Novel Heterocyclic Trans Olefin Analogues of *N*-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}arylcarboxamides as Selective Probes with High Affinity for the Dopamine D3 Receptor

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Dopamine D3 receptor subtypes have been hypothesized to play a pivotal role in modulating the reinforcing and drug-seeking effects induced by cocaine. However, definitive pharmacological investigations have been hampered by the lack of highly D3 receptor selective compounds that can be used in vivo. To address this problem, the potent and D3-receptor-selective antagonist NGB 2904 (**1**, 9H-fluorene-2-carboxylic acid {4-[(2,3-dichlorophenyl)-piperazin-1-yl]-butyl}-amide, K_i (hD3) = 2.0 nM, K_i ($hD2_L$) = 112 nM, D2/D3 selectivity ratio of 56) was chosen as a lead structure for chemical modification in an attempt to reduce its high lipophilicity (*c* log *D* = 6.94) while optimizing D3 receptor binding affinity and D2/D3 selectivity. A series of >30 novel analogues were synthesized, and their binding affinities were evaluated in competition binding assays in HEK 293 cells transfected with either $D2_L$, D3, or D4 human dopamine receptors using the high affinity, selective D2-like receptor antagonist ^{125}I-IABN. Structural diversity in the aryl amide end of the molecule was found to have a major influence on (sub)nanomolar D3 receptor affinity and D2/D3 selectivity, which was optimized using a more rigid *trans*-butenyl linker between the aryl amide and the piperazine. Several analogues demonstrated superior D3 receptor binding affinities and selectivities as compared to the parent ligand. Compound **29** (*N*-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-pyridine-2-yl-benzamide) displayed the most promising pharmacological profile (K_i (hD3) = 0.7 nM, K_i ($hD2_L$) = 93.3 nM, D2/D3 selectivity ratio of 133). In addition, this ligand inhibited quinpirole stimulation of mitogenesis at human dopamine D3 receptors transfected into Chinese hamster ovary (CHO) cells, with an EC_{50} value of 3.0 nM. Compound **29** was a nearly 5 times more potent antagonist at the D3 receptor than **1** (EC_{50} = 14.4 nM). Moreover, a decrease in *c* log *D* value of ∼2 orders of magnitude was determined for this novel D3-receptor-preferring ligand, compared to **1**. In summary, chemical modification of **1** has resulted in compounds with high affinity and selectivity for D3 receptors. The most promising candidate, compound **29**, is currently being evaluated in animal models of cocaine abuse and will provide an important tool with which to elucidate the role of D3 receptors in drug reinforcement in vivo.

Introduction

The D3 receptor, first described in 1990,[1] is a member of the D2-like receptor family, and possesses ∼50% overall homology to the D2 receptor subtype.[2] D3 receptors are localized in the limbic areas of the brain, specifically the islands of Calleja and the nucleus accumbens.[3] The discovery of D3-receptor-selective antagonists and partial agonists has received particular attention for the potential treatment of cocaine abuse since the compound BP 897 (**2**, Figure 1) was first reported to block cue-controlled cocaine seeking in rats.[4] Additional studies with **2**[5] and the potent and selective D3 antagonist SB-277011 (**3**)[6−8] further support the development of D3-receptor-selective ligands as potential cocaine abuse medications. Considerable progress in developing D3 receptor ligands as potential medications for neurological and neuropsychiatric disorders, in addition to drug abuse, has been made and recently reviewed.[9] However, chemical modification of the first generation drugs has been required to improve bioavailability for in vivo evaluation. For example, it was discovered that **3** was subject to metabolism by aldehyde oxidase, which predicts that this compound would be poorly bioavailable in humans, despite early preclinical success in animal models.[10] By replacement of the arylcyano moiety, which was subject to metabolism, with bioisosteres, GlaxoSmithKline recently reported a second generation D3 receptor antagonist with high pharmacological specificity that is metabolically stable, orally active, and CNS penetrant.[10]

In the 4-phenylpiperazine class of D3-receptor-selective ligands, significant structure−activity relationships (SAR) have been described wherein optimal D3-receptor-binding affinities were obtained when the phenylpiperazine moiety is linked to an aryl amide via a butyl chain.[11−14] Substitution of the phenylpiperazine ring was optimized with a 2,3-dichloro-substitution pattern,

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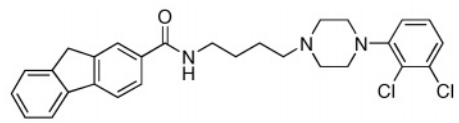
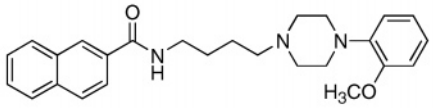
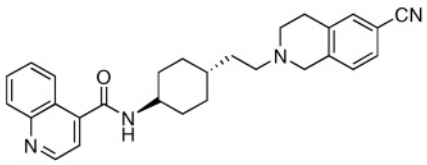


NGB 2904 (1)



BP 897 (2)



SB-277011 (3)

Figure 1. Some examples of D3 receptor selective ligands.

and the aryl amide functional group gave pharmacological selectivity when extended to a di- or triaryl ring system.[13,15] However, it was discovered that many of the most potent D3 receptor ligands were also highly lipophilic (*c* log *D* > 6),[15] which limited solubility and might compromise in vivo testing. Encouraging initial results with structurally more rigid analogues[15] obtained by unsaturation of the butyl linker and heterocyclic analogues of **1**[16] led us to investigate the combination of heterocyclic and substituted phenyl trans olefins as potential potent and selective probes for the dopamine D3 receptor that were less lipophilic than the first generation ligands.

Chemistry

The synthesis of the novel olefin analogues of *N*-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butyl}arylcarboxamides **7**−**36** was achieved by following a previously reported pathway.[15,17] As depicted in Scheme 1, the *N*-phthalimido-protected *trans*-butenyl bromide **4** was linked to 2,3-dichlorophenylpiperazine. Deprotection of the intermediate **5** to the primary amine **6** was achieved by treatment with hydrazine. Amidation either using the acid chloride under Schotten−Baumann conditions (method A) or using 1,1-carbonyldiimidazole (CDI, method B) gave the desired products generally in moderate to good yields. Compounds **42**, **43**,[11,12] and **44**[11,12] were prepared according to previously described methods[15,17] and analogous to their olefinic derivatives except the fully saturated derivative of **6** was used. All carboxylic acids were either commercially available or were prepared by literature methods. The resulting amides were converted to their appropriate salts for biological testing.

Results and Discussion

Thirty three novel ligands and several previously reported ligands[15] were evaluated in competition binding assays in HEK 293 cells transfected with either $D2_L$, D3, or D4 human dopamine receptors. 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-3β-yl] benzamide (^{125}I-IABN).[18] In addition, *c* log *D* values were calculated to provide a quantitative measure of lipophilicity to use in our drug design. These data are presented in Tables 1 and 2.

The effect on the binding affinities at the D2 and D3 receptors and D2/D3 selectivities induced by a substituent on the phenyl ring in the benzamides **7**−**25** is shown by comparison with the unsubstituted derivative **37** in Table 1. Generally, phenyl-ring substitution was well-tolerated at the D3 receptor (K_i = 0.4−3.8 nM). However, for these simple substituted benzamides, D2/D3 receptor binding selectivities were low to modest (D2/D3 = 2−34-fold). A small halogen substituent at the para-position on the phenyl ring did not have a significant impact on D2/D3 selectivity. However, the other substituents in the para position of the benzamide appeared to be the favored site for D2/D3 selectivity, and a para > meta > ortho pattern of D2/D3 receptor

