Heterocyclic Analogues of *N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)butyl)arylcarboxamides with Functionalized Linking Chains as Novel Dopamine D3 Receptor Ligands: Potential Substance Abuse Therapeutic Agents

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Dopamine D3 receptor antagonists and partial agonists have been shown to modulate drug-seeking effects induced by cocaine and other abused substances. Compound **6** [PG01037, (*N*-(4-(4-(2,3-dichlorophenyl)-piperazin-1-yl)-*trans*-but-2-enyl)-4-pyridine-2-ylbenzamide)] and related analogues are currently being evaluated in animal models of drug addiction. In these studies, a discrepancy between in vitro binding affinity, in vivo occupancy, and behavioral potency has been observed. The purpose of this study was to examine (1) modifications of the 2-pyridylphenyl moiety of **6** and (2) hydroxyl, acetyl, and cyclopropyl substitutions on the butylamide linking chain systematically coupled with 2-fluorenylamide or 2-pyridylphenylamide and 2-methoxy- or 2,3-dichloro-substituted phenylpiperazines to measure the impact on binding affinity, D2/D3 selectivity, lipophilicity, and function. In general, these modifications were well tolerated at the human dopamine D3 (hD3) receptor ($K_i = 1-5$ nM) as measured in competition binding assays. Several analogues showed >100-fold selectivity for dopamine D3 over D2 and D4 receptors. In addition, while all the derivatives with an olefinic linker were antagonists, in quinpirole-stimulated mitogenesis at hD3 receptors, several of the hydroxybutyl-linked analogues (**16**, **17**, **21**) showed partial agonist activity. Finally, several structural modifications reduced lipophilicities while retaining the desired binding profile.

Introduction

Nicotine, alcohol, cocaine, methamphetamine, and the opiates can stimulate brain reward pathways that may lead to abuse and addiction.[1] The dopamine receptor system plays a key role in numerous neuropsychiatric and neurological disorders, and investigation into mechanistic underpinnings and neuroadaptations within this family of receptors has been the focus of intensive research over the past decade. Recently, the dopamine D2-like receptor subtypes (D2, D3, D4) have been studied using imaging techniques in animal models as well as in human addicts to further delineate the molecular mechanisms responsible for the reinforcing effects of psychostimulants.[2−5]

In this pursuit, the dopamine D3 receptor subtype has been hypothesized to play a fundamental role in the abuse-related effects of cocaine and other drugs of abuse.[6−9] Hence, the need to develop novel, selective, and bioavailable dopamine D3 receptor ligands has been recently emphasized.[7,10−12] Further support for pursuing dopamine D3 receptor selective ligands as potential medications for drug abuse and addiction comes from the brain localization of D3 receptors, which are primarily expressed in limbic regions of the brain, including the nucleus accumbens. It has been hypothesized that D3 receptor blockade may antagonize drug reward and/or reinforcement while avoiding the risk of extrapyramidal side effects associated with the blockade of the more ubiquitous D2 receptors.[13]

The high degree of amino acid homology[13,14] within the binding sites of the dopamine D2-like receptors, especially between the D2 and D3 dopamine receptor subtypes, has provided a formidable challenge in the pursuit to discover dopamine D3-selective compounds. Thus far, high dopamine D2/D3 selectivity has typically been achieved with relatively large molecules characterized by a heterocyclic moiety bridged by an unsubstituted four-carbon chain or carbocycle to an extended or substituted arylamide or a corresponding bioisostere.[7,11] Arylcarboxylamides connected through a butyl chain to a 2,3-dichloro- or 2-methoxy-substituted phenylpiperazine such as the compounds **2**−**4** depicted in Figure 1 are well-studied examples of dopamine D3 receptor preferring compounds. Analogues **5** and **6** featuring a *trans*-butenyl linker with 2,3-dichlorophenylpiperazine have also been examined and found to display improved D2/D3 selectivity ratios compared to their saturated butyl counterparts.[15] The *trans*-cyclohexyl derivatives of the 4-phenylpiperazines also showed promising dopamine D3 receptor affinities.[16] However, the incorporation of shorter and longer linkers such as propyl and pentyl resulted in reduced dopamine D3 receptor affinity and/or selectivity over dopamine D2 or D4 receptors[17−19]

In addition to optimizing pharmacological selectivity, it is also important that these novel compounds be able to penetrate the blood brain barrier (BBB) and have appropriate pharmacokinetics to facilitate interpretation of in vivo results. Compounds **4** and **6** have been evaluated for D3 function in animal models of cocaine abuse and demonstrate D3 antagonism in vivo.[20,21] However, it has been our observation that relatively high doses of these as well as other D3-selective agents including **1** and **3** (Figure 1) are required for behavioral activity.[20,22,23] It is not known whether these required high doses are due to a low permeability surface area product of these agents for crossing the BBB, high peripheral metabolism, large uptake in some other

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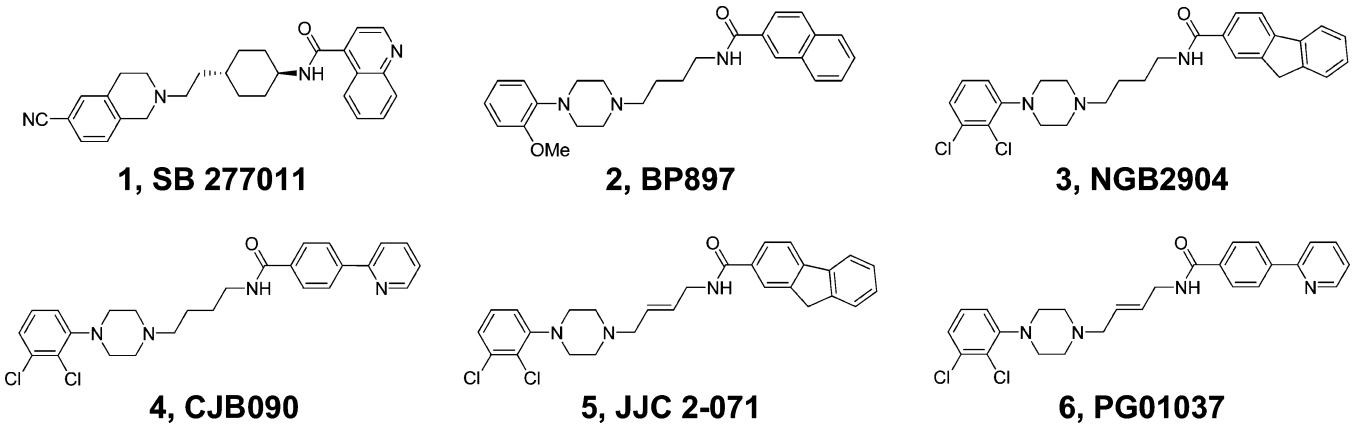


Figure 1. Selective pharmacological tools for the dopamine D3 receptor.

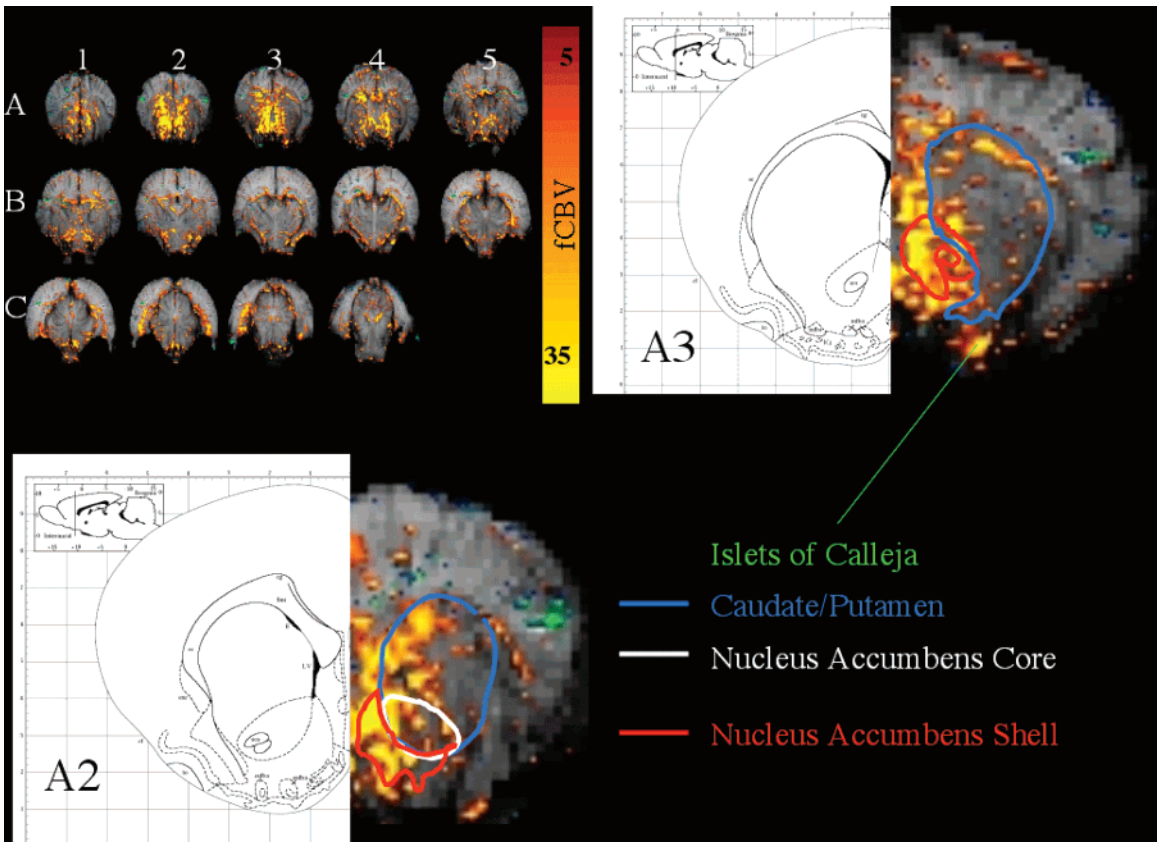


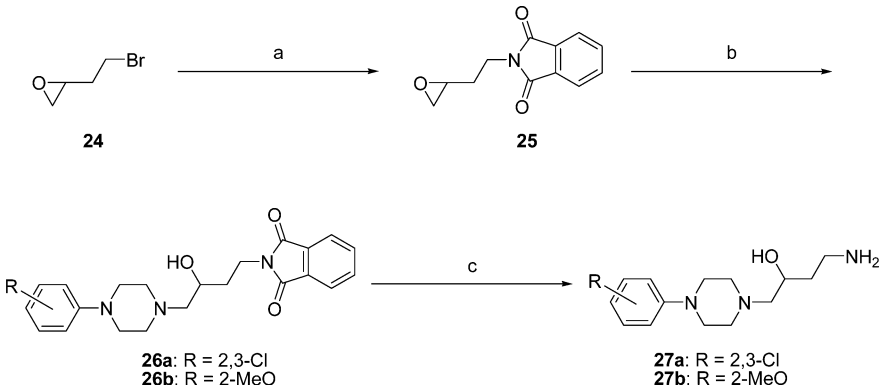
Figure 2. Maps of the hemodynamic response (rCBV) to 2 mg/kg iv compound **6** in a rat. The slices cover an anterior to posterior direction from Bregma +2.2 to −8.3. The color map shows statistically significant changes in cerebral blood volume (CBV). Also shown on the bottom left and top right are zoomed slices A2 and A3 with an overlay from a Paxinos atlas corresponding to the appropriate slices. The D3 antagonist produces rCBV changes in nucleus accumbens, islets of Calleja, and hippocampus consistent with the D3 receptor distribution. Note that there is little activation in the caudate/putamen showing great selectivity of D3 over D2 receptors.

