celite. The mother liquor was extracted with ethyl ether and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the product was purified by chromatography (25% EtOAc−hexane) to afford 1.9 g (19%) of product as a yellow solid: mp 64−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 6H), 7.71 (d, J = 8.4 Hz, 2H), 13.02 (s, 1H). Anal. ($C_{10}H_9FO_3$) C, H, N.

1-[3-Acetyl-2-(2-chloroethoxy)-5-fluorophenyl]ethanone (114). A solution of **113** (1.3 g, 6.6 mmol), 1-bromo-2-chloroethane (2.76 mL, 33 mmol), and K_2CO_3 (1.82 g, 13.2 mmol) in 2-butanone (60 mL) was heated to reflux for 24 h. The mixture was poured into water (150 mL), extracted with CH_2Cl_2 (3 × 150 mL), and washed with brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (30% EtOAc−hexanes) afforded 1.65 g (96%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (m, 2H), 4.09 (m, 2H), 7.38 (d, J = 7.9 Hz, 2H); MS EI *m/e* 258 (M^+).

Acetic Acid 3-Acetoxy-2-(2-chloroethoxy)-5-fluorophenyl Ester (115). To 30% hydrogen peroxide (24 mL) in anhydrous CH_2Cl_2 (142 mL) was added trifluoroacetic anhydride (136 mL) at 0 °C over 1 h. The resulting mixture was stirred at 0 °C for an additional 20 min. A solution of **114** (2.0 g) in CH_2Cl_2 (20 mL) was added to above mixture at 0 °C. The mixture was stirred at room temperature for 1 h and then quenched with saturated sodium bisulfate at 0 °C. The mixture was extracted with CH_2Cl_2, the organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (30% EtOAc−hexane) afforded 2.0 g (89%) of product as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 6H), 3.70 (m, 2H), 4.16 (m, 2H), 6.77 (m, 2H); MS EI *m/e* 290 (M^+); HRMS (ESI) *m/e* 313.0246 (M + Na^+), $C_{12}H_{12}FClO_5$ requires 313.0249.

7-Fluoro-2,3-dihydrobenzo[1,4]dioxin-5-ol (116). To a solution of **115** (2.0 g, 6.9 mmol) in ethanol−water (10 mL:10 mL) was added NaOH (0.82 g, 21 mmol) at 0 °C. The resulting mixture was stirred for 2.5 h at room temperature, and then the reaction was quenched with concentrated HCl. The mixture was extracted with CH_2Cl_2, and organic layer was dried

over anhydrous Na_2SO_4. The solvent was removed under vacuum to afford 1.2 g (100%) of product as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (s, 4H), 6.20 (dd. J = 9 Hz, 1H), 5.42 (br, 1H), 6.29 (dd, J = 9.6, 2.8 Hz, 1H); MS EI *m/e* 170 (M^+).

5-(2-Chloroethoxy)-7-fluoro-2,3-dihydrobenzo[1, 4]dioxine (117). To a solution of **116** (1.2 g, 7.1 mmol), 2-chloroethanol (1.2 mL, 17.7 mmol), and triphenylphosphine (4.6 g, 17.7 mmol) in anhydrous THF (40 mL) was slowly added DIAD (3.5 mL, 17.7 mmol). The reaction mixture was allowed to stir for 1 h, and the solvent was removed under vacuum. Chromatography (35% EtOAc−hexanes) afforded 1.6 g (98%) of product as a white solid: mp 97−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (t, J = 6.1 Hz, 2H), 4.22−4.29 (m, 6H), 6.25−6.32 (m, 2H); HRMS (ESI) *m/e* 233.0372 (M + H^+), $C_{10}H_{10}FClO_3$ requires 233.0375.

[2-(7-Fluoro-2,3-dihydrobenzo[1,4]dioxin-5-yloxy]-[3-(5-fluoro-1*H*-indole-3-ylpropyl]amine (31). A solution of **117** (0.45 g, 1.9 mmol), **49** (0.74 g, 3.9 mmol), and triethylamine (0.54 mL, 3.9 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 6.5 h at 120 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (5−10% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.38 g (51%) of product as a white solid: mp 143−144 °C; ^{1}H NMR (400 MHz, DMSO-d_4) δ 1.75 (m, 2H), 2.61 (t, J = 7.0 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 2.85 (t, J = 5.7 Hz, 2H), 3.98 (t, J = 5.7 Hz, 2H), 4.15−4.22 (m, 4H), 6.32−6.35 (m, 1H), 6.50 (dd, J = 10.8, 2.9 Hz, 1H), 6.86 (td, J = 9.0, 2.4 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 10.1, 2.2 Hz, 1H), 7.29 (dd, J = 8.8, 4.6 Hz, 1H). 10.83 (br s, 1H). The oxalate salt was prepared in ethanol: mp 202−203.5 °C. Anal. ($C_{21}H_{22}F_2N_2O_3 \cdot C_2H_2O_4$) C, H, N.