Scheme 1. Synthetic Strategy for Novel D3 Receptor Ligands

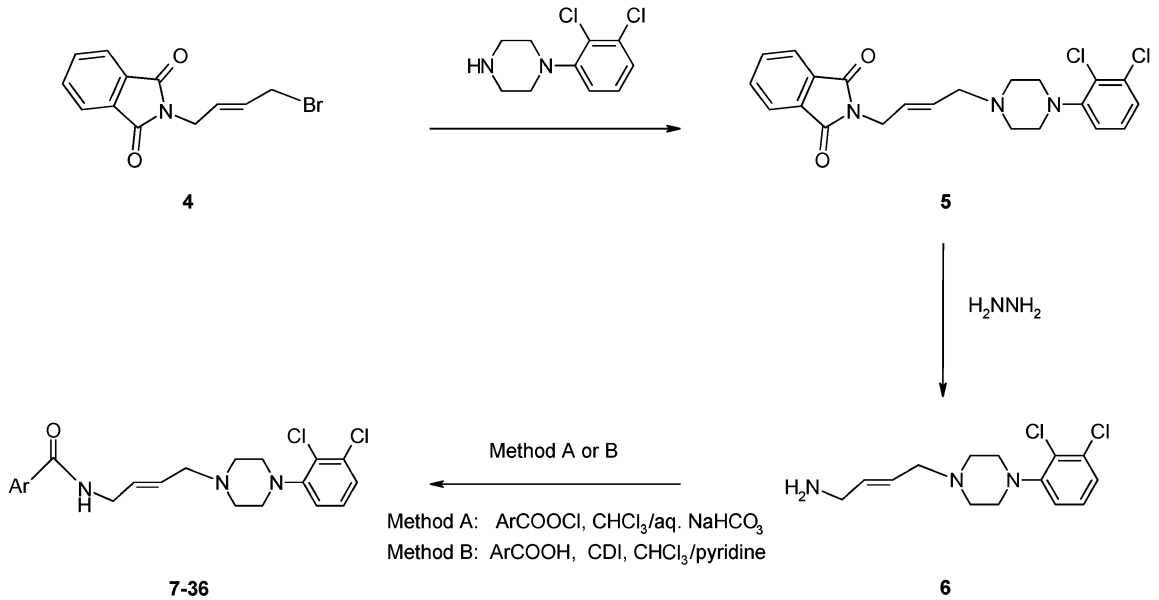
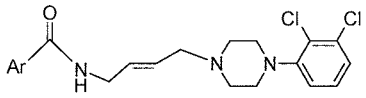
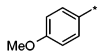
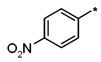


Table 1. Human D_2-Family Receptor Subtype Binding Data in HEK Cells for *trans*-Butenyl Benzamide Analogues

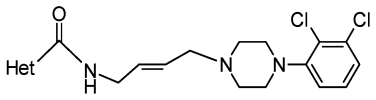


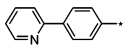
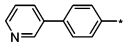
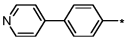
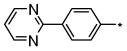
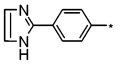
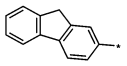
Compd.	Ar	*c* log *D*	D2	D3	D2/D3
			K_i [nM] ± SEM		
7		4.64	10.1 ± 1.8	1.2 ± 0.1	8
8		5.31	8.8 ± 0.7	1.7 ± 0.4	5
9		5.74	6.1 ± 0.4	1.0 ± 0.2	6
10		5.18	10.2 ± 2.8	1.3 ± 0.2	8
11		5.86	15.0 ± 2.9	2.7 ± 0.6	6
12		5.77	17.5 ± 3.6	2.6 ± 0.2	7
13		5.62	10.6 ± 2.4	3.8 ± 0.6	3
14		6.31	28.1 ± 3.0	3.2 ± 0.3	9
15		6.21	35.4 ± 7.6	3.4 ± 0.6	10
16		4.82	3.7 ± 1.1	0.6 ± 0.1	6
17		4.65	39.1 ± 6.4	3.0 ± 0.3	13
18		5.18	30.4 ± 3.8	1.2 ± 0.2	25
19		5.31	6.6 ± 1.9	0.8 ± 0.2	8
20		4.61	13.7 ± 4.8	0.4 ± 0.0	34
21		5.29	7.4 ± 0.4	3.4 ± 0.6	2
22		4.92	21.9 ± 4.0	2.3 ± 0.5	10
23		5.17	19.7 ± 3.6	0.7 ± 0.1	28
24		4.77	18.2 ± 4.6	2.2 ± 0.3	8
25		4.04	29.0 ± 9.4	2.0 ± 0.4	15
37		5.13	2.9 ± 1.0	0.8 ± 0.1	4

[a] The methods for the binding assays are described in the Experimental Methods section.[18] K_i values are the mean of at least three independent determinations. [b] Calculated partition coefficients at physiological pH (7.4); ACD/LogD Suite, Advanced Chemistry Development Inc., Toronto, Canada.

binding selectivities was generally followed. The iodobenzamides (**13**−**15**) had somewhat lower D3 receptor binding affinities than the unsubstituted derivative **37** (∼4−5-fold). For these iodo-substituted derivatives, the binding affinities at the D3 receptor appeared to be generally unaffected by the position of the substituent.

Table 2. Human D_2-Family Receptor Subtype Binding Data in HEK Cells for *trans*-Butenyl Heterocyclic Analogues[a]



Compd.	Het	*c* log *D*	D2	D3	D4	D2/D3	D4/D3
			Ki [nM] ± SEM				
26		3.93	16.9 ± 3.7	2.6 ± 0.6	n.d.	7	-
27		4.15	19.6 ± 5.3	2.5 ± 0.6	n.d.	8	-
28		3.75	31.2 ± 3.1	2.0 ± 0.6	n.d.	16	-
29		5.34	93.3 ± 12.0	0.7 ± 0.1	375 ± 18	133	540
30		5.27	54.5 ± 5.5	0.9 ± 0.3	520 ± 55	61	580
31		5.07	43.7 ± 5.1	0.9 ± 0.1	n.d.	49	-
32		5.54	45.7 ± 11	1.3 ± 0.1	n.d.	35	-
33		4.92	8.0 ± 1.0	0.3 ± 0.0	n.d.	27	-
34		5.31	65.5 ± 2.9	3.8 ± 0.9	1110 ± 560	17	292
35		7.10	149 ± 7.9	1.1 ± 0.0	1770 ± 390	135	1610
36		5.86	76.5 ± 14.0	2.1 ± 0.5	1070 ± 380	36	510
38[15]		7.07	168 ± 29	1.5 ± 0.1	1020 ± 160	112	680

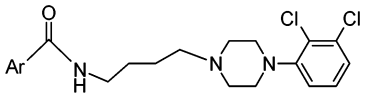
[a] K_i and *c* log *D* values were obtained as described in Table 1.

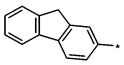
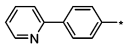
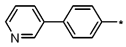
However, at the D2 receptor, the 2-iodo derivative **13** (K_i = 10.6 nM) showed a higher binding affinity than the 3-iodo benzamide **14** (K_i = 28.1 nM) and 4-iodo ligand **15** (K_i = 35.4 nM). The nitro derivatives (**21**−**23**) and the methoxylated ligands (**16**−**18**) exhibited similar SAR dependence on the position of substituent on the phenyl ring as the iodo-benzamides (**13**−**15**) at the D2 receptor. This effect was most pronounced for the methoxylated derivatives, wherein the 4-methoxy analogue **18** had a 10-fold lower affinity at the D2 receptor than the 2-methoxy ligand **16**. The 4-methoxy ligand **18** showed a comparable affinity at the D3 receptor (K_i = 1.2 nM) to the unsubstituted phenyl derivative **37**, resulting in a D2/D3 selectivity of 26. The 4-hydroxy **20** and the 4-nitro **23** derivatives demonstrated similar D2/D3 ratios of 34 and 28, respectively. Thus, the demethylation of **18** to form the 4-hydroxy ligand **20** led to higher affinities at both the D2 and the D3 receptors of K_i = 13.7 nM and K_i = 0.4 nM, respectively but did not significantly improve the D2/D3 selectivity.

The binding affinities at the human $D2_L$ and D3 receptors for the heterocyclic analogues with the *trans*-butenyl linker are depicted in Table 2 and compared to **38**.[15] The simple pyridine-substituted amides (**26**−**28**) were found to have low D2/D3 selectivities. All of these derivatives demonstrated similar binding affinities at the D3 receptor (K_i = 2.0−2.6 nM). However, moving the nitrogen atom around the pyridine ring appeared to follow a similar pattern as described above for the phenyl-substituted benzamides wherein the 4-pyridine-amido derivative exhibited the highest D2/D3 binding selectivity (16-fold). A phenyl spacer was introduced between the pyridine system and amide moiety to form the pyridine-benzamides **29**−**31**. Overall, these ligands exhibited significantly enhanced D2/D3 selectivities. Compared to the simple pyridine-amides (**26**−**28**), the affinities at D3 receptors improved slightly (K_i = 0.7−0.9 nM). Interestingly, the order of D2/D3 binding selectivity dependent on the nitrogen position on the pyridine moiety appeared to be reversed, whereas the 2-pyridylphenylbenzamide **29** showed the highest D2/D3 binding selectivity (133-fold).