organ or compartment, or alternative mechanisms. Preliminary evaluation of compound **6** and several related analogues for activity in the spot Ames test and Herg assay and for CaCo-2 absorption potential suggests that these compounds may be candidates for clinical development (personal communication with Dr. Jane Acri). Nevertheless, their restricted aqueous solubility may limit the validity of these predictive tests, and thus, investigating structural modifications that retain the desired pharmacological profile while reducing lipophilicity will likely improve water solubility and other physicochemical properties.

Pharmacologic Magnetic Resonance Imaging (phMRI)

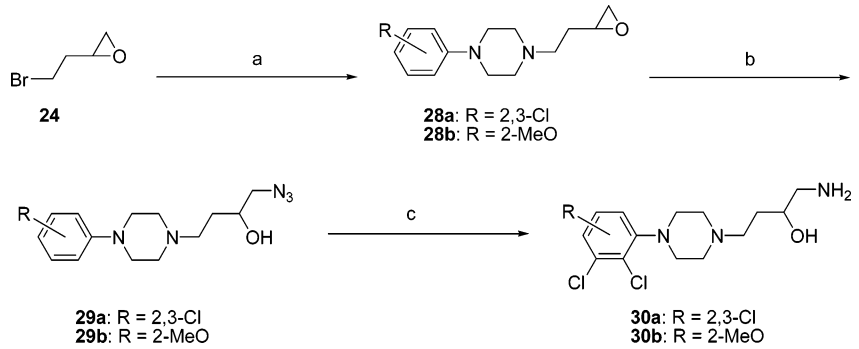
Pharmacologic magnetic resonance imaging studies (phMRI) were undertaken to determine whether or not compound **6** was entering the brain and occupying dopamine D3 receptor rich regions using previously published methods.[24,25] At a dose of 1.0 or 2.0 mg/kg (iv), **6** readily entered the brain and was localized in D3 receptor rich brain regions such as the islets of Calleja and the nucleus accumbens shell while eliciting much smaller changes in the caudate/putamen consistent with the much higher ratio of D3 receptors in the accumbens compared to the caudate/putamen[13] (Figure 2). In addition, the increases in regional cerebral blood volume (rCBV) in these regions established this agent as a D3 antagonist, comparable to **1**[26] because D3 and D2 agonists lead to decreases in rCBV and D2/D3 antagonists lead to increases in rCBV.[24,25] In Figure 2, the average of five rats at a dose of 2 mg/kg iv of compound **6** is shown. In these animals the average rCBV change integrated

Scheme 1. Synthesis of the 3-Hydroxylamines **27**[a]



[a] Reagents and conditions: (a) phthalimid potassium salt, DMF, microwave, 100 °C, 20 min; (b) 1-(2,3-dichlorophenyl)- or 1-(2-methoxyphenyl)piperazine, 2-PrOH, microwave, 90 °C, 20 min; (c) hydrazine, ethanol, microwave, 90 °C, 20 min.

Scheme 2. Synthesis of the 2-Hydroxylamines **30**[a]



[a] Reagents and conditions: (a) 1-(2,3-dichlorophenyl)- or 1-(2-methoxyphenyl)piperazine, potassium carbonate, acetone, reflux, 24 h; (b) sodium azide, ammonium chloride, DMF, 100 °C; 5 h; (c) triphenylphosphine, THF, room temperature, 16 h.

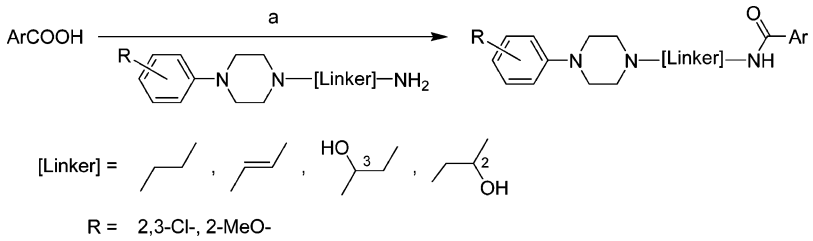
from 0 to 30 min was 8.9% in the accumbens versus 3.2% in the caudate/putamen (a ratio of 2.8). In addition, there was significant activation in the hippocampus as expected based on D3 receptor expression.[27] It was noted that there was an apparent discrepancy between the dose of compound **6** required for behavioral activity (e.g., 30−56 mg/kg)[20] compared to the dose that showed D3 receptor blockade in the phMRI studies. Although the behavioral studies used the sc route of administration while the phMRI studies used the iv route, there still seemed to be a significant dose difference. These results combined with the high D3 receptor affinity (K_i(D3) = 0.7 nM) in vitro suggested that either suboptimal pharmacokinetics were responsible or another mechanism may be involved in the behavioral actions of these dopamine D3 receptor antagonists.

In order to further address these possibilities, new ligands were designed with modifications of the amide linking chain incorporated to preserve and/or increase high affinity and dopamine D3 receptor selectivity while potentially improving the pharmacokinetics of these agents. Thus far, the optimal length and conformation of the linking chains have been established, but appended functionality on the linker has not been explored except recently.[19] The high lipophilicity of these drugs was our primary concern, and as such, we considered substitutions that might provide some additional polarity and thus reduce lipophilicity.[28] Using the established pharmacophore of the dopamine D3 selective ligands **3**[29] and **6**,[15] and the 2-methoxy substituted phenylpiperazine moiety, first introduced in the D3 partial agonist, **2**[13] (Figure 1), we investigated systematic substitutions on the saturated butyl linking chain while comparing the 2-methoxy- and 2,3-dichloro-substituted phenylpiperazines and the 2-pyridylphenyl to the 2-fluorenyl ring systems in the arylamide portion of the molecule. Several substitution patterns on the 2-pyridyl group of **6** were also investigated. Binding data at human dopamine D2-like receptors and D2/D3 selectivity for all analogues were compared to those for the parent ligands. For selected compounds, D2 and D3 functional data using the quinpirole-stimulated mitogenesis assay and binding data for the serotonin receptors $5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$ were also obtained.

Chemistry

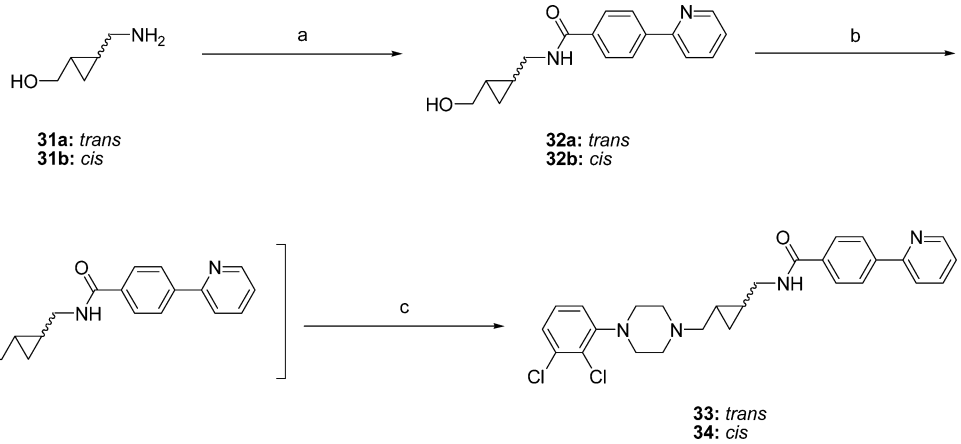
The racemic hydroxybutylamine intermediates **27** and **30** needed to prepare the 3-hydroxy derivatives **16**−**19** and 2-hydroxy analogues **21**−**23** were synthesized as depicted in Schemes 1 and 2. In both cases, the synthetic routes used bifunctional 2-(2-bromoethyl)oxirane (**24**)[30] as starting material. All key steps were found to be regioselective, and only the products depicted were isolated. The amines **27** (Scheme 1) were synthesized via a modified Gabriel synthesis. No side products were observed in the alkylation reaction to form the phthalimide **25**. The opening of the oxirane moiety occurred selectively at the least substituted side to yield the 3-hydroxyphthalimides **26**, which were then deprotected with hydrazine to afford the hydroxylamines **27**. In the case of the 2-hydroxylamines (**30**, Scheme 2) the butylpiperazine bond was formed first, followed by a regioselective opening of the epoxide with sodium azide and a Schlesinger-type reduction. The general reaction sequence was used to prepare the dopamine D3 receptor preferring analogues **2**−**23** incorporating a butyl, butenyl, or hydroxybutyl linking chain as depicted in Scheme 3. The required carboxylic acids were prepared according to literature procedures.[17,31] The general syntheses of the butylamines and the butenylamines have been described earlier.[15,17,32,33] Because of constraints of readily available starting material, the synthesis of the cyclopropyl

Scheme 3. Synthesis of Compounds **2**−**23**[a]



[a] Reagents and conditions: (a) CDI, pyridine or DCC, HOBt, DMF. **13** was prepared from **6** by N-oxidation (mCPBA, CH_2Cl_2, room temperature, 16 h). **20** was prepared from **16** by acetylation (NEt_3, CH_3COCl, room temperature, 16 h).

