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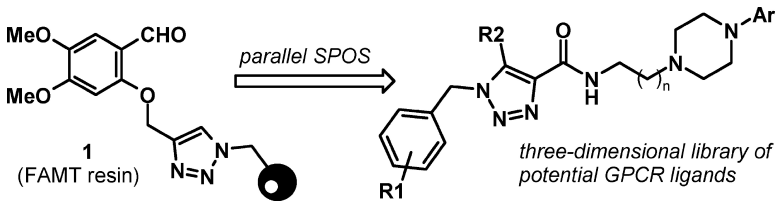
J. Comb. Chem., **2006**, 8 (2), 252-261• DOI: 10.1021/cc050127q • Publication Date (Web): 20 January 2006



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Click Chemistry on Solid Phase: Parallel Synthesis of *N*-Benzyltriazole Carboxamides as Super-Potent G-Protein Coupled Receptor Ligands

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Received September 23, 2005

The click chemistry-based backbone amide linker **1** was employed for an efficient and practical parallel synthesis of 1,2,3-triazole carboxamides when 1,3-dipolar cycloaddition was exploited for both the construction of a compound library and the functionalization of the resin. A three-step solid-phase-supported sequence included reductive amination by *N*-phenylpiperazinyl-substituted alkylamines, N-acylation by alkynoic acids, and azide-alkyne [3 + 2] cycloaddition. In most cases, cleavage under acidic conditions yielded the final products in excellent purities. A focused library of 60 target compounds was screened for G-protein coupled receptor binding employing eight biogenic amine receptors. Radioligand displacement experiments indicated a number of hit compounds revealing excellent receptor recognition when the methyl-substituted *N*-benzyltriazoles **29**, **40**, and **42** exhibited superior affinities for the α1 subtype (K_i = 0.056−0.058 nM).

Introduction

The impact of parallel solid phase organic synthesis (SPOS) has rapidly improved the efficiency of drug discovery in recent years. The methodology evolved to become a powerful tool for both lead-finding and lead optimization, revealing important advantages as the ease of reaction workup and the use of a large excess of reagents to drive a reaction to completion without the requirement of purification.[1] Since an appropriate linker displaying optimal reactivity and swelling is crucial for the success of any SPOS strategy, we prepared novel, functionalized resins, taking advantage of the concept of click chemisty.[2] Thus, 1,3-dipolar cycloaddition of alkynyl-substituted handles with azidomethyl polystyrene led to a new family of highly efficient BAL (backbone amide linker),[3] REM (regenerative Michael acceptor), and SPAn (solid/solution-phase annulation) resins.[4] Intending to apply the click linker **1** for our ongoing studies on G-protein coupled receptor ligands with unique selectivity and efficacy profiles,[5] we planned to take advantage of the concept of privileged structures[6] when a judicious bioisosteric replacement should be capable of providing ligands for more than one receptor (Scheme 1). For family A GPCRs, we identified carboxamides of type **2**, as such a privileged structure serving also as potential PET imaging agents.[7] On the basis of **2**, we herein present our investigations on the compound library **3** when the *N*-benzyl-1,2,3-triazole function, readily available by 1,3-dipolar cycloaddition, was exploited for both a pharmacophoric element and a structural moiety of BAL resin **1**.

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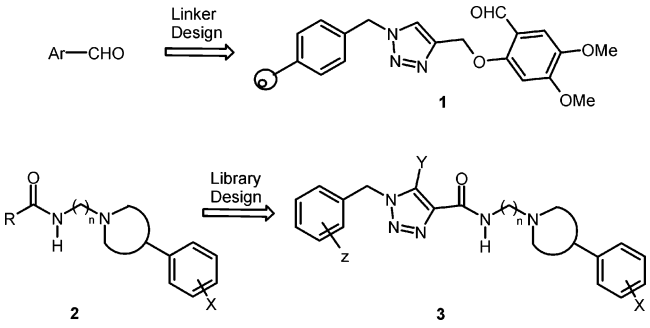
Scheme 1. *N*-Benzyl-1,2,3-triazoles as Linker Elements and Target Compounds