To further improve the hydrophilicity of **29**, a second nitrogen was introduced into the 5-position of the pyridine moiety or the pyridine moiety was replaced with an imidazole system. However, the 2,5-pyrimidine-benzamide derivative **32** as well as the imidazole ligand

Table 3. Human D_2-Family Receptor Subtype Binding Data in HEK Cells for Selected Butyl Analogues[a]



Compd.	Ar	D2	D3	D2/D3
		Ki [nM] ± SEM		
1		112 ± 22	2.0 ± 0.4	56
39[15]		39.3 ± 10.0	1.6 ± 0.5	25
40[15]		29.6 ± 9.0	1.4 ± 0.1	21
41[15]		24.8 ± 8.6	0.5 ± 0.2	50
42		18.2 ± 2.6	0.5 ± 0.1	36
43[11,12]		64.7 ± 8.9	0.8 ± 0.2	81
44[11,12]		44.8 ± 10.6	0.8 ± 0.3	56

[a] K_i values were obtained as described in Table 1.

33 showed a remarkable effect of the second nitrogen in reducing D2/D3 binding selectivity as compared to that of **29**, which was primarily due to an increase in binding affinities at D2 receptors. Although both compounds showed similar D2/D3 selectivities, their binding affinities at the D3 receptor were quite different. Compound **33** had a 4-fold higher binding affinity at the D3 receptor than that of **32** and was one of the most potent D3 ligands in the series. Its binding profile at both D2 and D3 receptors appeared to be similar to that of the 4-phenolic derivative **20** (Table 1).

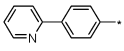
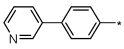
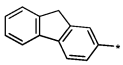
Additional rigid heterocyclic derivatives were further investigated wherein the 2-quinoxaline carboxylic acid derivative **34** showed relatively low affinity (K_i = 3.8 nM) at the D3 receptor and was only moderately D2/D3 selective. The benzothiophen analogue **35** showed higher selectivity than the benzofuran **36**, D2/D3 = 135 and 36, respectively. Thus, the D2/D3 binding profile for the benzothiophen derivative **35** was similar to that for the 2-pyridine-benzamide **29**. However, its relatively high lipophilicity (c log D = 7.10) would likely reduce its viability for further in vivo development.

Selected compounds with high D3 affinities were evaluated for binding at human D4 receptors. None of the compounds tested (Table 2) showed high binding affinities (K_i = 375−1770 nM) at D4 receptors and displayed D4/D3 selectivities in the range of 292−1610.

The question arose as to whether the introduction of a *trans*-butenyl linker between aryl amide and piperazine moiety uniformly improved D3 receptor binding affinity and D2/D3 selectivity. For comparison, binding affinities at the $D2_L$ and D3 human dopamine receptor for selected derivatives with a saturated butyl linker are depicted in Table 3. The *trans*-butenyl pyridine-benzamides derivatives **29** and **30** (Table 2) were compared to the respective compounds with the butyl linker (**41**[15] and **42**). Within both sets of pyridine-benzamides, the affinities at the D3 receptor were similar, for example, for the 2-pyridine-benzamides **29** and **41**, the K_i = 0.7 and 0.5 nM, respectively. However, there was a significant difference for the binding affinities at the D2 receptor. Compound **41** (K_i = 24.8 nM) had a nearly 4-fold higher affinity at this receptor than **29** (K_i = 93.3 nM), resulting in an overall improved D2/D3 selectivity for the *trans*-butenyl derivative. The *trans*-butenyl vs butyl ligand pairs **38/1** and **35/43** showed a similar relationship with the saturated derivative having higher binding affinities at the D2 receptor while the binding affinity at D3 receptor was similar or unaffected. Though, as can be shown for the saturated analogue **43** (K_i ($D2_L$) = 64.7 nM) and the olefinic derivative **35** (K_i ($D2_L$) = 149 nM), the effect on D2 binding affinity was somewhat less pronounced than that for **41** vs **29**. However, the 4-iodo benzamide **39** (K_i (D3) = 1.6 nM), which featured a butyl linker between the amide moiety and the piperazine system, had a ∼2-fold higher affinity at the D3 receptor than the *trans*-butenyl ligand **15** (Table 1, K_i = 3.4 nM). Both ligands demonstrated similar binding affinities at the D2 receptor of 39.3 and 35.4 nM. So that overall, for olefinic ligand **15**, the D2/D3 binding selectivity was reduced. Other examples were the benzofuran pairs (**36** and **44**) and the quinoxaline derivatives (**34** and **40**), where the introduction of the trans olefinic linker has a small but negative impact on binding affinity at D3. The saturated benzothiophen **43** and the benzofuran **44** analogues were previously reported to have extraordinary D3 affinities and D2/D3 selectivities.[11,12] However, under our assay conditions, these analogues demonstrated significantly lower D2/D3 selectivities. Although introduction of the trans-olefinic linker to give **36** did not serve to improve binding affinity or selectivity at D3 receptors, this modification to the benzothiophen analogue resulted in one of the most potent and selective analogues in the series, **35**. In total, the replacement of the saturated butyl linker with a trans olefin did not uniformly improve D3 binding affinity and selectivity. The impact of saturation was thus dependent on the aryl terminus of the individual compound. Nevertheless, the compounds of most interest for further investigation, in terms of pharmacological profile and lipophilicity, possessed the trans-olefin linker.

Binding affinities have commonly been used to predict SAR for the D3 receptor and D2/D3 selectivities. Generally, if in vitro functional data is obtained, then only the D3 receptor activity is reported. The reasons for evaluating D2 intrinsic activity were twofold: (1) to determine if selectivity based on potencies in the functional assay corresponded to in vitro binding selectivity and (2) when these compounds are evaluated behaviorally, it will be important to know their intrinsic activity at D2 receptors as this will likely play a role in vivo, especially at the higher doses. In this study, intrinsic activities for selected compounds were determined in functional assays using stimulation (agonist) or inhibition of quinpirole stimulation (antagonist) of mitogenesis in human dopamine D3 or D2 receptors transfected into Chinese hamster ovary (CHO) cells (Table 4). All of the compounds evaluated were antago-

Table 4. Functional Assays Using Inhibition of Quinpirole Stimulation in Cloned Human Dopamine D_2 and D_3 Receptors Transfected into CHO Cells for Selected Analogues

Compd.	Ar	D_2	D_3	D_2/D_3
		EC_{50} [nM] ± SEM[a]		
15		162 ± 51	24.1 ± 3.4	7
18		61.8 ± 21.0	4.79 ± 1.8	13
20		8.29 ± 2.10	1.0 ±0.1	8
23		13.8 ± 1.0	2.2 ± 0.5	6
29		80.9 ± 6.7	3.0 ± 0.7	27
30		36.4 ± 0.3	2.9 ± 0.4	13
35		254 ± 35	9.6 ± 0.6	26
36		111 ± 18	18.7 ± 2.8	6
43[11,12]		95 ± 18	4.9 ± 0.3	19
44[11,12]		118 ± 14	9.0 ± 1.4	13
1		1280 ± 270	14.4 ± 0.5	89
37[15]		16.1 ± 4.3	7.7 ± 1.6	2

[a] These data were obtained through the service of CTDP, Division of Treatment Research and Development, NIDA, using a contract (N01DA-1-8816) protocol.

nists in these functional tests. Although the D2/D3 selectivities established in the binding assays for these novel *trans*-butenyl analogues corresponded to the D2/D3 selectivities found in this functional assay, the ratios depicting selectivity were significantly lower (up to 6-fold) than those in the binding assays.