Scheme 4. Synthesis of the Dimethylcyclopropyl Analogues **33** and **34**[a]



[a] Reagents and conditions: (a) CDI, 4-pyridin-2-ylbenzoic acid, pyridine, room temperature; (b) trifluoromethanesulfonic anhydride, CH_2Cl_2, room temperature, 4 h; (c) 2,3-dichlorophenylpiperazine, sodium bicarbonate, acetonitrile, reflux, 16 h.

derivatives **33** and **34** (Scheme 4) featured a formation of the amide bond prior to the addition of the phenylpiperazine moiety. Both the *trans* amide **32a** and its *cis* isomer **32b** were prepared from the corresponding cyclopropylamines **31**.[34] Conversion of the hydroxyl group to a triflate leaving group followed by alkylation with 2,3-dichlorophenylpiperazine gave the isomeric cyclopropyl derivatives **33** and **34** in good yield.

Pharmacological Results and Discussion

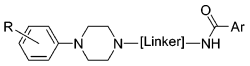
All ligands were evaluated in competition binding assays in HEK 293 cells transfected with human $D2_L$, D3, or D4 dopamine receptors.[15] The displaced radioligand was the high-affinity, selective D2-like receptor antagonist 2,3-dimethoxy-5-((^{125}I)-iodo-*N*-(9-benzyl-9-azabicyclo(3.3.1)nonan-3-yl) benzamide (^{125}I-IABN).[35] In addition, clogP values and polar surface areas (PSA) were calculated to provide a measure of lipophilicity and predicted brain penetration, respectively.[36,37] These data are presented in Table 1. Selected compounds were also evaluated in a quinpirole-stimulated mitogenesis assay for functional activity at dopamine D2 and D3 receptors (Table 2) and for binding affinities at the serotonin $5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$ receptors (Table 3).

Substituent effects at the 2-pyridyl moiety of **6** on D2 and D3 receptor binding affinities and D2/D3 selectivities were examined with analogues **9**−**12**. As depicted in Table 1, the 6-oxa derivative **9** was equiactive to **6** at D3 receptors. However, **9** had a 4-fold higher affinity at dopamine D2 receptors, resulting in a lower D2/D3 selectivity ratio than **6**. On the other hand, compared to **6**, the 6-methyl substituted analogue **10** had little effect on binding at either dopamine D2 or dopamine D3 receptors. Indeed, the effects of the 6-methyl substitution were mostly directed toward the serotonin $5HT_{1A}$ subtype (Table 3). Compound **10** showed a nearly 4-fold lower binding affinity than **6** and thus a 221-fold $5HT_{1A}$/D3 selectivity. Interestingly, compared to **6** (IC_{50}(D2) = 80.0 nM), the 6-methyl substituted analogue **10** was 16-fold less potent at the dopamine D2 receptor (EC_{50}(D2) = 1300 nM), making it the most functionally D3 selective analogue (194-fold) in the series (Table 2).

Pyridyl N-oxidation (**12**) retained high dopamine D3 affinity (K_i = 1.1 nM) comparable to the parent compound **6**. However, as was observed with the 6-oxa analogue **9**, an oxa modification of the pyridyl moiety led to a 4-fold higher binding affinity for **12** at the dopamine D2 receptor compared to **6**, thus reducing D2/D3 selectivity (3-fold). In contrast, the 1-piperazine *N*-oxide **13** showed a 70-fold lower binding affinity at the dopamine D3 receptor and a 12-fold lower binding affinity at the dopamine D2 receptor. Hence, these results show that while the oxidation products of the pyridyl moiety negatively affect D2/D3 selectivity, oxidation of the 1-nitrogen of the piperazine ring is most detrimental to high binding affinity at both D2 and D3 receptors. These analogues could be oxidative metabolites of **6**, and thus this information may be important for determining pharmacological effects due to drug metabolism in vivo.

The olefinic linked derivatives with the 2-methoxy substituted phenylpiperazine (**14** and **15**) were less D2/D3 selective (up to 6-fold) than their corresponding 2,3-dichloro analogues (**6** and **5**). For example, the 2-methoxyphenyl analogue **14** demonstrated a 4-fold lower binding affinity at the dopamine D3 receptor than the corresponding 2,3-dichloro derivative **6**. On the other hand, in the fluorenylamide series the 2-methoxy compound **15** had a >3-fold higher binding affinity at the dopamine D2 receptor than the 2,3-dichloro analogue **5**, while the binding affinity at the dopamine D3 receptor was unaffected by this modification. The compounds with a saturated butyl linking chain showed similar structure−activity relationships (SAR). No difference was observed in the

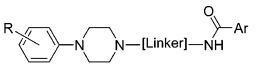
Table 1. Human D_2-like Family Receptor Subtype Binding Data in HEK Cells



Compd.	Ar	[Linker]	R	clogP	PSA	D2	D3	D4	D2/D3	D4/D3
						K_i (nM) ± SEM				
3 (NGB2904)			2,3-diCl	5.5	35.6	112 ± 22	2.0 ± 0.4	ND	56	-
4 (CJB090)			2,3-diCl	4.9	48.5	24.8 ± 8.6	0.4 ± 0.2	ND	50	-
5 (JJC 2-071)			2,3-diCl	6.0	35.6	168 ± 29	1.5 ± 0.1	1020 ± 160	112	680
6 (PG01037)			2,3-diCl	4.8	48.5	93.3 ± 12	0.7 ± 0.1	375 ± 18	133	540
7			2-OCH_3	4.5	44.8	55.4 ± 5.2	0.3 ± 0.1	425 ± 3	185	1420
8			2-OCH_3	3.4	57.7	28.3 ± 6.4	0.4 ± 0.1	ND	71	-
9			2,3-diCl	3.5	77.7	23.6 ± 5.7	0.6 ± 0.1	ND	39	-
10			2,3-diCl	5.4	48.5	105 ± 24	1.4 ± 0.3	ND	75	-
11			2,3-diCl	5.2	48.5	92 ± 9.4	1.6 ± 0.4	ND	58	-
12			2,3-diCl	3.1	70.3	25.8 ± 3.1	1.1 ± 0.3	ND	23	-
13			2,3-diCl[a]	5.0	71.5	1160 ± 230	49.2 ± 9.3	ND	24	-
14			2-OCH_3	3.3	57.7	69 ± 13	2.9 ± 1.1	ND	24	-
15			2-OCH_3	4.5	44.8	48.4 ± 7.3	1.2 ± 0.1	ND	40	-
16			2,3-diCl	4.4	68.7	267 ± 20	3.0 ± 0.2	4620 ± 200	89	1540
17			2,3-diCl	5.6	55.8	319 ± 54	1.8 ± 0.0	16400 ± 2600	177	9110
18			2-OCH_3	2.8	77.9	284 ± 48	2.8 ± 0.8	1490 ± 150	101	532
19			2-OCH_3	3.9	65.0	249 ± 14	1.8 ± 0.3	1230 ± 330	138	683
20			2,3-diCl	5.3	74.8	134 ± 28	11.7 ± 1.0	ND	11	-
21			2,3-diCl	4.3	68.7	28.4 ± 6.4	0.5 ± 0.1	ND	57	-
22			2,3-diCl	5.5	55.8	84 ± 5.3	2.5 ± 0.3	ND	34	-
23			2-OCH_3	3.8	65.0	68.4 ± 6.4	1.3 ± 0.4	ND	53	-
33			2,3-diCl	4.8	48.5	53.7 ± 1.0	1.0 ± 0.2	ND	54	-
34			2,3-diCl	4.8	48.5	1050 ± 90	160 ± 30	1460 ± 120	7	9

[a] 4-(2,3-Dichlorophenyl)piperazine 1-oxide.

Table 2. In Vitro Functional Data at D_2-like Receptors for Selected Ligands[a]



Compd.	Ar	[Linker]	R	D2	D3
				IC_{50} (nM)	
3 (NGB2904)			2,3-diCl	1280 ± 270	14.4 ± 0.5
4 (CJB090)			2,3-diCl	92.0 ± 4.9 (20)[b]	6.3 ± 1.7 (30)[b]
5 (JJC 2-071)			2,3-diCl	ND	173 ± 9.6 (44)[b,c]
6 (PG01037)			2,3-diCl	80.9 ± 6.7	3.0 ± 0.7
7			2-OCH_3	224 ± 80	2.2 ± 0.8
8			2-OCH_3	107 ± 18 114 ± 9.5 (17)[b]	2.9 ± 1.0
9			2,3-diCl	41 ± 8	1.0 ± 0.2
10			2,3-diCl	1300 ± 320	6.7 ± 2.6
11			2,3-diCl	368 ± 113	25.6 ± 8.5
12			2,3-diCl	22.9 ± 2.0 231 ± 1 (31)[b]	1.2 ± 0.0
14			2-OCH_3	175 ± 17	42.6 ± 7.9
15			2-OCH_3	179 ± 48	18.9 ± 4.2
16			2,3-diCl	15.8 ± 2.7 (26)[b]	1.0 ± 0.1 (48)[b]
17			2,3-diCl	ND	42.0 ± 1.3 (26)[b]
18			2-OCH_3	ND	12.8 ± 1.3
20			2,3-diCl	ND	3.9 ± 1.4 (47)[b]
21			2,3-diCl	88.3 ± 16	5.4 ± 1.8 3.4 ± 0.5 (20)[b]
33			2,3-diCl	672 ± 66 150 ± 36 (17)[b]	14.3 ± 2.6

[a] Data were obtained through the NIDA Addiction Treatment Discovery Program contract with SRI (N01DA-1-8816). [b] Partial agonist activity: EC_{50} (% stimulation). [c] This compound is a very weak partial agonist and likely functions as an antagonist in vivo.

binding profile at dopamine D2 and D3 receptors within the saturated 2-pyridylphenyl analogues **4** and **8**, regardless of the substituent on the phenylpiperazine. However, the 2-methoxyfluorenyl derivative **7** was found to have both high affinity at the dopamine D3 receptor (K_i(D3) = 0.3 nM) and lower affinity at D2 (K_i = 55.4 nM), resulting in the highest (185-fold) D2/D3 selectivity ratio of the series.