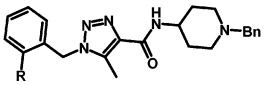
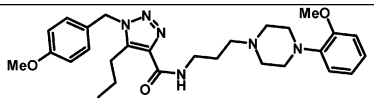


Results and Discussion

1,2,3-Triazoles that are easily accessible by 1,3-dipolar cycloaddition have never been introduced into dopaminergic or adrenergic agents, although triazole-based 5-HT receptor ligands are described in the literature.[8] To explore the applicability of mono- and disubstituted 1,2,3-triazole carboxamides as pharmacophoric elements within the privileged structure **2**, we developed a BAL resin-based SPO synthesis[9] when we tried to take advantage of our recently established formylaryloxymethyltriazole (FAMT) resin **1**, easily available by copper-catalyzed 1,3-dipolar cycloaddition[10] with azidomethyl polystyrene and the respective propargyloxy-substituted benzaldehyde.[3] The plan of synthesis involved structural variations on both aromatic residues and the alkyl spacer, resulting in the triazole carboxamides of type **4** bearing three points of diversity (Scheme 2). Immobilization of aminoalkyl piperazine residues by reductive amination of **1** should de followed by acylation with different activated alkynoic acids, [3 + 2] cycloaddition employing benzyl azides as 1,3-dipolar agents, and subsequent hydrolytic removal of the product from the solid support.

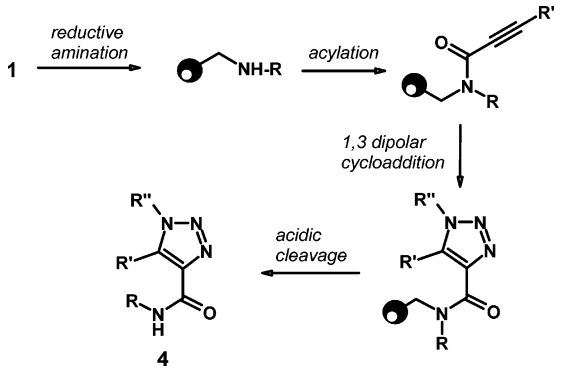
10.1021/cc050127q CCC: $33.50
Published on Web 01/20/2006

Table 1. Optimization Results for 1,3-Dipolar Cycloaddition[a]

	 **4a**: R=H **4b**: R=Br		 **4c**	
conditions for cycloaddition	yield (%)	purity (%)	yield (%)	purity (%)
DMSO, 180°C, 30 min microwave heating.	**4a**: 62 **4b**: 53	92 78	37	95
DMF, 150°C, 36 h, conventional heating	**4a**: 62 **4b**: 57	96 84	34[b]	98

[a] Reductive amination, acyclation, and acidic cleavage were performed according to the reaction conditiones given in Scheme 3. [b] 48 h of heating is required for the completeness of the reaction.

Scheme 2. Strategy for the SPO Synthesis of 1,2,3-Triazole Carboxamides



Optimization of Crucial Reactions. Since we aimed to generate a compound collection facilitating an in vitro screening without performing purification by chromatography, superior reaction conditions had to be elaborated by investigating a model reaction sequence. After immobilization of 4-amino-1-benzylpiperidine by reductive amination of the BAL resin **1**, FT-IR-based monitoring of the N-alkynoylation showed a very low degree of conversion when variations of the reaction conditions indicated that the success depended on the nature of the activating reagents. Whereas the components HOAt, HOBt, or HATU resulted in decomposition of the alkyne partial structure, butynoic acid could be readily attached when activated by 5 equiv of DIC. Since the reactivity of alkynyl carboxamides toward [3 + 2] cycloadditions with azides is known to be poor when compared to the respective esters,[11] A. Katritzky and collaborators took advantage of a microwave-assisted process[12] that resulted, however, in the formation of both 1,4- and 1,5-substituted regioisomers. To ensure the applicability of the precursors planned to be used in the library production, we employed benzyl-, 3-bromobenzyl-, and 4-methoxybenzyl-substituted azides as representative building blocks. Synthesis of the model compounds **4a**−**c** was performed using both microwave technology and conventional heating. In fact, microwave irradiation at 180 °C for 30 min in DMSO and conventional heating in a parallel synthesis reactor at 150 °C for 36 h gave in all cases comparable yields and purities.