All olefinic derivatives were found to be antagonists at the D3 as well as at the D2 receptors. The pyridine-benzamido derivatives **29** and **30** showed similar potencies of EC_{50} = 3.0 and 2.9 nM, respectively. In this in vitro bioassay both compounds were nearly 5-fold more potent as D3 receptor antagonists than the parent compound **1**. As in the binding assays, the differences between the pyridine-benzamide **29** and **30** were more pronounced at the D2 receptor. Further, both compounds were also more potent than **1** at the D2 receptor, 16-fold and 35-fold, respectively. Although **29** appeared to be moderately D3-selective (D2/D3 = 27), the D2/D3 selectivity for **30** was lower (13-fold). Thus, overall D2/D3 selectivity was found to be lower for **29** than for the parent compound **1** even though it was ~5-fold more potent as a D3 receptor antagonist. The thiophene derivative **35** displayed a similar D2/D3 selectivity based on potencies in the functional assay to **29** but was somewhat less potent as a D3 receptor antagonist (~3-fold). Replacement of the sulfur by an oxygen atom in the furan derivative **36** resulted in a 4-fold loss of D2/D3 selectivity. As in the binding assay, the furan derivative **36** was less potent at the D3 receptor but more potent at the D2 receptor than **35**. The unsubstituted benzamide **37** was found to be essentially non-selective in this functional assay. A substitution in the 4-position improved D2/D3 selectivity based on potencies in the functional assay. The 4-methoxy derivative **18** was found to be 6-fold more D2/D3 selective than **37**. The 4-hydroxy derivative **20** was the most potent antagonist prepared in this series (EC_{50} = 1.0 nM), but it lacked significant D2/D3 selectivity (D2/D3 = 8). At this time, we are unclear as to whether the in vitro binding or functional assays have greater predictive power for in vivo potency and selectivity. As these assays are performed in cell lines, under nonphysiological conditions, it is imperative to further evaluate these compounds in vivo and perhaps in additional in vitro functional tests in an attempt to bring clarity to the current D2/D3 selectivity inconsistencies.

Conclusions

Thirty three novel heterocyclic or substituted arylamides were prepared with either a saturated or a trans olefinic butyl linking chain and a 2,3-dichlorophenylpiperazine terminus. These compounds were evaluated in vitro for both binding and function at $hD2_L$ and hD3 receptors, and selected analogues were tested for binding at hD4 receptors. Most of these novel analogues displayed high affinities for D3 receptors (K_i = 0.3−3.8 nM), and all of the compounds synthesized were D3 receptor selective in both binding and function as D3 antagonists.

For selected compounds, the affinities at the hD4 receptor were low, and thus the D4/D3 selectivity was >290-fold. Discrepancies in K_i values across laboratories appear to be dependent on cell lines, radioligands, and assay conditions, which make comparisons to literature values difficult. This conundrum has been noted for D3 agonists, as well.[3,19] Likewise, a lack of correspondence between binding affinities and the commonly used mitogenesis assay also provides a complication to drug design in this area. Hence, compounds that have been reported in other laboratories to have extraordinarily high binding affinities and selectivities (**1**, **43**, and **44**) were discovered to have comparable pharmacological profiles in our binding assays to several of our analogues and significantly reduced selectivities in this functional assay. Overall, compound **29** demonstrated the most interesting pharmacological profile, in this series, and is currently being evaluated in a number of in vivo models of drug abuse. In summary, the design and synthesis of high-affinity D3 receptor ligands has been accomplished in this structural class and several related structural classes of D3 receptor ligands.[11−14] D3 receptor selectivity will have to be further determined in additional in vitro and, importantly, in vivo assays to further elucidate the role of the D3 receptor in neuropsychiatric disorders and drug abuse.

Experimental Methods

Chemistry. All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis, Inc. and used without further purification. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on Bruker AC-300 or 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 deuterated chloroform ($CDCl_3$, 77.5 ppm, CD_3OD 49.3). Infrared spectra were recorded as a neat film on NaCl plates with a Perkin-Elmer Spectrum RX I FT-IR system. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within ±0.4% of calculated values. All column chromatography was performed using the silica gel (Merck, 230−400 mesh, 60 Å) and $CHCl_3/CH_3OH$ 10:1) as eluting solvent unless otherwise indicated. For the amide formation reactions, absolute amylene-stabilized chloroform was used. If not otherwise stated, then all spectroscopic data and yields refer to the free base. Compounds **43** and **44** were prepared according to literature procedures[11,12] and were tested as oxalate salts.

General Procedures. Procedure A. The appropriate benzoic acid was converted into its corresponding acid chloride by treatment with thionyl chloride, and this intermediate was reacted with **6** in a Schotten−Baumann-type reaction as described previously.[17] The crude product was purified either by chromatography or by recrystallization of its appropriate salt.

Procedure B. In a typical conversion, CDI (0.11 g, 0.66 mmol) was added to a solution of the appropriate benzoic acid (0.66 mmol) in 2 mL of absolute pyridine, and the mixture was stirred under argon for 1 h. After that time, a solution of **6** (0.20 g, 0.66 mmol) in 5 mL of absolute chloroform was added, and the mixture was stirred overnight. All volatiles were removed in vacuo, and the residue was purified by chromatography to give the title compound.