Pairs of D3 compounds with an aliphatic linker and varied substituents on the phenylpiperazine (2-methoxy vs 2,3-dichloro) have been synthesized previously, and for example, Chu et al. have demonstrated that the 2-benzofuranylamides showed no difference in binding profiles regardless of the substitution of the phenylpiperazine.[38] On the other hand, Bettinetti et al.,[18] using somewhat different assay conditions, reported a more than 3-fold higher binding affinity at the dopamine D2 receptors for the 2-methoxy compared to the 2,3-dichloro analogues for the same compounds, while the binding affinities at the dopamine D3 receptor were unaffected. On the basis of these and the present studies, it is clear that both the 2-methoxy and the 2,3-dichlorophenyl substitutions give high D3 binding affinities and, depending on the linking chain and the nature of the arylamide, varying selectivities over the other dopamine and serotonin receptors are achieved. These findings are important for radioligand and imaging agent development[39−41] but may also affect ligand selection for in vivo studies, as the most D3-selective compound might not be the best candidate if other physicochemical properties are determined to be superior for another analogue.[42]

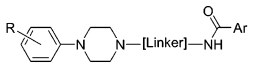
In the mitogenesis assay (Table 2), both fluorenylamides **3** and **7** were determined to be antagonists at D3 receptors, and corresponding with the binding data, the 2-methoxyphenylpiperazine **7** (IC_{50}(D3) = 2.2 nM) was 7 times more potent functionally than the corresponding 2,3-dichloro substituted analogue **3** (IC_{50}(D3) = 14.4 nM). Incidentally, **3** and **7** were found to have similar D2/D3 selectivities of 89-fold and 102-fold, respectively, in the mitogenesis assay. In contrast to the 2,3-dichloro substituted partial agonist **4**, the corresponding 2-methoxy derivative **8** demonstrated antagonism in the functional assay at the dopamine D3 receptor.

In the 5-HT binding assays (Table 3), the 2,3-dichloro derivatives generally showed lower 5-HT_{1A} receptor binding affinities, resulting in somewhat higher 5-HT_{1A}/D3 selectivities than the corresponding the 2-methoxy analogues. However, the 2-methoxy derivatives with saturated linking chains (**7** and **8**) were at least 5-fold more 5-HT_{2C}/D3 selective than the corresponding 2,3-dichloro compounds (**3** and **4**), an observation that had been reported earlier.[38] In contrast, in the olefinic series of analogues (**14**, **6**, **15**, **5**), selectivities of the 5-HT_{2C} receptor over the dopamine D3 receptor were essentially unaffected by the substitution pattern on the phenylpiperazine moiety.

Overall, the hydroxybutyl linker was well tolerated at the dopamine D3 receptor, resulting in up to 177-fold dopamine D2/D3 selectivity (e.g., compound **17**). Binding affinities at the dopamine D3 receptor and D2/D3 selectivity of the 3-hydroxybutyl derivatives were determined by the arylamide moiety and were independent of the substitution on the phenylpiperazine (2,3-dichloro vs 2-methoxy). The 2-pyridylphenyl analogues **16** and **18** not only showed similar binding affinities at D3 receptors but also displayed no difference in binding affinity at the $5HT_{1A}$ receptor, resulting in similarly low $5HT_{1A}$/D3 selectivities (<13-fold). However, in line with the aliphatic analogues **4** and **8**, the 2-methoxy derivative **18** demonstrated 18-fold higher $5HT_{2A}$/D3 and 37-fold higher $5HT_{2C}$/D3 selectivities than **16**. Acetylation (**20**) of the hydroxyl group of **16** was not well tolerated at the dopamine D3 receptor presumably because of steric hindrance.

Compared to the 3-hydroxybutyl analogue **16**, the 2-hydroxybutyl derivative **21** was determined to have higher binding affinities at both D2 and D3 receptors, by 9- and 6-fold, respectively. Interestingly, the 2-hydroxybutyl analogue **21** and the butyl analogue **4** shared a very similar binding profile,

Table 3. Binding Affinities for Serotonin Receptor Subtypes for Selected Ligands[a]



Compd.	Ar	[Linker]	R	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$	D_3	$5HT_{1A}/D3$	$5HT_{2A}/D3$	$5HT_{2C}/D3$
				K_i(nM)						
3 (NGB2904)			2,3-diCl	2040 ± 130	679 ± 150	411 ± 120	2.0 ± 0.4	1020	340	206
4 (CJB090)			2,3-diCl	23.4 ± 6.1	22.9 ± 1.6	52.7 ± 2.2	0.4 ± 0.2	59	57	132
5 (JJC 2-071)			2,3-diCl	941 ± 110	330 ± 110	132 ± 8	1.5 ± 0.1	627	220	88
6 (PG01037)			2,3-diCl	85.4 ± 6.1	62.4 ± 7.1	47 ± 16	0.7 ± 0.1	122	89	67
7			2-OCH_3	34 ± 0.1	156 ± 0.9	326 ± 47	0.3 ± 0.1	113	520	1087
8			2-OCH_3	6.71 ± 0.3	228 ± 3.3	736 ± 23	0.4 ± 0.1	17	570	1840
9			2,3-diCl	29.7 ± 0.2	15.5 ± 3.8	10.6 ± 0.0	0.6 ± 0.1	50	26	18
10			2,3-diCl	309 ± 39	92.7 ± 16	96.4 ± 1.1	1.4 ± 0.3	221	66	69
11			2,3-diCl	92 ± 8.3	46.9 ± 5.4	31 ± 2.3	1.6 ± 0.4	58	29	19
12			2,3-diCl	60.6 ± 4.3	57.9 ± 0.6	74.3 ± 2.9	1.1 ± 0.3	55	53	68
13			2,3-diCl[b]	666 ± 34	105 ± 4.5	112 ± 4.8	49.2 ± 9.3	14	2	2
14			2-OCH_3	21.7 ± 3.5	75.3 ± 1.1	256 ± 33	2.9 ± 1.1	7	26	88
15			2-OCH_3	71.8 ± 2.1	65.7 ± 12	176 ± 14	1.2 ± 0.1	60	55	147
16			2,3-diCl	34.3 ± 0.3	42.3 ± 9.1	115 ± 20	3.0 ± 0.2	11	14	38
17			2,3-diCl	1810 ± 350	545 ± 150	2830 ± 360	1.8 ± 0.0	1006	303	1572
18			2-OCH_3	36.2 ± 7	695 ± 20	3940 ± 130	2.8 ± 0.8	13	248	1407
20			2,3-diCl	117 ± 12	88.7 ± 7.5	84.3 ± 5.3	11.7 ± 1.0	10	7	7
21			2,3-diCl	15.1 ± 2.4	15.4 ± 2.8	25.2 ± 3.2	0.5 ± 0.1	30	31	50
33			2,3-diCl	59 ± 6.4	47.1 ± 5.9	79.3 ± 12	1.0 ± 0.2	59	47	79
34			2,3-diCl	982 ± 120	883 ± 43	626 ± 40	160 ± 30	6	6	4

[a] Data were obtained through the NIDA Addiction Treatment Discovery Program contract with SRI (N01DA-1-8816). [b] 4-(2,3-Dichlorophenyl)piperazine 1-oxide.

suggesting that the 2-OH may not provide a point of contact at the receptor binding site, in potential contrast to substitution in the 3-position. This observation appears to be independent of the structure of the arylamide compared to **3**. The 2-hydroxy analogue **22** also showed a similar binding profile.

As expected, the introduction of a hydroxyl group into the butyl linking chain resulted in somewhat lower clogP values, predicting decreased lipophilicity, compared to the corresponding parent olefinic or aliphatic compounds. The calculated polar surface area (PSA)[36] was significantly increased (by 20 $Å^2$). Values less than 75 $Å^2$ are considered as being favorable for brain penetration. Coupled with their favorable binding profiles, several of these new analogues have been selected for in vivo evaluation.

The *trans*-cyclopropyl linking chain was found to be well tolerated at the dopamine D3 receptor. Compound **33** (K_i(D3) = 1.0 nM) showed a similar binding profile compared to the *trans*-olefin **6** (K_i(D3) = 0.7 nM), not only at the dopamine D3 receptor but also at the serotonin $5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$ receptors. In contrast, the *cis*-cyclopropyl analogue **34** demonstrated a 160-fold lower binding affinity at the dopamine D3 receptor than the *trans*-isomer **33**. Interestingly, the binding affinities at the dopamine D2 receptor and the serotonin receptors were somewhat less affected by the *cis* conformation of the linker, up to 19-fold lower compared to the *trans* derivative. Thus, the D2/D3 selectivity of **34** was low (7-fold), indicating that a *trans* geometry of the linker is pivotal to achieving optimal dopamine D3 affinity and D2/D3 selectivity. This correlates well with results reported earlier for other phenylpiperazines with an olefinic linking chain, where a *trans* olefin was the preferred conformation compared to the *cis* olefin.[19,33] Thus, the difference in the observed binding affinities at dopamine D3 receptors may further support the hypothesis that an extended linear arrangement is the most probable bioactive conformation of the phenylpiperazine class of dopamine D3 receptor preferring ligands.[43]

Summary and Conclusions

On the basis of the parent compounds **3** and **6**, a series of analogues were prepared to further explore SAR at dopamine D3 receptors and to optimize "druglike" properties[44] without significantly modifying the pharmacological profile. Modifications to the 2-pyridylphenylamide of **6** were generally well tolerated at D3 receptors but had a small detrimental effect on D2/D3 selectivity. The 2-methoxy vs 2,3-dichloro substitution on the phenylpiperazine moiety was equally tolerated at the dopamine D3 receptors, although modifications to the rest of the molecule caused changes in selectivities. Hydroxyl substitutions in the linking butyl chain were also well tolerated and produced one of the most selective compounds in this structural class reported to date (**17**). This substitution provided a H-bond donor moiety in a part of the molecule that did not adversely affect binding but does reduce lipophilicity, which may be important for improved solubility and permeability of these molecules for in vivo studies.[44] Limited steric tolerance at the 3-position of the linking chain was suggested on the basis of the significant decrease in binding affinity of the acetylated analogue. This corresponds to a similar finding with methyl substitution at this position[19] in a related series of dopamine D3 antagonists. The cyclopropyl analogues do not provide any improvement over the olefin analogues but served to further confirm the *trans* conformation of the linker as being optimal at dopamine D3 receptors. Both partial agonists and antagonists were identified in the mutagenesis assay for function at dopamine D3 receptors. At this time, the only consistent structural feature that predicts efficacy is structural rigidity in the linking chain. As with other D3 agents with structurally rigid linkers, such as in **1**, all of the olefins and cyclopropyl analogues were D3 antagonists, whereas compounds with saturated linkers were either antagonists or partial agonists in the mitogenesis assay. Although the arylamide portion of a similar series of molecules has been suggested to predict efficacy,[43] our combined studies of >100 related analogues to date have not confirmed this finding. Whether or not the mitogenesis or other in vitro functional tests can predict D3 efficacy in vivo will be the topic of future investigation because this information will be instructive for medication development. In summary, a series of novel high affinity and D3 selective compounds have been synthesized whose clogP and PSA values predict "druglike" properties. These compounds will provide novel tools with which to further elucidate the role of dopamine D3 receptors in drug abuse, in vivo, and may serve as leads for therapeutic agents for the treatment of addiction.