6-Fluorochroman (119). A mixture of 6-fluoro-4-chromanone (2 g, 12 mmol) and 10% palladium on carbon (1 g) in concentrated hydrochloric acid (20 mL) and ethanol (30 mL) was hydrogenated for 20 h. The catalyst was filtered, and the solvent was removed under vacuum. The residue was dissolved in EtOAc (100 mL), washed with 1 N NaOH (6 × 200 mL) and water (3 × 150 mL), dried over anhydrous Na_2SO_2, and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 1.41 g (77%) of product as a clear oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95−2.00 (m, 2H), 2.77 (t, J = 6.6 Hz, 2H), 4.15 (t, J = 5.2 Hz, 2H), 6.69−6.80 (m, 3H); MS EI *m/e* 152 (M^+).

6-Fluorochroman-8-carbaldehyde (120). To a solution of **119** (0.7 g, 4.6 mmol) in anhydrous CH_2Cl_2 (20 mL) were added $TiCl_4$ (1.57 g, 8.3 mmol) and α,α′-dichloromethyl methyl ether (0.53 g, 4.6 mmol) slowly at 0 °C. The reaction mixture was allowed to reach room temperature slowly and stirred for 16 h. The reaction mixture was poured into ice/water, extracted with CH_2Cl_2 (3 × 100 mL), and washed with saturated Na_2CO_3 (5 × 150 mL) and brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to afford 0.75 g (90%) of a yellow solid: mp 55−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03−2.09 (m, 2H), 2.83 (t, J = 6.6 Hz, 2H), 4.28 (t, J = 5.3 Hz, 2H), 6.92−7.00 (m, 1H), 7.29−7.32 (m, 1H), 10.36 (d, J = 3.3 Hz, 1H). Anal. ($C_{10}H_9FO_2$) C, H, N.

6-Fluoro-8-hydroxychroman (121). To a solution of **120** (8.6 g, 48 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (100 mg) in anhydrous CH_2Cl_2 (60 mL) at 0 °C was added mCPBA (12.4 g, 70 mmol) portionwise. The reaction mixture was allowed to reflux for 16 h. The excess mCBPA was destroyed by adding 10% sodium sulfite. The benzoic acid was filtered off, and the filtrate was extracted with CH_2Cl_2 (3 × 150 mL) and washed with water (3 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum, and the crude product (10.2 g, 52 mmol) was dissolved in ethanol−water (200 mL, 1:1). To the above solution was added NaOH (6.2 g, 160 mmol) at 0 °C. After 30 min the ice bath was removed and the reaction mixture was allowed to stir for 3 h at room temperature. The solvent was evaporated, and the residue was neutralized with concentrated HCl (pH 7). The mixture was extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL), the organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (25% EtOAc−hexanes) afforded 6.9 g (79%) of product as a white solid: mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99−2.05 (m, 2H), 2.74 (t, J = 6.6 Hz, 2H), 4.22 (t, J = 5.3 Hz, 2H), 5.59 (d, J = 1.6 Hz, 1H), 6.28−6.32 (m, 1H), 6.47−6.51 (m, 1H). Anal. ($C_9H_9FO_2$) C, H, N.

2-(6-Fluorochroman-8-yloxy)ethyl Chloride (122). A solution of **121** (5.5 g, 33 mmol), 1-bromo-2-chloroethane (16.4 g, 114 mmol), and K_2CO_3 (16 g, 114 mmol) in 2-butanone (60 mL) was heated to reflux for 24 h. The mixture was poured into water (150 mL), extracted with CH_2Cl_2 (3 × 150 mL), and washed with brine (3 × 100 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 5.74 g (75%) of product as a white solid: mp 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.97−2.00 (m, 2H), 2.76 (t, J = 6.6 Hz, 2H), 3.82 (t, J = 6.2 Hz, 2H), 4.21−4.24 (m, 4H), 6.40−6.44 (m, 1H), 6.47−6.50 (m, 1H). Anal. ($C_{11}H_{12}FClO_2$) C, H, N.

2-(6-Fluorochroman-8-yloxy)ethylazide (123). A solution of **122** (4.13 g, 0.018 mol) and sodium azide (2.33 g, 0.036 mol) in anhydrous DMF (60 mL) was allowed to stir at 60 °C for 18 h. The mixture was poured into water (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was washed with water (3 × 100 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (20% EtOAc−hexanes) afforded 4.12 g (97%) of product as a clear oil: H NMR (400 MHz, $CDCl_3$) δ 1.98 (m, 2H), 2.76 (t, J = 6.6 Hz, 2H), 3.65 (t, J = 5.5 Hz, 2H), 4.13 (t, J = 5.5 Hz, 2H), 4.22 (t, J = 5.3 Hz, 2H), 6.48 (dd, J = 9.9, 3.0 Hz, 1H), 6.42 (dd, J = 8.6, 2.8 Hz, 1H). Anal. ($C_{11}H_{12}FN_3O_2$) C, H, N.