4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enylamine (6). A suspension of 4-(2,3-dichlorophenyl)-piperazine (7.55 g, 32.8 mmol), 2-(4-*trans*-bromo-but-2-enyl)-isoindole-1,3-dione (**4**)[20] (9.19 g, 32.8 mmol), and sodium bicarbonate (13.7 g, 161 mmol) in acetonitrile (100 mL) was heated to 80 °C under an atmosphere of argon for 5 h. Subsequently, most of the inorganic salts were removed by filtration of the hot (CAUTION!) reaction mixture. The N-protected intermediate **5** crystallized out of the filtrate and was taken up in a minimum amount of chloroform. After filtration and evaporation of the solvent, 10.9 g (77%) was obtained as a solid. $R_f = 0.45$ (ethyl acetate). Mp 144−146 °C ($CHCl_3$). IR (film): ν 1714. ^1H NMR ($CDCl_3$): δ 2.62 (s, br., 4H), 3.05−3.06 (m, 6H), 4.31 (m, 2H), 5.69−5.82 (m, 2H), 6.95 (m, 1H), 7.10−7.16 (m, 2H), 7.69−7.75 (m, 2H), 7.81−7.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 39.04, 51.21, 53.18, 60.09, 118.60, 123.31, 124.54, 127.17, 127.44, 127.47, 129.91, 132.12, 133.99, 151.21, 167.90. Deprotection of **5** was achieved in a solution (5.12 g, 11.9 mmol) of absolute ethanol (150 mL) under an atmosphere of argon, to which hydrazine (0.75 mL, 24 mmol) was added, and the reaction mixture was allowed to stir at reflux for 2.5 h. The reaction mixture was cooled (0 °C) and filtered, and solvent was removed under reduced pressure. The residue was purified by column chromatography to give the title compound (2.71 g, 76%) as an oil. $R_f = 0.49$ ($CHCl_3/CH_3OH/N(C_2H_5)_3$ 10:1:1). IR (film): ν 3358. ^1H NMR ($CDCl_3$): δ 1.50 (s, br., 2H), 2.64 (s, br., 4H), 3.06 (m, 6H), 3.34 (m, 2H), 5.64−5.84 (m, 2H), 6.96 (m, 1H), 7.11−7.17 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 43.50, 51.24, 53.15, 60.38, 118.58, 124.53, 126.56, 127.42, 127.46, 133.97, 134.71, 151.22.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-2-fluorobenzamide (7)** was prepared from 2-fluorobenzoic acid and **6** according to procedure A. Yield: 96%. $R_f =$ 0.34 ($CHCl_3/CH_3OH$ 10:1, 1% NH_4OH). Mp (hydrochloride, methanol/diethyl ether) 164 °C. IR (film): ν 3354, 1649. ^1H NMR ($CDCl_3$): δ 2.66 (s, 4H), 3.09 (s, 6H), 4.13 (m, 2H), 5.72−5.85 (m, 2H), 6.94 (m, 1H), 7.07−7.19 (m, 2H), 7.26 (m, 1H), 7.43−7.54 (m, 2H), 8.05−8.15 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 41.34, 46.26, 52.17, 56.67, 115.94 ($J_{CF} = 25$), 118.57, 120.87 ($J_{CF} = 11$), 124.52, 124.78 ($J_{CF} = 3$), 127.41, 128.72, 129.60, 132.04 ($J_{CF} = 2$), 133.28 ($J_{CF} = 9$), 133.94, 151.16, 160.55 ($J_{CF} = 247$), 163.01. Anal. ($C_{21}H_{22}Cl_2FN_3O\cdot 2HCl$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-3-fluorobenzamide (8)** was prepared from 3-fluorobenzoic acid and **6** according to procedure A. Yield: 67%. $R_f =$ 0.34 ($CHCl_3/CH_3OH$ 10:1). Mp (hydrochloride, methanol/diethyl ether) 124−126 °C. IR (film): ν 3314, 1643. ^1H NMR ($CDCl_3$): δ 2.63 (s, 4H), 3.05−3.07 (m, 6H), 4.08 (m, 2H), 5.76−5.78 (m, 2H), 6.62 (t, J 5.4, 1H), 6.96 (m, 1H), 7.10−7.22 (m, 3H), 7.37 (m, 1H), 7.50−7.57 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 42.32, 51.88, 53.88, 60.78, 114.54 ($J_{CF} = 23$), 118.67 ($J_{CF} =$ 21), 118.72, 122.45 ($J_{CF} = 3$), 124.68, 127.50, 129.13, 129.56, 130.26 ($J_{CF} = 8$), 133.99, 136.63 ($J_{CF} = 6$), 151.00, 162.48 ($J_{CF} =$ 246), 165.74. Anal. ($C_{21}H_{22}Cl_2FN_3O\cdot HCl\cdot 0.25H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-fluorobenzamide (9)** was prepared from 4-fluorobenzoic acid and **6** according to procedure B. Yield: 73%. Mp (hydrochloride, methanol/diethyl ether) 56 °C. IR (film): ν 3302, 1645. ^1H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.06−3.08 (m, 6H), 4.08 (m, 2H), 5.76 (s, 1H), 6.19 (s, 1H), 6.93 (m, 1H), 7.36−7.40 (m, 4H), 7.76 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 41.93, 51.55, 53.53, 60.46, 115.44 ($J_{CF} = 22$), 118.43, 124.39, 127.23, 128.74, 129.02 ($J_{CF} = 8$), 129.44, 130.32, 133.71, 150.75, 164.19 ($J_{CF} =$ 249), 165.72. Anal. ($C_{21}H_{22}Cl_2FN_3O\cdot 1.5HCl\cdot H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-2-chlorobenzamide (10)** was prepared from 2-chlorobenzoic acid and **6** according to procedure A. Yield: 67%. $R_f =$ 0.37 ($CHCl_3/CH_3OH$ 10:1). Mp (hydrochloride, methanol/diethyl ether) 64 °C. IR (film): ν 3282, 1645. ^1H NMR ($CDCl_3$): δ 2.65 (s, 4H), 2.92−3.08 (m, 6H), 4.08 (s, 2H), 5.79 (s, 2H), 6.55 (m, 1H), 6.94 (m, 1H), 7.10−7.14 (m, 2H), 7.27−7.37 (m, 2H), 7.60 (d, J = 7.1, 1H), 7.73 (d, J = 8.3, 1H). ^{13}C NMR ($CDCl_3$): δ 39.85, 49.58, 51.51, 58.53, 116.98, 122.92, 123.64, 125.43, 126.56, 127.37, 127.50, 127.78, 128.41, 128.55, 128.96, 129.64, 132.33, 133.42, 149.55, 164.72. Anal. ($C_{21}H_{22}Cl_3N_3O\cdot HCl\cdot 1.25H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-3-chlorobenzamide (11)** was prepared from 3-chlorobenzoic acid and **6** according to procedure A and purified by recrystallization of its oxalate from acetone. Yield: 66%. $R_f =$ 0.48 ($CHCl_3/CH_3OH$ 10:1). Mp (oxalate, acetone) 108−111 °C. IR (film): ν 3309, 1641. ^1H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.07−3.08 (m, 6H), 4.07 (m, 2H), 5.75−5.77 (m, 2H), 6.28 (m, 1H), 6.93 (dd, J = 6.7, 2.7, 1H), 7.09−7.14 (m, 2H), 7.34 (t, J = 7.6, 1H), 7.44 (dd, J = 7.4, 1.6, 1H), 7.62 (d, J = 7.4, 1H), 7.74 (t, J = 1.6, 1H). ^{13}C NMR ($CDCl_3$) δ 42.20, 51.77, 53.76, 60.68, 118.66, 124.63, 125.05, 127.29, 127.46, 129.15, 129.46, 129.89, 131.52, 133.96, 134.69, 136.11, 150.98, 165.65. Anal. ($C_{21}H_{22}Cl_3N_3O\cdot(COOH)_2\cdot CH_3COCH_3$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-chlorobenzamide (12)** was prepared from 4-chlorobenzoic acid and **6** according to procedure A. Yield: 79%. $R_f =$ 0.39 ($CHCl_3/CH_3OH$ 10:1). Mp (hydrochloride, methanol/diethyl ether) 69 °C. IR (film): 3310, 1642. ^1H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.06−3.07 (m, 6H), 4.07 (m, 2H), 5.76−5.77 (m, 2H), 6.68 (t, J = 5.2, 1H), 6.95 (m, 1H), 7.10−7.16 (m, 2H), 7.36 (d, J = 8.6, 2H), 7.73 (d, J = 8.6, 2H). ^{13}C NMR ($CDCl_3$) δ 41.52, 51.12, 53.18, 60.14, 118.61, 124.63, 127.46, 128.41, 128.78, 129.83, 132.74, 133.99, 137.71, 151.09, 166.24. Anal. ($C_{21}H_{22}Cl_3N_3O\cdot HCl\cdot 0.5H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-2-iodobenzamide (13)** was prepared from 2-iodobenzoic acid and **6** according to procedure B. Yield: 54%. $R_f =$ 0.47 ($CHCl_3/CH_3OH$ 10:1). Mp (hydrochloride, methanol/diethyl ether) 121−123 °C. IR (film): ν 3272, 1644. ^1H NMR ($CDCl_3$): δ 2.65 (s, 4H), 3.06−3.10 (m, 6H), 4.09 (m, 2H), 5.75−5.89 (m, 2H), 6.00 (m, 1H), 6.95 (m, 1H), 7.06−7.17 (m, 3H), 7.34−7.41 (m, 2H), 7.85 (d, J = 7.7, 1H). ^{13}C NMR ($CDCl_3$): δ 41.35, 51.10, 53.02, 60.10, 92.45, 118.49, 124.41, 127.31, 127.76, 128.02, 129.19, 130.85, 132.52, 133.80, 139.65, 141.13, 142.03, 151.05, 169.10. Anal. ($C_{21}H_{22}Cl_2IN_3O\cdot HCl\cdot H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-3-iodobenzamide (14)** was prepared from 3-iodobenzoic acid and **6** according to procedure A and purified as its oxalate from acetone. Yield: 56% (oxalate). $R_f = 0.38$ ($CHCl_3/CH_3OH$ 10:1). Mp (oxalate, acetone) 138−142 °C. ^1H NMR ($CDCl_3$): δ 2.48 (s, 4H), 3.02 (s, 6H), 4.05 (m, 2H), 5.74−5.75 (m, 2H), 6.92 (m, 1H), 7.04−7.14 (m, 4H), 7.77 (t, J 7.7,