Experimental Methods

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 instrument. Proton chemical shifts are reported as parts per million (δ ppm) relative to tetramethylsilane (0.00 ppm) as an internal standard. Coupling constants are measured in hertz (Hz). Chemical shifts for ^{13}C NMR spectra are reported as δ relative to the deuterium signal of the solvent ($CDCl_3$, 77.5 ppm; CD_3OD, 49.3 ppm). Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within 0.4% of calculated values. If not stated otherwise, all final compounds were purified by column chromatography (silica gel, Merck, 230−400 mesh, 60 Å) or thin layer chromatography (silica gel, Analtech, 1000 μm) using EtOAc/$CHCl_3$ (5:5:1), 1% triethylamine or $CHCl_3$/MeOH (10:1), 1% triethylamine as an eluent. Microwave reactions were performed in a CEM Discover Labmate system equipped with a 80 mL pressure vessel. Yields and reaction conditions are not optimized. Generally, yields and spectroscopic data refer to the free base. The procedures to determine the binding affinities at the human dopamine D2-like receptors[15] and the binding affinities at the serotonin $5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$ receptors[45] and the functional mitogenesis assay[45] have been published earlier.

General Procedure for the Synthesis of Carboxylic Acid Amides. The 1-imidazole adduct appropriate carboxylic acid was reacted with the suitable secondary amine derivative as described previously.[15] The crude product was purified by chromatography, structurally characterized, and then converted into its oxalate or hydrochloride salt for biological evaluation.

***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-9*H*-fluorene-2-carboxamide (7). 7** was prepared from 9*H*-fluorene-2-carboxylic acid and 4-(4-(2-methoxyphenyl)piperazin-1-yl)butylamine[32] according to the general procedure. Yield: 74%. Mp (hydrochloride): 208−210 °C. ^{1}H NMR ($CDCl_3$): δ 1.67−1.73 (m, 4H), 2.47 (t, *J* 6.7, 2H), 2.65 (s, 4H), 3.04 (s, 4H), 3.51 (q, *J* 6.1, 2H), 3.84 (s, 3H), 3.91 (s, 2H), 6.82−6.88 (m, 4H), 6.98 (dt, *J* 7.8, 4.6, 1H), 7.35 (td, *J* 7.4, 1.2, 1H), 7.40 (t, *J* 7.0, 1H), 7.55 (d, *J* 7.0, 1H), 7.75−7.77 (m, 2H), 7.81 (d, *J* 8.0, 1H), 7.96 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 25.0, 27.9, 37.3, 40.5, 50.93, 53.9, 55.8, 58.5, 111.5, 118.6, 120.1, 121.0, 121.4, 123.4, 124.4, 125.6, 126.3, 127.4, 128.0, 133.8, 141.2, 141.6, 143.8, 144.4, 145.1, 152.7, 168.6. Anal. ($C_{29}H_{33}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-4-pyridin-2-ylbenzamide (8). 8** was prepared from 4-pyridin-2-ylbenzoic acid hydrochloride and 4-(4-(2-methoxyphenyl)piperazin-1-yl)butylamine[32] according to the general procedure. Yield: 53%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 1.67−1.74 (m, 4H), 2.49 (t, *J* 6.84, 2H), 2.67 (s, 2H), 3.07 (s, 2H), 3.51 (q, *J* 6.0, 2H), 3.84 (s, 3H), 6.83 (m, 5H), 7.26 (m, 1H), 7.73−7.79 (m, 2H), 7.89 (d, *J* 8.2, 2H), 8.06 (d, *J* 8.6, 2H), 8.71 (dt, *J* 4.7, 1.3, 1H). ^{13}C NMR ($CDCl_3$): δ 24.8, 27.9, 40.4, 50.8, 53.9, 55.8, 58.5, 111.6, 118.7, 121.3, 121.4, 123.1, 123.4, 127.4, 127.9, 135.6, 137.3, 142.5, 150.3, 152.7, 156.7, 167.8. Anal. ($C_{27}H_{32}N_4O_2 \cdot (COOH)_2 \cdot 0.75H_2O$) C, H, N.

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-*trans*-but-2-enyl)-4-(6-oxo-1,6-dihydropyridin-2-yl)benzamide (9).** A suspension of 0.12 g (0.53 mmol) of 4-(6-oxo-1,6-dihydropyridin-2-yl)benzoic acid, 0.13 g (0.64 mmol) of dicyclohexylcarbodiimide, 0.1 g (0.7 mmol) of 1-hydroxbenzotriazole hydrate in 15 mL of DMF was treated at 0 °C with 0.16 g (0.53 mmol) of 4-(4-(2,3-chlorophenyl)-piperazin-1-yl)-*trans*-but-2-enylamine[15] and 0.17 mL (1.2 mmol) of triethylamine. The reaction mixture was stirred at room temperature for 3 days and filtered. The solvent was removed in vacuo, and the residue was taken up in saturated sodium bicarbonate and $CHCl_3$. The combined organics were dried with sodium sulfate and concentrated, and the crude product was purified by thin layer chromatography. Yield: 0.10 g (38%). ^{1}H NMR ($CDCl_3$): δ 2.67

(s, 4 H), 3.06 (s, 6 H), 4.11 (m, 2H), 5.74−5.83 (m, 2H), 6.51−6.54 (m, 2H), 6.70 (t, *J* 5.3, 1 H), 6.95 (dd, *J* 6.7, 2.9, 1H), 7.11−7.17 (m, 2H), 7.50 (dd, *J* 9.1, 7.0, 1H), 7.72 (d, *J* 8.3, 2 H), 7.85 (d, *J* 8.4, 2 H). ^{13}C NMR ($CDCl_3$): δ 40.6, 50.2, 52.3, 59.4, 105.9, 17.9, 118.1, 124.1, 126.3, 126.6, 126.7, 127.0, 127.3, 130.2, 133.2, 135.0, 135.7, 141.6, 145.6, 150.4, 164.5, 167.0. Anal. ($C_{26}H_{26}Cl_2N_4O_2 \cdot 1.5(COOH)_2$) C, H, N.

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-*trans*-but-2-enyl)-4-(6-methylpyridin-2-yl)benzamide (10). 10** was prepared from 4-(6-methylpyridin-2-yl)benzoic acid hydrochloride and 4-(4-(2,3-chlorophenyl)piperazin-1-yl)-*trans*-but-2-enylamine[15] according to the general procedure. Yield: 18%. Mp (oxalate): 125−126 °C. ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 7H), 3.08 (s, 6H), 4.12 (m, 2H), 5.78−5.80 (m, 2H), 6.42 (s, br, 1H), 6.95 (d, *J* 6.7, 2.7, 1H), 7.11−7.16 (m, 3H), 7.55 (d, *J* 7.7, 1H), 7.65 (t, *J* 7.6, 1H), 7.87 (d, *J* 8.7, 2H), 8.05 (d, *J* 8.3, 2H). ^{13}C NMR ($CDCl_3$): δ 25.2, 42.0, 51.7, 53.7, 60.7, 118.3, 119.1, 122.8, 125.0, 127.5, 127.8, 127.9, 129.4, 130.2, 134.4, 134.7, 137.5, 143.1, 151.7, 156.0, 159.0, 167.4. Anal. ($C_{27}H_{28}Cl_2N_4O \cdot 2(COOH)_2$) C, H, N.

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-*trans*-but-2-enyl)-4-(3-methylpyridin-2-yl)benzamide (11). 11** was prepared from 4-(3-methylpyridin-2-yl)benzoic acid hydrochloride and 4-(4-(2,3-chlorophenyl)piperazin-1-yl)-*trans*-but-2-enylamine[15] according to the general procedure. Yield: 55%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.65 (s, 4H), 3.07−3.10 (m, 6H), 6.12 (m, 2H), 5.78−5.82 (m, 2H), 6.49 (t, *J* 5.5, 1H), 6.95 (dd, *J* 6.5, 2.9, 1H), 7.12−7.16 (m, 2H), 7.21 (dd, *J* 7.6, 4.8, 1H), 7.57−7.62 (m, 3H), 7.86 (dt, *J* 8.6, 2.0, 2H), 8.53 (dt, *J* 4.2, 0.8, 1H). ^{13}C NMR ($CDCl_3$): δ 20.4, 42.0, 51.7, 53.7, 60.7, 119.1, 123.0, 125.0, 127.3, 127.9, 129.4, 129.7, 130.3, 131.4, 134.2, 134.4, 139.2, 144.1, 147.5, 151.6, 158.0, 167.5. Anal. ($C_{27}H_{28}Cl_2N_4O \cdot 1.5(COOH)_2 \cdot 0.5C_3H_7OH \cdot 0.5H_2O$) C, H, N.

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-*trans*-but-2-enyl)-4-(pyridin-*N*-oxide-2-yl)benzamide (12). 12** was prepared from 4-(pyridin-*N*-oxide-2-yl)benzoic acid and 4-(4-(2,3-dichlorophenyl)-piperazin-1-yl)-*trans*-but-2-enylamine[15] according to the general procedure. Yield: 27%. ^{1}H NMR ($CDCl_3$): δ 2.91 (s, br, 4H), 3.06 (m, 6H), 4.07 (m, 2H), 5.71−5.82 (m, 2H), 6.93−6.96 (m, 2H), 7.12−7.15 (m, 2H), 7.27−7.31 (m, 1H), 7.36 (t, *J* 7.54, 1H), 7.45 (d, *J* 7.83, 1.74, 1H), 7.86 (m, 4H), 8.33 (d, *J* 6.65, 0.78, 1H). ^{13}C NMR ($CDCl_3$): δ 41.8, 51.4, 53.4, 60.4, 118.9, 124.8, 125.4, 126.5, 127.3, 127.7, 127.7, 128.9, 129.7, 130.3, 134.2, 135.5, 135.6, 140.7, 148.7, 151.39, 166.9. Anal. ($C_{26}H_{26}Cl_2N_4O_2 \cdot 1.5(COOH)_2$) C, H, N.