2-(6-Fluorochroman-8-yloxy)ethylamine (124). A solution of **123** (4.12 g, 0.017 mol) and triphenylphosphine (6.83 g, 0.026 mol) in THF (80 mL) and water (1.5 mL) was allowed to stir for 18 h at room temperature. The solvent was removed under vacuum and the product purified by chromatography (EtOAc removed triphenylphosphine and triphenylphosphine oxide and 40% MeOH−CH_2Cl_2 plus NH_4OH) afforded 3.45 g (94%) as a white solid: mp 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (m, 2H), 2.75 (t, J = 6.6 Hz, 2H), 3.10 (t, J = 5.3 Hz, 2H), 3.98 (t, J = 5.3 Hz, 2H), 4.10 (t, J = 5.3 Hz, 2H), 6.37 (dd, J = 8.8, 3.0 Hz, 1H), 6.47 (dd, J = 10.1, 2.9 Hz, 1H). Anal. ($C_{11}H_{14}FNO_2$) C, H, N.

[2-(6-Fluorochroman-8-yloxy)ethyl]-[2-(1*H*-indol-3-yl)-ethyl]amine (32). A solution of **124** (0.41 g, 2.2 mmol), 3-(2-bromoethyl)indole (0.25 g, 1.1 mmol), and triethylamine (0.23 g, 2.2 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 12 h at 90 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.15 g (34%) of product as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (m, 2H), 2.68 (t, J = 6.4 Hz, 2H), 2.83−2.98 (m, 6H), 3.99 (t, J = 5.7 Hz, 2H), 4.05 (t, J = 5.0 Hz, 2H), 6.45 (M, 1H), 6.68 (dd, J = 10.3, 2.8 Hz, 1H), 6.96 (m, 1H), 7.05 (m, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.50 (m, 1H), 10.79 (br s, 1H). The oxalate salt was prepared in ethanol: mp 213-214 °C. Anal. ($C_{21}H_{23}FN_2O_2 \cdot C_2H_2O_4$) C, H, N.

[2-(6-Fluorochroman-8-yloxy)ethyl]-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]amine (33). A solution of **124** (0.26 g, 1.1 mmol), 2-(5-fluoro-1*H*-indol-3-yl)ethylamine (0.45 g, 2.1 mmol), and triethylamine (0.30 mL, 2.1 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 14 h at 90 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under vacuum. Chromatography (10%

MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.19 g (48%) of product as a yellow oil. The oxalate salt was prepared in ethanol: mp 201−203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (m, 2H), 2.70 (t, J = 6.4 Hz, 2H), 3.01 (t, J = 8.6 Hz, 2H), 3.26 (t, J = 8.6 Hz, 2H), 3.36 (t, J = 5.1 Hz, 2H), 4.03 (t, = 5.0 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 6.54 (dd, J = 9.0, 2.9 Hz, 1H), 6.77 (dd, J = 10.3, 2.8 Hz, 1H), 6.92 (dd, J = 9.4, 2.4 Hz, 1H), 7.29−7.36 (m, 3H), 11.07 (br s, 1H). Anal. ($C_{21}H_{22}F_2N_2O_2 \cdot 1C_2H_2O_4$) C, H, N.

[2-(6-Fluorochroman-8-yloxy)ethyl]-[3-(5-fluoro-1*H*-indol-3-yl)propyl]amine (34). A solution of **122** (0.25 g, 7.1 mmol), **49** (0.42 g, 2.2 mmol), and triethylamine (0.22 g, 2.2 mmol) in anhydrous DMSO (20 mL) was allowed to stir for 14 h at 90 °C. The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water (3 × 150 mL), dried over anhydrous NaS_2O_4, and filtered, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2 plus NH_4OH) afforded 0.25 g (60%) as a white solid: mp 137−138.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79−1.89 (m, 4H), 2.66−2.71 (m, 4H), 2.77 (t, J = 7.0 Hz, 2H), 3.01 (t, J = 5.5 Hz, 2H), 4.03−4.08 (m, 4H), 6.49 (dd, J = 9.2, 3.1 Hz, 1H), 6.71 (dd, J = 10.5, 2.8 Hz, 1H), 6.88 (td, J = 9.2, 2.6 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 10.1, 2.6 Hz, 1H), 7.32 (dd, J = 8.8, 4.4 Hz, 1H), 10.87 (br s, 1H). The oxalate salt was prepared in 2-propanol: mp 214−215 °C. Anal. ($C_{22}H_{24}F_2N_2O_2 \cdot 1.5C_2H_2O_4$) C, H, N.

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