1H), 8.13 (t, *J* 1.5, 1H). ^{13}C NMR ($CDCl_3$): δ 41.45, 51.03, 52.99, 60.12, 94.09, 118.45, 124.35, 126.14, 127.21, 127.32, 128.79, 129.36, 129.98, 133.74, 135.91, 136.25, 140.07, 150.99, 165.73. Anal. ($C_{21}H_{22}Cl_2IN_3O\cdot(COOH)_2$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-iodobenzamide (15)** was prepared from 4-iodobenzoic acid and **6** according to procedure A and purified as its oxalate salt from acetone. Yield: 96% (oxalate). R_f = 0.37 ($CHCl_3/CH_3OH$ 10:1). Mp (oxalate, acetone) 181−183 °C. ^{1}H NMR ($CDCl_3$): δ 2.62 (m, 4H), 3.04−3.06 (m, 6H), 4.06 (m, 2H), 5.75 (m, 2H), 6.50 (t, *J* = 5.4 Hz, 1H), 6.94 (dd, *J* = 6.1, 3.5 Hz, 1H), 7.15 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 41.51, 51.20, 53.17, 60.15, 98.44, 118.57, 124.54, 127.43, 128.54, 129.12, 129.42, 133.74, 133.94, 137.68, 151.14, 166.49. Anal. ($C_{21}H_{22}Cl_2IN_3O\cdot(COOH)_2$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-2-methoxy-benzamide (16)** was prepared from 2-methoxybenzoic acid and **6** according to procedure A. Yield: 78%. R_f = 0.56 (CH_3Cl/CH_3OH 10:1, 1% NH_4OH). Mp (fumarate, ethanol) 189 °C. IR (film): ν 3401, 1653. ^{1}H NMR ($CDCl_3$): δ 2.51−2.65 (m, 4H), 2.97−3.10 (m, 6H), 3.93 (s, 3H), 4.11 (m, 2H), 5.68−5.86 (m, 2H), 6.84−7.14 (m, 5H), 7.48 (m, 1H), 8.20 (dd, *J* 7.8, 1.9, 1H). ^{13}C NMR ($CDCl_3$): δ 40.96, 51.03, 55.77, 60.07, 111.17, 118.52, 121.13, 121.25, 24.43, 127.30, 127.35, 127.58, 130.49, 132.14, 132.66, 133.81, 151.06, 157.32, 164.99. Anal. ($C_{22}H_{25}Cl_2N_3O_2\cdot(CHCOOH)_2\cdot0.5H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-3-methoxy-benzamide (17)** was prepared from 3-methoxybenzoic acid and **6** according to procedure A and purified by recrystallization as its fumarate from acetone. Yield: 55% (fumarate). R_f = 0.40 ($CHCl_3/CH_3OH$ 10:1). Mp (fumarate, acetone) 122−124 °C. IR (film): ν 3317, 1641. ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 4H), 2.95 (s, 6H), 3.83 (s, 3H), 4.07 (s, 2H), 5.66−5.83 (m, 2H), 6.92 (m, 1H), 7.08−7.15 (m, 3H), 7.26−7.32 (m, 2H), 7.38 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 41.35, 50.87, 52.91, 55.28, 59.93, 112.34, 117.48, 118.54, 118.70, 124.51, 127.31, 127.38, 128.07, 129.39, 130.26, 133.84, 135.75, 150.94, 159.64, 167.11. Anal. ($C_{22}H_{25}Cl_2N_3O_2\cdot(CHCOOH)_2\cdot0.5H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-methoxy-benzamide (18)** was prepared from 4-methoxybenzoic acid and **6** according to procedure A and purified by recrystallization of its oxalate salt from acetone. Yield: 51% (oxalate). R_f = 0.45 ($CHCl_3/CH_3OH$ 10:1). Mp (oxalate, acetone) 167−172 °C. IR (film): ν 3320, 1635. ^{1}H NMR ($CDCl_3$): δ 2.51−2.71 (m, 4H), 2.97−3.13 (m, 6H), 3.79 (s, 3H), 3.94 (m, 2H), 5.75−5.83 (m, 2H), 6.50 (t, *J* = 5.5, 1H), 6.96−6.85 (m, 3H), 7.09−7.28 (m, 2H), 7.98 ("d", *J* = 8.6, 2H). ^{13}C NMR ($CDCl_3$): δ 42.14, 51.91, 54.13, 56.29, 61.11, 114.19, 119.03, 124.96, 127.04, 127.82, 129.05, 129.07, 130.42, 134.30, 151.39, 162.27, 166.86. Anal. ($C_{22}H_{25}Cl_2N_3O_2\cdot(COOH)_2\cdot H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-2-hydroxy-benzamide (19)** was prepared from 2-hydroxybenzoic acid and **6** according to procedure B. Yield: 34%. R_f = 0.47 ($CHCl_3/CH_3OH$ 10:1). Mp (hydrochloride, methanol/diethyl ether) 121 °C. IR (film): ν 3329, 1638. ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 4H), 3.05−3.07 (m, 6H), 4.08 (m, 2H), 5.75−5.78 (m, 2H), 6.80−6.97 (m, 4H), 7.10−7.16 (m, 2H), 7.37 (m, 1H), 7.45 (dd, *J* = 8.0, 1.5, 1H). ^{13}C NMR ($CDCl_3$): δ 41.74, 51.84, 53.83, 60.68, 114.25, 118.65, 118.67, 118.71, 124.59, 125.40, 127.43, 128.94, 129.51, 133.91, 134.19, 150.93, 161.18, 169.35. Anal. ($C_{21}H_{23}Cl_2N_3O_2\cdot2HCl$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-hydroxy-benzamide (20)** was prepared from 4-hydroxybenzoic acid and **6** according to procedure B. Yield: 51%. R_f = 0.42 ($CHCl_3/CH_3OH$ 10:1). Mp (hydrochloride, methanol/diethyl ether) 148 °C. IR (film): ν 3309, 1633. ^{1}H NMR ($CDCl_3$): δ 2.69 (m, 4H), 3.05−3.08 (m, 6H), 4.01 (m, 2H), 5.70−5.75 (m, 2H), 6.67 (t, *J* = 5.5, 1H), 6.76 (d, *J* = 8.6, 2H), 6.88 (m, 1H), 7.07−7.19 (m, 2H), 7.56 (d, *J* = 8.6, 2H). ^{13}C NMR ($CDCl_3$): δ 41.23, 50.62, 53.00, 60.01, 115.60, 118.65, 124.75, 124.93, 126.66, 127.35, 127.51, 129.00, 131.27, 133.93, 150.74, 160.43, 167.71. Anal. ($C_{21}H_{23}Cl_2N_3O_2\cdot2HCl\cdot0.5H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-2-nitrobenzamide (21)** was prepared from 2-nitrobenzoic acid and **6** according to procedure A. Yield: 90%. R_f = 0.42 ($CHCl_3/CH_3OH$ 10:1, 1% NH_4OH). Mp (hydrochloride, methanol/diethyl ether) 144 °C. IR (film): ν 3272, 1649. ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 4H), 2.93−2.94 (m, 6H), 3.90 (m, 2H), 5.59−5.73 (m, 2H), 6.74 (t, *J* 5.7, 1H), 6.83 (m, 1H), 7.00−7.07 (m, 2H), 7.35−7.54 (m, 3H), 7.85 (dd, *J* = 8.0, 1.0, 1H). ^{13}C NMR ($CDCl_3$): δ 41.34, 50.97, 52.92, 59.94, 118.47, 124.20, 124.34, 127.12, 127.36, 128.55, 128.99, 129.01, 130.23, 132.57, 133.48, 133.68, 146.19, 150.97, 166.24. Anal. ($C_{21}H_{22}Cl_2N_4O_3\cdot HCl\cdot1.5H_2O$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-3-nitrobenzamide (22)** was prepared from 3-nitrobenzoic acid and **6** according to procedure A. Yield: 71%. R_f = 0.37 ($CHCl_3/CH_3OH$ 10:1). Mp (hydrochloride, methanol/diethyl ether) 158 °C. IR (film): ν 3307, 1645, 1529, 1349. ^{1}H NMR ($CDCl_3$): δ 2.67 (s, 4H), 3.07−3.10 (m, 6H), 4.12 (m, 2H), 5.74−5.87 (m, 2H), 6.58 (t, *J* = 5.0, 1H), 6.95 (m, 1H), 7.10−7.17 (m, 2H), 7.65 (t, *J* = 7.9, 1H), 8.18 ("d", *J* = 7.7, 1H), 8.35 (ddd, *J* = 8.2, 2.1, 1.0, 1H), 8.61 (t, *J* = 1.9, 1H). ^{13}C NMR ($CDCl_3$): δ 41.81, 51.22, 53.25, 60.15, 118.62, 121.75, 124.64, 126.11, 127.48, 129.11, 129.66, 129.90, 133.31, 134.02, 136.01, 148.16, 151.15, 164.86. Anal. ($C_{21}H_{22}Cl_2N_4O_3\cdot2HCl$) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-nitrobenzamide (23)** was prepared from 4-nitrobenzoic acid and **6** according to procedure A and purified as its oxalate from acetone. Yield: 72% (oxalate). R_f = 0.35 ($CHCl_3/CH_3OH$ 10:1). Mp (oxalate, acetone) 186−189 °C. ^{1}H NMR ($CDCl_3$): δ 2.81 (s, 4H), 3.08−3.13 (m, 6H), 4.13 (m, 2H), 5.81−5.83 (m, 2H), 6.64 (m, 1H), 6.95 (m, 1H), 7.11−7.17 (m, 2H), 7.95 (d, *J* = 8.8, 2H), 8.25 (d, *J* = 8.8, 2H). ^{13}C NMR ($CDCl_3$): δ 41.71, 50.99, 53.07, 60.08, 109.56, 118.60, 123.74, 124.69, 127.42, 127.48, 128.18, 129.00, 129.49, 130.26, 133.98, 139.94, 149.52, 150.97, 165.25. Anal. ($C_{21}H_{22}Cl_2N_4O_3\cdot2(COOH)_2\cdot1.5H_2O$) C, H, N.