4-(2,3-Dichlorophenyl)-1-(4-(4-(pyridin-2-yl)benzamido)-*trans*-but-2-enyl)piperazine 1-Oxide (13). A solution of **6** (288 mg, 0.60 mmol) in 10 mL of dichloromethane was treated at 0 °C with *m*-chloroperbenzoic acid (0.16 g, 77%, 0.72 mmol). After being stirred for 16 h at room temperature, the reaction mixture was successively washed with saturated sodium bicarbonate solution, H_2O, and brine and dried with sodium sulfate. The volatiles were removed in vacuo, and the residue was purified by preparative thin layer chromatography. Yield: 93 mg (32%). Mp (hydrochloride): foam. ^{1}H NMR (CD_3OD): δ 3.23−3.29 (m, 4H), 3.50−3.61 (m, 4H), 3.99 (d, *J* 6.5, 1H), 4.13 (d, *J* 4.6, 1H), 6.04−6.18 (m, 2H), 7.18 (dd, *J* 7.8, 3.9, 1H), 7.24−7.28 (m, 2H), 7.40 (m, 1H), 7.91−7.93 (m, 2H), 7.99 (d, *J* 8.4, 2H), 8.06 (d, *J* 8.7, 2H), 8.64 (dt, *J* 4.8, 1.2, 1H). ^{13}C NMR ($CDCl_3$): δ 41.0, 45.5, 63.5, 72.0, 119.3, 120.0, 121.6, 123.1, 125.4, 127.0, 127.3, 127.7, 128.0, 133.8, 134.6, 137.8, 137.9, 142.2, 149.3, 150.1, 156.4, 168.3. Anal. ($C_{26}H_{26}Cl_2N_4O_2 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)-*trans*-but-2-enyl)-4-pyridin-2-ylbenzamide (14). 14** was prepared from 4-pyridin-2-ylbenzoic acid hydrochloride and 4-(4-(2-methoxyphenyl)-piperazin-1-yl)-*trans*-but-2-enylamine according to the general procedure. Yield: 65%. Mp (hydrochloride): 168−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 4H), 3.12 (s, 6H), 3.86 (s, 3H), 4.13 (m, 2H), 5.78−5.85 (m, 2H), 6.43 (m, 1H), 6.85−7.02 (m, 4H), 7.27 (s, 2H), 7.77 (s, 2H), 7.90 (d, *J* 7.5, 2H), 8.06 (d, *J* 8.1, 2H), 8.72 (d, *J* 3.1, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 41.0, 50.9, 53.7, 55.8, 60.7, 111.6, 118.7, 121.3, 121.4, 123.2, 123.5, 127.5, 127.9, 129.1, 130.5, 135.0, 137.4, 141.6, 142.7, 150.3, 152.7, 156.7, 167.4. Anal. ($C_{27}H_{30}N_4O_2 \cdot 3HCl \cdot 4H_2O$) C, H, N.

***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)-*trans*-but-2-enyl)-9*H*-fluorene-2-carboxamide (15). 15** was prepared from 9*H*-fluorene-2-carboxylic acid and 4-(4-(2-methoxyphenyl)piperazin-1-yl)-*trans*-but-2-enylamine according to the general procedure. Yield: 61%. Mp (hydrochloride): 224−226 °C. ^{1}H NMR ($CDCl_3$): δ 2.68 (s, 4H), 3.09−3.10 (m, 6H), 3.86 (s, 3H), 3.94 (s, 2H), 4.13 (m, 2H), 5.81−5.83 (m, 2H), 6.32 (t, *J* 5.4, 1H), 6.85 (dd, *J* 8.2, 1.2, 1H), 6.89−6.96 (m, 2H), 7.00 (m, 1H), 7.35 (td, *J* 7.3, 1.3, 1H), 7.40 (td, *J* 7.4, 1.6, 1H), 7.57 (d, *J* 7.4, 1H), 7.78−7.83 (m, 3H), 7.99 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 37.4, 42.0, 51.0, 53.8, 55.8, 60.8, 111.6, 118.7, 120.2, 121.0, 121.4, 123.4, 124.3, 125.7, 126.2, 127.5, 128.1, 129.3, 130.4, 133.1, 141.1, 141.7, 143.9, 144.5, 145.4, 152.7, 168.0. Anal. ($C_{29}H_{31}N_3O_2 \cdot 3HCl$) C, H, N.

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-4-pyridin-2-ylbenzamide (16). 16** was prepared from 4-pyridin-2-ylbenzoic acid hydrochloride and **27a** according to the general procedure. Yield: 52%. Mp (hydrochloride): foam. ^{1}H NMR ($CDCl_3$): δ 1.62 (m, 1H), 1.83 (m, 1H), 2.39−2.46 (m, 2H), 2.58 (m, 2H), 2.82 (m, 2H), 3.05 (s, 4H), 3.45 (m, 1H), 3.89 (m, 2H), 4.00 (s, 1H), 6.91 (dd, *J* 7.1, 2.5, 1H), 7.08−7.15 (m, 2H), 7.23 (ddd, *J* 5.89, 4.83, 2.58, 1H), 7.50 (dd, *J* 5.9, 3.7, 1H), 7.70−7.76 (m, 2H), 7.88 (d, *J* 8.3, 2H), 8.02 (d, *J* 8.3, 2H), 8.67 (dt, *J* 4.8, 1.2, 1H). ^{13}C NMR ($CDCl_3$): δ 33.7, 38.8, 51.6, 53.5, 63.9, 66.6, 118.3, 120.5, 122.3, 124.3, 126.6, 127.1, 127.1, 133.6, 134.4, 136.4, 141.5, 149.3, 150.5, 155.7, 166.3. Anal. ($C_{26}H_{28}Cl_2N_4O_2 \cdot 2HCl \cdot 0.5(2\text{-PrOH}) \cdot 1.5H_2O$) C, H, N.

***N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-9*H*-fluorene-2-carboxamide (17). 17** was prepared from 9*H*-fluorene-2-carboxylic acid and **27a** according to the general procedure. Yield: 58%. Mp (oxalate): 188−190 °C. ^{1}H NMR (oxalate, $CDCl_3$, 5% D_2O): δ 1.60−1.69 (1H, m), 1.83−1.87 (1H, m), 2.42−2.50 (2H, m), 2.61 (2H, m), 2.86−2.87 (2H, m), 3.07 (4H, s), 3.45−3.52 (1H, m), 3.87−3.94 (4H, m), 6.94−8.00 (10H, m). ^{13}C NMR (oxalate, $CDCl_3$, 5% D_2O): δ 33.6, 37.2, 38.6, 51.6, 53.5, 63.9, 66.7, 118.8, 119.9, 120.8, 124.1, 125.0, 125.4, 126.0, 127.2, 127.7, 127.8, 127.8, 133.1, 134.3, 141.0, 143.6, 144.3, 145.0, 151.3, 167.4, 167.8. Anal. ($C_{28}H_{29}Cl_2N_3O_2 \cdot (COOH)_2$) C, H, N.

***N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-4-pyridin-2-ylbenzamide (18). 18** was prepared from 4-pyridin-2-ylbenzoic acid hydrochloride and **27b** according to the general procedure. Yield: 47%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 1.63 (m, 1H), 1.84 (m, 1H), 2.43 (m, 2H), 2.64 (m, 2H), 2.88 (m, 2H), 3.11 (s, 4H), 3.46 (m, 1H), 3.86 (s, 3H), 4.94 (m, 2H), 6.86 (dd, *J* 7.4, 1.2, 1H), 6.92−6.94 (m, 2H), 7.01 (m, 1H), 7.23 (m), 7.52 (dd, *J* 5.9, 3.7, 1H), 7.74−7.79 (m, 2H), 7.91 (d, *J* 8.3, 2H), 8.05 (d, *J* 8.3, 2H), 8.71 (dt, *J* 4.8, 1.2, 1H). ^{13}C NMR ($CDCl_3$): δ 33.0, 38.3, 50.5, 53.2, 55, 63.5, 66.3, 110.9, 117.9, 120.6, 120.7, 122.4, 122.8, 126.7, 127.2, 134.6, 136.6, 140.8, 141.7, 149.6, 152.0, 156.1, 166.7. Anal. ($C_{27}H_{32}N_4O_2 \cdot 2(COOH)_2 \cdot 0.5H_2O$) C, H, N.

***N*-(3-Hydroxy-4-(4-(2-methoxyphenyl)piperazin-1-yl)-butyl)-9*H*-fluorene-2-carboxamide (19). 19** was prepared from 9*H*-fluorene-2-carboxylic acid and **27b** according to the general procedure. Yield: 45%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 1H), 1.83 (m, 1H), 2.43 (m, 2H), 2.87 (m, 2H), 3.10 (s, 4H), 3.47 (m, 1H), 3.86 (s, 3H), 3.89-3.99 (m, 6H), 6.86 (d, *J* 7.4, 1H), 6.91−6.94 (m, 2H), 7.01 (m, 1H), 7.32−7.41 (m, 2H), 7.45 (dd, *J* 5.9, 3.5, 1H), 7.55 (d, *J* 7.4, 1H), 7.77−7.83 (m, 3H), 8.00 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 33.3, 36.9, 38.5, 50.7, 55.3, 63.8, 66.6, 111.1, 118.1, 119.6, 120.5, 120.9, 123.1, 123.8, 125.2, 125.8, 126.9, 127.5, 133.0, 140.7, 141.0, 143.3, 144.0, 144.6, 152.2, 167.5. Anal. ($C_{29}H_{33}N_3O_3 \cdot (COOH)_2 \cdot H_2O$) C, H, N.

1-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-4-(4-(pyridin-2-yl)-benzamido)butan-2-yl Acetate (20). A solution of **16** (0.25 g, 0.5 mmol) in 10 mL of CH_2Cl_2 was treated with 70 μL (0.75 mmol) of acetic anhydride followed by 140 μL (1.0 mmol) of triethylamine. After being stirred for 16 h, the mixture was washed with sodium bicarbonate solution, dried with sodium sulfate, and purified by flash chromatography. Yield: 0.22 g (82%). Mp (oxalate): foam.

^{1}H NMR ($CDCl_3$): δ 1.84 (m, 1H), 2.05 (m, 1H), 2.12 (s, 3H), 2.52 (dd, *J* 13.2, 5.2, 1H), 2.65 (m, 5H), 2.99 (s, 4H), 3.25 (dq, *J* 9.7, 5.00, 1H), 3.81 (dt, *J* 12.3, 5.7, 1H), 5.19 (m, 1H), 6.89 (dd, *J* 7.7, 1.8, 1H), 7.06−7.17 (m, 3H), 7.26 (ddd, *J* 6.1, 4.8, 2.44, 1H), 7.73−7.76 (m, 2H), 7.93 (d, *J* 8.6, 2H), 8.07 (d, *J* 8.6, 2H), 8.70 (td, *J* 4.83, 1.50, 1.50, 1H). ^{13}C NMR ($CDCl_3$): δ 21.0, 32.4, 36.1, 51.3, 53.7, 61.5, 69.6, 118.6, 120.8, 122.7, 124.5, 127.0, 127.4, 127.5, 133.9, 134.7, 136.9, 142.1, 149.8, 151.1, 156.2, 167.1, 171.5, Anal. ($C_{28}H_{30}Cl_2N_4O_3 \cdot 1.5(COOH)_2 \cdot H_2O$) C, H, N.