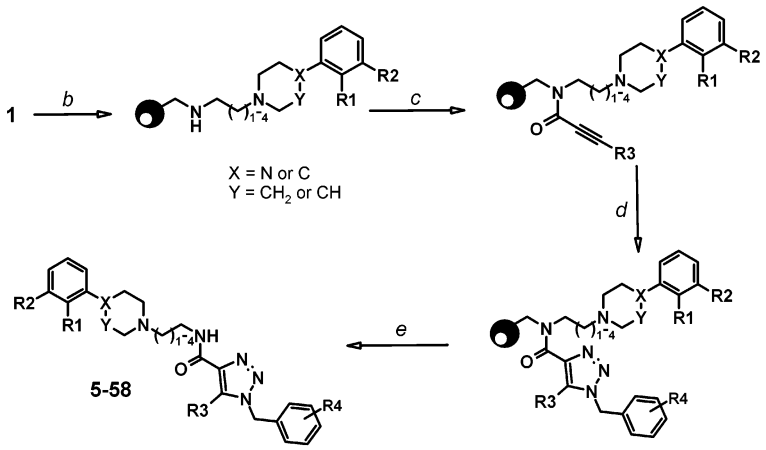
HPLC, ^{1}H NMR, and LC/MS analysis clearly indicated that the expected triazole-4-carboxamide regioisomers were formed exclusively and in high purities. On the basis of the results shown in Table 1, the syntheses proved to be suitable, robust, and reproducible for the production of a 3D library. Since the parallelization of the conventional heating requires substantially less technical sophistication than parallel microwave-assisted synthesis, we decided to perform the library production without microwave technology.

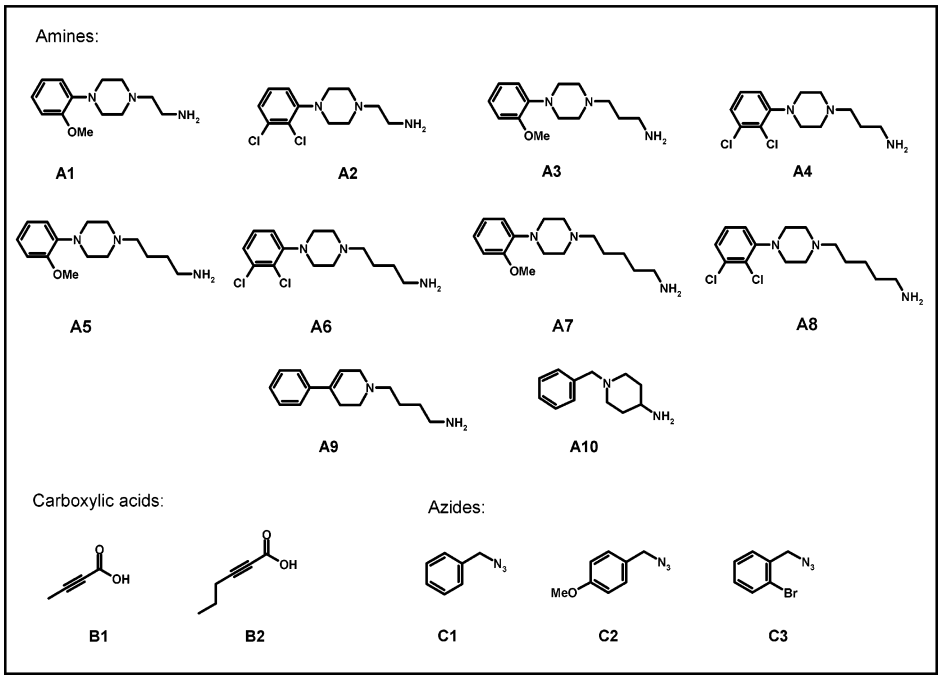
3D-Library Production. According to the procedure described above, 60 *N*-benzyltriazole carboxamides were prepared by combination of 10 primary amines, two alkynoic acids, and three benzyl azides, as depicted in Scheme 3.