2-Amino-*N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-benzamide (24) was prepared from 2-aminobenzoic acid and **6** according to procedure B. Yield: 46%. R_f = 0.36 ($CHCl_3/CH_3OH$ 10:1, 1% NH_4OH). Mp (hydrochloride, methanol/diethyl ether) 122 °C. ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.06−3.07 (m, 6H), 4.02 (m, 2H), 5.53 (s, br., 2H), 5.74−5.77 (m, 2H), 6.30 (t, *J* = 5.3, 1H), 6.59−6.96 (m, 2H), 6.94 (m, 1H), 7.09−7.22 (m, 3H), 7.33 (dd, *J* = 7.9, 1.2, 1H). ^{13}C NMR ($CDCl_3$): δ 40.99, 51.13, 53.11, 60.14, 115.76, 116.45, 117.22, 118.55, 124.50, 127.09, 127.37, 127.41, 128.53, 129.99, 132.26, 133.89, 148.69, 151.10, 169.07. Anal. ($C_{21}H_{24}Cl_2N_4O\cdot2HCl\cdot H_2O$) C, H, N.

3-Amino-*N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-benzamide (25) was prepared from 3-aminobenzoic acid and **6** according to procedure B. Yield: 41%. R_f = 0.32 ($CHCl_3/CH_3OH$, 10:1). Mp (hydrochloride, chloroform/diethyl ether) 131 °C. IR (film): ν 3340, 1639. ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.05−3.12 (m, 6H), 3.73 (s, br., 2H), 4.05 (m, 2H), 5.74−5.75 (m, 2H), 6.43 (t, *J* = 5.5, 1H), 6.76 (m, 1H), 6.94 (m, 1H), 7.05−7.19 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 41.33, 51.12, 53.13, 60.16, 113.72, 116.22, 117.84, 118.58, 124.54, 127.39, 127.44, 128.49, 129.36, 130.00, 133.92, 135.55, 146.87, 151.11, 167.59. Anal. ($C_{21}H_{24}Cl_2N_4O\cdot3HCl\cdot0.33CHCl_3$) C, H, N.

Pyridine-2-carboxylic acid-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-amide (26) was prepared from pyridine-2-carboxylic acid and **6** according to procedure A. Yield: 30%. R_f = 0.41 ($CHCl_3/CH_3OH$ 10:1, 1% NH_4OH). Mp (hydrochloride, methanol/diethyl ether) 171 °C. IR (film): ν 3390, 1671. ^{1}H NMR ($CDCl_3$): δ 2.65 (s, 4H), 3.07−3.09 (m, 6H), 4.13 (m, 2H), 5.78−5.81 (m, 2H), 6.95 (m, 1H), 7.10−7.17 (m, 2H), 7.43 (m, 1H), 7.83 (m, 1H), 8.19−8.21 (m, 2H), 8.55 (d, *J* = 4.8, 1H). ^{13}C NMR ($CDCl_3$): δ 40.75, 51.18, 53.16, 60.22, 118.56, 122.22, 124.51, 126.15, 127.41, 128.51, 129.78, 133.93,

137.31, 148.01, 149.75, 151.16, 164.06. Anal. ($C_{20}H_{22}Cl_2N_4O$·3HCl) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-nicotinamide (27)** was prepared from nicotinoyl chloride hydrochloride and **6** according to procedure A. Yield: 61%. R_f = 0.34 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp (hydrochloride, methanol/diethyl ether) 151 °C. IR (film): ν 3294, 1644. ^{1}H NMR ($CDCl_3$): δ 2.62 (s, br., 4H), 3.05 (s, br., 6H), 4.10 (m, 2H), 5.77−5.79 (m, 2H), 6.94 (m, 1H), 7.12−7.15 (m, 2H), 7.22 (t, J = 5.4, 1H), 7.35 (dd, J = 7.9, 4.8, 1H), 8.14 (d, J = 7.9, 1H), 8.68 (d, J = 3.8, 1H), 9.03 (s, br, 1H). ^{13}C NMR ($CDCl_3$): δ 41.42, 51.06, 53.04, 60.02, 118.46, 123.33, 124.41, 127.25, 127.34, 129.07, 129.25, 130.06, 133.79, 135.04, 147.92, 150.93, 151.93, 165.37. Anal. ($C_{20}H_{22}Cl_2N_4O$·3HCl·1.25H_2O) C, H, N.

Pyridine-4-carboxylic acid-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-amide (28) was prepared from pyridine-4-carboxylic acid and **6** according to procedure A. Yield: 68%. Mp (hydrochloride, methanol/diethyl ether) 133−135. IR (film): ν 3308, 1651. ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 4H), 3.06 (s, 6H), 4.10 (s, 2H), 5.77 (s, 2H), 6.94 (m, 1H), 7.13−7.16 (m, 2H), 7.66 (d, J = 5.6, 2H), 8.69 (d, J = 5.6, 2H). ^{13}C NMR ($CDCl_3$): δ 41.47, 51.01, 53.02, 59.97, 118.49, 120.93, 124.49, 127.26, 127.39, 129.09, 129.14, 133.81, 141.46, 150.29, 150.95, 165.28. Anal. ($C_{20}H_{22}Cl_2N_4O$·3HCl·0.5H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-pyridine-2-yl-benzamide (29).** In alteration of procedure B, 4-pyridine-2-yl-benzoic acid hydrochloride[21] was treated with 2 equiv of CDI in pyridine. After 1 h at room temperature, the reaction mixture was hydrolyzed with water and extracted with chloroform. The intermediate imidazoline derivative was reacted with **6** in the usual manner. The crude amide was purified by flash chromatography and was converted into its hydrochloride for pharmacological evaluation. Yield: 62%. R_f = 0.51 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp (hydrochloride, 2-propanol) 230−232 °C. IR (film): ν 3299, 1638. ^{1}H NMR ($CDCl_3$): δ 2.62 (s, 4H), 3.06 (s, 6H), 4.11 (m, 2H), 5.76−5.79 (m, 2H), 6.78 (t, J = 5.5, 1H), 6.92 (m, 1H), 7.09−7.16 (m, 2H), 7.26 (m, 1H), 7.74−7.76 (m, 2H), 7.90 (d, J = 8.3, 2H), 8.04 (d, J = 8.2, 2H), 8.69 (d, J = 4.6, 1H). ^{13}C NMR ($CDCl_3$): δ 41.48, 51.16, 53.14, 60.17, 118.55, 120.79, 122.70, 124.49, 126.92, 127.37, 127.41, 128.84, 129.75, 133.89, 134.49, 136.86, 142.10, 149.73, 151.12, 156.08, 166.90. Anal. ($C_{26}H_{26}Cl_2N_4O$·2HCl·3H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-pyridine-3-yl-benzamide (30)** was prepared from 4-pyridine-3-yl-benzoic acid hydrochloride[21] and **6** employing an alteration of procedure B as described for **29**. Yield: 31%. R_f = 0.42 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp (oxalate, ethanol) 194−196 °C. IR (film): ν 3297, 1641. ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.06−3.10 (m, 6H), 4.14 (m, 2H), 5.79−5.81 (m, 2H), 6.61 (t, J = 5.6, 1H), 6.93−6.97 (m, 1H), 7.13−7.16 (m, 2H), 7.39 (m, 1H), 7.62−7.65 (m 2H), 7.86−7.93 (m, 3H), 8.62 (dd, J = 4.8, 1.5, 1H), 8.84 (d, J = 2.0, 1H). ^{13}C NMR ($CDCl_3$): δ 41.52, 51.21, 53.20, 60.21, 118.57, 123.66, 124.57, 127.17, 127.21, 127.44, 127.79, 128.97, 129.73, 133.96, 134.42, 135.49, 140.81, 148.21, 149.08, 151.14, 166.74. Anal. ($C_{26}H_{26}Cl_2N_4O$·$(COOH)_2$·2H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-pyridine-4-yl-benzamide (31)** was prepared from 4-pyridine-4-yl-benzoic acid hydrochloride[21] and **6** employing an alteration of procedure B as described for **29**. Yield: 57%. R_f = 0.40 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp (oxalate, ethanol) 192 °C. IR (film): ν 3288, 1648. ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.05−3.07 (m, 6H), 4.13 (m, 2H), 5.77−5.79 (m, 2H), 6.53 (s, 1H), 6.93 (m, 1H), 7.08−7.13 (m, 2H), 7.49 (m, 2H), 7.66 (m, 2H), 7.89 (m, 2H), 8.51 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 42.29, 51.90, 53.87, 60.82, 118.75, 121.78, 124.73, 127.29, 127.57, 127.92, 129.12, 129.76, 134.04, 134.86, 147.10, 150.30, 151.06, 166.41. Anal. ($C_{26}H_{26}Cl_2N_4O$·$(COOH)_2$·0.5H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-pyrimidin-2-yl-benzamide (32)** was prepared from 4-pyrimidine-2-yl-benzoic acid hydrochloride[21] and **6** employing an alteration of procedure B as described for **29**. Yield: 33%. R_f = 0.31 ($CHCl_3$/CH_3OH 10:1). Mp (hydrochloride, methanol/diethyl ether) 186 °C. ^{1}H NMR ($CDCl_3$): δ 2.62 (s, 4H), 3.05 (s, 6H), 4.10 (s, 2H), 5.72−5.82 (m, 2H), 6.53 (t, J = 5.2, 1H), 6.91 (dd, J = 6.8, 2.5, 1H), 7.10−7.13 (m, 2H), 7.20 (t, J = 4.7, 1H), 7.88 (d, J = 8.2, 2H), 8.47 (d, J = 8.2, 2H), 8.78 (d, J 4.7, 2H). ^{13}C NMR ($CDCl_3$): δ 42.23, 51.85, 53.82, 60.78, 118.71, 119.70, 124.64, 127.30, 127.50, 128.35, 129.07, 129.71, 133.94, 136.14, 140.32, 151.05, 157.14, 163.48, 166.66. Anal. ($C_{25}H_{25}Cl_2N_5O$·2HCl·2H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-(1*H*-imidazol-2-yl)-benzamide (33)** was prepared from 4-(1*H*-imidazol-2-yl)-benzoic acid[22] and **6** according to procedure B. Yield: 32%. R_f = 0.32 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp (oxalate, ethanol) 176 °C. IR (film): ν 3203, 1634. ^{1}H NMR ($CDCl_3$): δ 2.66 (m, 4H), 3.04−3.10 (m, 6H), 4.01 (d, J 4.3, 2H), 5.72−5.83 (m, 2H), 7.04 (dd, J 6.8, 2.5, 1H), 7.15−7.21 (m, 4H), 7.87−7.94 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 42.60, 52.26, 54.34, 61.32, 119.84, 125.46, 125.87, 127.95, 128.66, 131.75, 133.87, 134.43, 134.86, 146.39, 151.91, 168.49. Anal. ($C_{24}H_{25}Cl_2N_5O$·2$(COOH)_2$).