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-hydroxybutyl)-4-(pyridin-2-yl)benzamide (21). 21** was prepared from 4-pyridin-2-ylbenzoic acid and **30a** according to the general procedure. Yield: 52%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 1.63 (ddd, *J* 14.6, 6.0, 3.4, 1H), 1.81 (dtd, *J* 14.5, 10.9, 10.8, 3.9, 1H), 2.72 (m, 6H), 3.07 (s, 4H), 3.34 (ddd, *J* 13.4, 7.6, 4.6, 1H), 3.77 (ddd, *J* 13.4, 6.7, 3.4, 1H), 4.07 (m, 1H), 6.77 (t, *J* 5.3, 1H), 6.93 (dd, *J* 7.4, 2.2, 1H), 7.13−7.19 (m, 2H), 7.28 (m, 1H), 7.76−7.81 (m, 2H), 7.91 (d, *J* 8.6, 2H), 8.07 (d, *J* 8.6, 2H), 8.72 (td, *J* 4.8, 1.4, 1.4, 1H). ^{13}C NMR ($CDCl_3$): δ 28.8, 45.8, 51.4, 53.3, 57.5, 72.7, 118.7, 120.9, 122.8, 125.0, 127.1, 127.5, 127.6, 127.7, 134.2, 134.8, 137.0, 142.2, 149.9, 150.9, 156.3, 167.3. Anal. ($C_{26}H_{28}Cl_2N_4O_2 \cdot (COOH)_2 \cdot H_2O$), C, H, N.

***N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-hydroxybutyl)-9*H*-fluorene-2-carboxamide (22). 22** was prepared from 9*H*-fluorene-2-carboxylic acid and **30a** according to the general procedure. Yield: 68%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 1.63 (m, 1H), 1.78 (m, 1H), 2.63 (s, 2H), 2.72−2.84 (m, 2H), 2.87 (s, 2H), 3.07 (s, 4H), 3.34 (m, 1H), 3.77 (ddd, 13.7, 7.0, 3.5, 1H), 3.94 (s, 2H), 4.07 (m, 1H), 6.90 (dd, *J* 5.4, 2.0, 1H), 7.12−7.18 (m, 2H), 7.36 (t, *J* 5.3, 1H), 7.37 (t, *J* 5.4, 1H), 7.41 (d, *J* 7.0, 1H), 7.81−7.82 (m, 3H), 8.00 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 28.9, 37.0, 45.9, 51.4, 53.4, 57.5, 72.8, 118.7, 119.8, 120.7, 124.0, 125.0, 125.3, 126.0, 127.1, 127.6, 127.7, 127.8, 133.0, 134.2, 140.8, 143.6, 144.2, 145.0, 150.9, 168.0. Anal. ($C_{28}H_{29}Cl_2N_3O_2 \cdot 2.5HCl \cdot 0.5EtOAc \cdot 1.75H_2O$) C, H, N.

***N*-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)-2-hydroxybutyl)-9*H*-fluorene-2-carboxamide (23). 23** was prepared from 9*H*-fluorene-2-carboxylic acid and **30b** according to the general procedure. Yield: 42%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 1.62 (ddd, *J* 9.9, 6.1, 3.4, 1H), 1.80 (m, 1H), 2.63 (s, 2H), 2.76 (m, 2H), 2.88 (s, 2H), 3.10 (s, 4H), 3.33 (ddd, *J* 13.4, 7.7, 4.5, 1H), 3.78 (ddd, *J* 13.4, 6.8, 3.4, 1 H), 3.80 (s, 3H), 3.91 (s, 2H), 4.06 (m, 1H), 6.83−6.87 (m, 2H), 6.89−6.92 (m, 2H), 7.01 (ddd, *J* 8.0, 5.8, 3.3, 1H), 7.34 (td, *J* 7.4, 1.3, 1H), 7.39 (td, *J* 7.5, 1.3, 1H), 7.55 (d, *J* 7.5, 1H), 7.79 (dd, *J* 7.9, 0.5, 1H), 7.82 (dd, *J* 8.1, 1.5, 1H), 8.00 (d, *J* 0.7, 1H). ^{13}C NMR ($CDCl_3$): δ 28.8, 36.9, 45.8, 50.6, 53.5, 55.4, 57.4, 72.6, 111.2, 118.2, 119.7, 120.6, 121.0, 123.2, 123.9, 125.2, 125.9, 127.0, 127.6, 132.9, 140.7, 140.8, 143.4, 144.0, 144.8, 152.2, 167.9. Anal. ($C_{29}H_{33}N_3O_3 \cdot (COOH)_2 \cdot 1.25H_2O$) C, H, N.

2-(Oxiran-2-yl)ethylisoindoline-1,3-dione (25). A suspension of 1.84 g (10.0 mmol) of phthalimid potassium salt in 20 mL of DMF was treated with 2.27 g (15.0 mmol) of **24**[30] in the microwave (pressure vessel, P_{max}, 150 W, cooling, 100 °C, 20 min). The cooled reaction mixture was filtered, diluted with EtOAc (20 mL), and washed with H_2O (2 × 10 mL). The organic phase was dried was sodium sulfate and the volatiles were removed in vacuo to give **25** (1.68 g, 78%) as a foam, which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 1.86 (m, 1H), 2.00 (m, 1H), 2.46 (m, 1H), 2.73 (t, *J* 3.9, 1H), 3.00 (m, 1H), 3.89 (m, 2H), 7.70−7.74 (m, 2H), 7.83−7.87 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 31.7, 35.2, 46.5, 50.4, 123.4, 132.2, 134.1, 168.4.

2-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-isoindoline-1,3-dione (26a). A sample of 2.1 g (9.0 mmol) of 1-(2,3-dichlorophenyl)piperazine in 40 mL of 2-PrOH was reacted in the microwave (pressure vessel, P_{max}, 150 W, cooling, 90 °C, 20 min) with 2.0 g (9.0 mmol) of **25**. The solvent was removed in vacuo, and the foamy residue was washed with 10 mL of 2-PrOH. Yield: 2.96 g (73%). ^{1}H NMR ($CDCl_3$): δ 1.79 (m, 2H), 2.42 (m, 2H), 2.56 (s, 2H), 2.79 (m, 2H), 3.02 (s, 4H), 3.60 (s, 1H), 3.74−3.83 (m, 3H), 6.90 (m, 1H), 7.06−7.11 (m, 2H), 7.67 (m, 2H), 7.81 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 33.9, 35.3, 51.4, 53.4, 63.8, 64.5, 118.2, 122.7, 124.1, 127.0, 131.6, 133.4, 133.4, 150.4, 167.7.

2-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)-3-hydroxybutyl)-isoindoline-1,3-dione (26b). 26b was prepared from 1-(2-methoxyphenyl)piperazine and **25** in a fashion similar to that described above for **26**. Yield: 28%. Mp: 192−194 °C. ^{1}H NMR ($CDCl_3$): δ 1.79 (q, *J* 6.8, 2H), 2.41 (m, 2H), 2.61 (s, 2H), 2.85 (s, 2H), 3.07 (s, 4H), 3.77 (m, 1H), 3.85 (s, 3H), 3.91 (m, 2H), 6.86 (d, *J* 7.0, 1H), 6.91−6.95 (m, 2H), 7.00 (m, 1H), 7.85 (dd, *J* 5.5, 3.0, 2H), 7.71 (dd, *J* 5.4, 3.1, 2H). ^{13}C NMR ($CDCl_3$): δ 33.8, 35.4, 50.9, 53.6, 55.6, 64.1, 64.7, 111.3, 118.4, 121.2, 123.2, 123.4, 132.4, 134.1, 141.4, 152.4.

4-Amino-1-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (27a). A sample of 4.48 g (10.0 mmol) of **26a** was fully dissolved in 25 mL of EtOH and treated with 0.48 g (15.0 mmol) of hydrazine in the microwave (pressure vessel, P_{max}, 150 W, cooling, 90 °C, 20 min). The cooled reaction mixture was filtered, and the filtrate was evaporated in vacuo. Both the distillation residue and the initial precipitate were partitioned between $CHCl_3$ and 20% potassium carbonate solution. The layers were separated and the aqueous layer was dried with sodium sulfate to give the title compound as an oil, which was used without further purification. Yield: 2.25 g (71%). ^{1}H NMR ($CDCl_3$): δ 1.56 (m, 2H), 2.40 (m, 2H), 2.61 (s, 2H), 2.80 (s, 2H), 2.97−3.05 (m, 9H), 3.89 (m, 1H), 6.92 (dd, *J* 6.3, 3.1, 1H), 7.09−7.14 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 37.4, 39.7, 51.5, 53.6, 64.5, 66.3, 118.3, 124.2, 127.1, 133.5, 150.6.

4-Amino-1-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (27b). 27b was prepared from **26b** in a fashion similar to that described above for **27a**. Yield: 69%. Wax. ^{1}H NMR ($CDCl_3$): δ 1.59 (m, 2H), 2.41 (m, 2H), 2.57 (m, 2H), 2.79−2.81 (m, 9H), 3.86 (s, 3H), 3.91 (m, 1H), 6.86 (d, *J* 7.5, 1H), 6.91−6.96 (m, 2H), 6.98−7.03 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 37.3, 39.7, 50.9, 53.6, 55.5, 64.5, 66.2, 111.2, 118.3, 121.1, 123.1, 141.3, 152.3.

1-(2,3-Dichlorophenyl)-4-(2-(oxiran-2-yl)ethyl)piperazine (28a). An amount of 2.31 g (10.0 mmol) of 1-(2,3-dichlorophenyl)-piperazine was added to a suspension of 2.27 g (15.0 mmol) of **24** and 4.15 g (30.0 mmol) of potassium carbonate in 150 mL of acetone, and the reaction mixture was refluxed for 24 h. The reaction mixture was filtered and the volatiles were removed in vacuo to give an oil (2.86 g, 95%), which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 1.72 (m, 1H), 1.83 (m, 1H), 2.53 (dd, *J* 5.0, 2.7, 1H), 2.61 (ddd, *J* 8.3, 6.5, 3.0, 2H), 2.66 (s, 4H), 2.79 (dd, *J* 4.9, 4.0, 1H), 3.01 (m, 1H), 3.07 (s, 4H), 6.96 (dd, *J* 6.5, 3.1, 1H), 7.11−7.19 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 30.2, 47.1, 51.0, 51.4, 53.3, 55.0, 118.6, 124.6, 127.5, 134.0, 151.3.