The immobilization of the amines **A1**−**A10** to the FAMT resin **1** in the presence of $NaBH(OAc)_3$ was randomly monitored by using FT-IR. The reactions were considered to be complete when the absorption band at 1680 cm^{-1} had disappeared. Amide bond formation with the alkynoic acids **B1** or **B2** was promoted by using DIC in CH_2Cl_2 when the presence of resin-bound carboxamide could be qualitatively ascertained by FT-IR displaying the appearance of the significant absorption bands at 2200 cm^{-1} (C≡C) and at 1625 cm^{-1} (CON). The subsequent 1,3-dipolar cycloaddition step using the azides **C1**−**C3** was performed at 150 °C for 48 h in a commercial parallel reactor. Completeness of the reaction was indicated by the disappearance of the absorption band at 2200 cm^{-1} (C≡C). Finally, the cleavage from the solid support was enabled by treatment with TFA (2% in methylene chloride) to afford the crude products **4a**−**c** and **5**−**61**. The yields of the cleavage products varied between 9 and 69% (Table 2), whereas better yields were obtained when amines bearing longer alkyl spacers were used. Fortunately, the average purity of the target compounds was 89.6% when only four members of the library displayed purities below 60% (**53**, **54**, **55**, and **57**). According to the LC/MS data, the reason for the low purities in these four cases is partial oxidation of the products. Because most of the compounds show high to excellent purities, the triazole formation can be considered to work smoothly. Otherwise, the respective alkynoyl carboxamides should be found in the LC/MS chromatograms. Presumably, a combination of incomplete reductive amination and acylation as well as undesirable cleavage during the cycloaddition or the frequent washing steps leads to the moderate yields. Representative chromatograms of two library members are depicted in Figure 1.

It is worthy to note that exclusively the regioselective

Scheme 3. Solid-Phase-Supported Synthesis of Test Compounds **4c** and **5**−**57**[a]





[a] Test compounds **4a**,**b** and **58**−**61** were prepared analogously using amine A10 for reductive amination. [b]Amines A1−A9, $Na(OAc)_3BH$, CH_2Cl_2, rt, 24 h. [c]Acid B1 or B2, DIC, CH_2Cl_2, rt, 2 × 7 h. [d]Azides C1−C3, DMF, 150 °C, 48 h. [e]TFA 2% in CH_2Cl_2, rt, 2 h.

formation of triazole-4-carboxamide was observed in the final products. COSY and NOE spectra of some of the derivatives confirm the identity of this regioisomer. The regioselectivity obtained for all the library members during the cycloaddition step can be explained by the high steric hindrance at the solid-supported alkyne promoting formation of the less hindered triazole.

Screening. Crude compounds were evaluated in vitro for binding affinity to the human $D2_{long}$, $D2_{short}$, D3, and D4 receptors, as well as to the porcine D1 and α1 receptor, and 5-HT_1, 5-HT_{2A} receptors in a screening assay. Thereby, the displacement of the radioligands [^{3}H]spiperone (D2, D3, D4), [^{3}H]SCH 23390 (D1), [^{3}H]prazosin (α1), [^{3}H]8-HO-DPAT (5-HT_{1A}), and [^{3}H]ketanserin 5-HT_2) was investigated in the presence of 10 μM, 100 nM, and 1 nM concentrations of the test compounds (Table 3).

In general, the test compounds bearing C4 and C5 alkyl chains revealed high affinities for the D2, D3, and D4 receptors with a preference for the D3 subtype, when the dichlorophenylpiperazine derivative **37** turned out to be the most potent D3 binder. Surprisingly, a series of compounds exhibits outstanding radioligand displacement at the α1 receptor, mainly when the molecule features a methoxyphenyl moiety and a C4 or C5 alkyl chain. Interestingly, some of the strong α1 binders (e.g., **29**, **41**, **44**) also displayed high selectivity over the D3 receptor (Table 3). Some hits were also detected for the serotoninergic receptors, when **30** revealed strongest radioligand displacement from the 5-HT1 subtype.