Quinoxaline-2-carboxylic acid-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-amide (34). Prepared from quinoxaline-2-carboxylic acid and **6** according to procedure B. Yield: 67%. R_f = 0.44 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp. (oxalate, ethanol) 148 °C. IR (film): ν 3397, 1671. ^{1}H NMR ($CDCl_3$): δ 3.06−3.12 (m, 4H), 3.91 (s, 6H), 4.21 (m, 2H), 5.84−5.87 (m, 2H), 6.94 (m, 1H), 7.08−7.14 (m, 2H), 7.79−7.89 (m, 2H), 8.09 (m, 1H), 8.14−8.20 (m, 2H), 9.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 40.78, 51.02, 53.04, 60.02, 118.43, 124.37, 127.24, 127.30, 128.84, 129.26, 129.30, 129.41, 130.68, 131.42, 133.76, 140.01, 143.15, 143.67, 150.97, 162.92. Anal. ($C_{23}H_{23}Cl_2N_5O$·$(COOH)_2$·0.25H_2O) C, H, N.

Benzo[*b*]thiophene-2-carboxylic acid-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-amide (35) was prepared from benzo[*b*]thiophene-2-carboxylic acid and **6** according to procedure A. Yield: 92%. R_f = 0.62 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp (oxalate, ethanol) 78 °C. IR (film): ν 3304, 1628. ^{1}H NMR ($CDCl_3$): δ 2.65 (s, 4H), 3.05−3.07 (m, 6H), 4.10 (m, 2H), 5.73−5.79 (m, 2H), 6.74 (s, br., 1H), 6.90 (m, 1H), 7.08−7.16 (m, 2H), 7.34−7.42 (m, 2H), 7.51−8.12 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 41.52, 50.96, 53.02, 60.00, 118.57, 122.63, 124.58, 124.84, 124.98, 125.25, 126.27, 127.42, 127.47, 128.60, 129.87, 133.91, 138.35, 139.03, 140.77, 150.99, 162.19. Anal. ($C_{23}H_{23}Cl_2N_3OS$·$(COOH)_2$) C, H, N.

2-Benzofuran-2-carboxylic acid {4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-amide (36) was prepared from 2-benzofuran-2-carboxylic acid and **6** according to procedure B. Yield: 70%. R_f = 0.65 ($CHCl_3$/CH_3OH 10:1). Mp (hydrochloride, methanol/diethyl ether) 242−244 °C. IR (film): ν 3314, 1648. ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.07−3.90 (m, 6H), 4.13 (m, 2H), 5.71−5.82 (m, 2H), 6.83 (t, J = 5.4, 1H), 6.85 (m, 1H), 7.09−7.16 (m, 2H), 7.28 (m, 1H), 7.41 (m, 1H), 7.47−7.50 (m, 2H), 7.65 (d, J = 7.7, 1H). ^{13}C NMR ($CDCl_3$): δ 40.65, 51.18, 53.18, 60.14, 110.46, 111.65, 118.55, 122.68, 123.66, 124.51, 126.85, 127.41, 127.51, 129.10, 129.26, 133.92, 148.54, 151.13, 154.63, 158.60. Anal. ($C_{23}H_{23}Cl_2N_3O_2$·HCl·H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)-piperazin-1-yl]-butyl}-4-pyridine-3-yl-benzamide (42)** was prepared from 4-pyridine-3-yl-benzoic acid hydrochloride[21] and 4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-butylamine[15,17] employing an alteration of procedure B as described for **29**. Yield: 33%. R_f = 0.44 ($CHCl_3$/CH_3OH 10:1, 1% NH_4OH). Mp (hydrochloride, chloroform/diethyl ether) 189 °C. IR (film): ν 3299, 1640. ^{1}H NMR ($CDCl_3$): δ 1.64−1.74 (m, 4H), 2.61 (s, 4H), 3.00 (s, 4H), 3.51 (q, J = 6.1, 2H), 6.86 (dd, J = 7.6, 2.0, 1H), 7.05−7.15 (m, 2H), 7.26 (t, J = 5.3, 1H), 7.36 (dd, J = 7.9, 4.8, 1H), 7.61 (d, J = 8.3, 1H), 7.85 (m, 1H), 7.90 (d, J = 8.3, 1H), 8.60 (dd, J = 4.8, 1.5, 1H), 8.81 (d, J = 2.2, 1H). ^{13}C NMR ($CDCl_3$): δ 24.43, 27.48, 40.07, 51.09, 53.22, 58.02, 118.47, 123.66, 124.51, 127.07, 127.34, 127.42, 127.86, 133.90, 134.36, 134.55, 135.47, 140.45, 148.12, 149.00, 151.07, 167.21. Anal. ($C_{26}H_{28}Cl_2N_4O$·3HCl·0.33$CHCl_3$) C, H, N.

Dopamine Receptor Binding Assays. A filtration binding assay was used to characterize the binding properties of membrane-associated receptors. For human $D2_L$, D3, and D4 dopamine receptors expressed in HEK 293 cells, tissue homogenates (50 mL) were suspended in 50 mM Tris-HCl/150 mM NaCl/10 mM EDTA buffer pH 7.5 and incubated with 50 μL of ^{125}I-IABN at 37 °C for 60 min. Nonspecific binding was determined using 25 μM (+)-butaclamol. For competition experiments, the radioligand concentration was generally equal to 0.5 times the K_d value, and the concentration of the competitive inhibitor ranged over 5 orders of magnitude. Binding was terminated by the addition of cold wash buffer (10 mM Tris-HCl/150 mM NaCl, pH 7.5) and filtration over glass-fiber filters (Schleicher and Schuell No. 32). Filters were washed with 10 mL of cold buffer, and the radioactivity was measured using a Packard Cobra gamma counter. Estimates of the equilibrium dissociation constant and maximum number of binding sites were obtained using unweighted nonlinear regression analysis of data modeled according to the equation describing mass action binding. Data from competitive inhibition experiments were modeled using nonlinear regression analysis to determine the concentration of inhibitor that displaced 50% of the specific binding of the radioligand. Competition curves were modeled for a single site, and the IC_{50} values were converted to equilibrium dissociation constants (K_i values) using the Cheng−Prusoff[23] correction. Mean K_i values SEM are reported for at least three independent experiments.

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Supporting Information Available: Elemental Analyses. This information is available free of charge via the Internet at http://pubs.acs.org.

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