1-(2-Methoxyphenyl)-4-(2-(oxiran-2-yl)ethyl)piperazine (28b). 28b was prepared from **24** and 1-(2-methoxyphenyl)piperazine in a fashion similar to that described above for **28a**. Yield: 87%. ^{1}H NMR ($CDCl_3$): δ 2.60 (m, 2H), 2.67 (s, 4H), 2.78 (dd, *J* 4.9, 4.0), 3.00 (m, 1H), 3.10 (s, 4H), 3.86 (s, 3H), 6.86 (dd, *J* 7.8, 1.3, 1H), 6.88−7.03 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 30.2, 47.2, 50.7, 51.0, 53.5, 55.2, 55.4, 111.2, 118.3, 121.1, 123.0, 141.4, 152.3.

1-Azido-4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (29a). A suspension of 0.75 g (2.5 mmol) of **28a**, 0.24 g (3.8 mmol) of sodium azide, and 0.27 g (5.0 mmol) of ammonium chloride in 5 mL of DMF was heated at 100 °C for 5 h. The reaction mixture was partitioned between 10 mL of $CHCl_3$ and 10 mL of H_2O. The aqueous organic layer was extracted twice with 10 mL of $CHCl_3$ and dried over sodium sulfate, and the volatiles were removed in vacuo. The residue was purified by flash chromatography to give **29a** as an oil. Yield: 0.44 g (51%). ^{1}H NMR ($CDCl_3$): δ 1.56 (ddd, *J* 14.7, 6.5, 3.4, 1H), 1.81 (m, 1H), 2.62 (s, 2H), 2.75 (m, 2H), 2.87 (s, 2H), 3.07 (s, 4H), 3.27 (dd, *J* 5.1, 1.4, 2H), 4.04 (dtd, *J* 7.9, 5.3, 2.6, 1H), 6.52 (s, 1H), 6.93 (dd, *J* 7.2, 2.4, 1H), 7.12−7.19 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 28.4, 51.3, 53.3, 56.5, 57.3, 73.0, 118.7, 124.9, 127.6, 134.1, 150.9.

1-Azido-4-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (29b). 29b was prepared from **28b** in a fashion similar to that described above for **29a**. Yield: 15%. ^{1}H NMR ($CDCl_3$): δ 1.55 (ddd, *J* 14.6, 6.7, 3.6, 1H), 1.80 (m, 1H), 2.62 (s, 2H), 2.74 (m, 2H), 2.89 (s, 2H), 3.09 (s, 4H), 3.24 (dd, *J* 11.6, 4.1, 1H), 3.29 (dd, *J* 11.6,

4.9, 1H), 3.86 (s, 3H), 4.03 (dtd, *J* 9.8, 5.5, 2.5, 1H), 6.86 (d, *J* 8.0, 1H), 6.89−6.95 (m, 2H), 7.01 (ddd, *J* 8.0, 5.1, 4.1, 1H). ^{13}C NMR ($CDCl_3$): δ 28.4, 50.7, 53.5, 53.5, 55.4, 56.6, 57.4, 73.0, 111.2, 118.3, 121.1, 123.2, 140.9, 152.3.

1-Amino-4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (30a). A solution of **29a** (0.41 g, 1.2 mmol) and 1.87 g (7.2 mmol) of triphenylphosphine in 20 mL of a THF/H_2O mixture (10:1 v/v) was stirred at room temperature for 16 h. The volatiles were removed in vacuo and the residue was taken up in 2-PrOH (5 mL) and treated with ethereal hydrochloric acid to give the desired amine as a hydrochloride (0.33 g, 77%). ^{1}H NMR ($CDCl_3$): δ 1.53 (ddd, *J* 14.5, 6.8, 4.0, 1H), 1.71 (m, 1H), 2.61 (s, 2H), 2.65−2.77 (m, 4H), 2.84 (s, 2H), 3.07 (m, 4H), 3.77 (m, 1H), 6.93 (dd, *J* 7.0, 2.5, 1H), 7.12−7.17 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 29.0, 48.3, 51.3, 53.3, 74.9, 118.6, 124.8, 127.5, 134.0, 150.9.

1-Amino-4-(4-(2-methoxyphenyl)piperazin-1-yl)butan-2-ol (30b). 30b was prepared from **29b** in a fashion similar to that described above for **30a**. Yield: 13%. ^{1}H NMR ($CDCl_3$): δ 1.52 (ddd, *J* 14.5, 6.5, 3.9, 1H), 1.71 (m, 1H), 2.54−2.77 (m, 4H), 2.86 (s, 2H), 3.09 (s, 4H), 3.77 (m, 1H), 3.87 (s, 3H), 6.86 (d, *J* 7.9, 1H), 6.90−6.95 (m, 2H), 7.00 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 29.0, 48.4, 50.7, 53.6, 55.4, 57.6, 75.2, 111.2, 118.3, 121.1, 123.2, 141.0, 152.3.

***N*-(2-Hydroxymethyl-*trans*-cyclopropylmethyl)-4-pyridin-2-ylbenzamide (32a). 32a** was prepared from 4-pyridin-2-ylbenzoic acid hydrochloride and **31a**[34] according to the general procedure. Yield: 43%. ^{1}H NMR ($CDCl_3$): δ 0.45 (m, 2H), 0.99 (m, 2H), 3.01−3.07 (m, 4H), 3.50 (dt, *J* 14.0, 5.5, 2H), 3.71 (dd, *J* 11.0, 4.7, 2H), 4.09 (s, 1H), 7.23 (m 1H), 7.40 (t, *J* 4.7, 1H), 7.67 (d, *J* 7.8, 1H), 7.71 (m, 1H), 7.87 (d, *J* 7.8, 2H), 7.94 (d, *J* 7.8, 2H), 8.65 (d, *J* 3.9, 1H). ^{13}C NMR ($CDCl_3$): δ 8.6, 16.9, 20.4, 44.2, 66.0, 121.1, 122.8, 126.9, 127.7, 134.8, 137.1, 141.9, 149.7, 156.3, 167.8.

***N*-(2-Hydroxymethyl-*cis*-cyclopropylmethyl)-4-pyridin-2-ylbenzamide (32b). 32b** was prepared from 4-pyridin-2-ylbenzoic acid hydrochloride and **31b**[34] according to the general procedure. Yield: 55%. ^{1}H NMR ($CDCl_3$): δ 0.16 (t, *J* 5.4, 1H), 0.76 (m, 1H), 1.23 (m, 2H), 2.12 (m, 1H), 3.24 (t, *J* 11.0, 1H), 4.23 (m, 1H), 4.53 (m, 1H), 7.26 (m, 1H),), 7.68 (d, *J* 7.8, 1H), 7.74 (td, *J* 7.8, 16, 1H), 7.88 (d, *J* 8.6, 2H), 7.92 (d, *J* 8.6, 2H), 8.66 (d, *J* 3.9, 1H). ^{13}C NMR ($CDCl_3$): δ 8.3, 15.7, 39.8, 62.5, 121.4, 127.2, 127.7, 134.9, 137.3, 142.0, 149.8, 156.6, 167.0.

***N*-(2-(4-(2,3-Dichlorophenyl)piperazin-1-ylmethyl)-*trans*-cyclopropylmethyl)-4-pyridin-2-ylbenzamide (33).** To a solution of **32a** (0.59 g, 2.1 mmol) and triethylamine (0.64 g, 6.3 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonic acid anhydride (0.55 g, 3.2 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 h. All volatiles were removed in vacuo, and to the residue was added 0.44 g (5.3 mmol) of sodium bicarbonate and CH_3CN (10 mL). The mixture was refluxed for 16 h, filtered, and concentrated in vacuo. The residue was purified by flash chromatography. Yield: 0.12 g, 20%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 0.48 (dt, *J* 8.3, 5.0, 1H), 0.60 (dt, *J* 8.5, 5.0, 1H), 0.96 (m, 1H), 2.25 (dd, *J* 12.7, 7.3, 1H), 2.49 (dd, *J* 12.7, 5.9, 1H), 2.70 (s, 4H), 3.03 (4, 1H), 3.40 (t, *J* 6.14, 2H), 6.58 (t, *J* 5.2, 1H), 6.89 (dd, *J* 7.96, 1.61, 1H), 7.07 (t, *J* 7.98, 1H), 7.13 (dd, *J* 8.0, 1.6, 1H), 7.28 (m, 1H), 7.73−7.81 (m, 2H), 7.91 (d, *J* 8.53, 2H), 8.06 (d, *J* 8.6, 2H), 8.71 (d, *J* 4.7, 1H). ^{13}C NMR ($CDCl_3$): δ 10.5, 15.7, 18.3, 44.5, 51.6, 53.7, 62.9, 119.0, 121.3, 123.2, 125.0, 127.5, 127.9, 134.4, 135.2, 137.4, 142.6, 150.3, 151.6, 156.6, 167.5. Anal. ($C_{27}H_{28}Cl_2N_4O\cdot(COOH)_2\cdot H_2O$) C, H, N.

***N*-(2-(4-(2,3-Dichlorophenyl)piperazin-1-ylmethyl)-*cis*-cyclopropylmethyl)-4-pyridin-2-ylbenzamide (34). 34** was prepared from **32b** in a fashion similar to that described for **33**. Yield: 38%. Mp (oxalate): foam. ^{1}H NMR ($CDCl_3$): δ 0.14 (dd, *J* 10.0, 5.0, 1H), 0.67 (dt, *J* 7.9, 5.1, 1H), 0.93 (m, 1H), 1.41 (m, 1H), 2.73 (t, *J* 12.4, 1H), 3.02 (s, 4H), 3.31−3.51 (m, 6H), 4.08 (dd, *J* 12.0, 5.2, 1H), 6.32 (s, 1H), 6.93 (dd, *J* 6.9, 1.7, 1H), 7.13−7.18 (m, 2H), 7.28−7.34 (m, 3H), 7.79 (dt, *J* 11.4, 4.6, 2H), 8.10 (d, *J* 7.8, 2H), 8.73 (d, *J* 4.8, 1H). ^{13}C NMR ($CDCl_3$): δ 9.9, 17.2, 18.2, 46.3, 50.8, 51.4, 63.7, 127.6, 127.7, 127.8, 128.4, 134.2, 137.1, 140.4, 150.0, 151.0, 156.6, 161.7. Anal. ($C_{27}H_{28}Cl_2N_4O\cdot2(COOH)_2$) C, H, N.

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Supporting Information Available: Results from microanalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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