Binding affinities (K_i). K_i values were determined for the most promising library members in purified form (purity > 95%) and derived from the dose−response curves by nonlinear regression analysis. When a hill slope below −0.7 was observed, a biphasic curve was calculated. Selection was based on the screening results, whereas mainly compounds achieved from the amines A5−A8 turned out to be the most promising candidates. Additionally, K_i values for some

Table 2. Purities and Yields of Library Products

no.	building blocks	APCI-MS $(M+1)^+$	MW	purity LC/MS (%)	crude yield (%)	no.	building blocks	APCI-MS $(M+1)^+$	MW	purity LC/MS (%)	crude yield (%)
5	A1B1C1	435.2	434.54	92	9	**34**	A6B1C1	501.6	501.46	97	40
6	A1B1C2	465.2	464.57	91	14	**35**	A6B1C2	532.0	531.48	93	25
7	A1B1C3	513.7	513.44	96	22	**36**	A6B1C3	581.0	580.35	97	64
8	A1B2C1	463.3	462.60	87	25	**37**	A6B2C1	530.0	529.51	98	55
9	A1B2C2	493.1	492.62	96	12	**38**	A6B2C2	560.0	559.54	97	45
10	A1B2C3	542.2	541.49	82	24	**39**	A6B2C3	609.0	608.41	97	31
11	A2B1C1	473.5	473.40	96	12	**40**	A7B1C1	477.3	476.62	100	58
12	A2B1C2	503.9	503.43	91	9	**41**	A7B1C2	507.4	506.65	93	69
13	A2B1C3	553.0	552.30	100	27	**42**	A7B1C3	555.9	555.52	80	66
14	A2B2C1	501.8	501.46	96	21	**43**	A7B2C1	505.5	504.68	95	48
15	A2B2C2	531.8	531.48	95	20	**44**	A7B2C2	536.0	534.70	94	51
16	A2B2C3	581.0	580.35	100	37	**45**	A7B2C3	584.6	583.57	94	60
17	A3B1C1	449.2	448.57	87	30	**46**	A8B1C1	515.9	515.49	90	63
18	A3B1C2	479.4	478.59	93	28	**47**	A8B1C2	546.0	545.51	94	52
19	A3B1C3	527.9	527.46	97	36	**48**	A8B1C3	595.0	594.38	99	62
20	A3B2C1	477.4	476.62	86	51	**49**	A8B2C1	544.1	543.54	98	56
4c	A3B2C2	507.4	506.65	93	23	**50**	A8B2C2	573.4	573.57	86	51
21	A3B2C3	556.0	555.52	95	41	**51**	A8B2C3	623.0	622.44	98	51
22	A4B1C1	488.9	487.43	94	25	**52**	A9B1C1	430.1	429.50	91	41
23	A4B1C2	518.0	517.46	96	25	**53**	A9B1C2	460.3	459.60	56	40
24	A4B1C3	567.0	566.33	80	46	**54**	A9B1C3	509.8	508.40	46	33
25	A4B2C1	516	515.49	90	26	**55**	A9B2C1	458.3	457.60	39	47
26	A4B2C2	545.9	545.51	99	46	**56**	A9B2C2	486.0	486.65	89	49
27	A4B2C3	595.0	594.38	81	60	**57**	A9B2C3	537.0	536.52	59	65
28	A5B1C1	463.3	462.60	91	44	**4a**	A10B1C1	390.2	389.50	91	51
29	A5B1C2	493.4	492.62	85	49	**58**	A10B1C2	420.3	419.50	89	42
30	A5B1C3	541.9	541.49	95	51	**4b**	A10B1C3	468.7	468.40	85	46
31	A5B2C1	491.5	490.65	86	53	**59**	A10B2C1	418.3	417.60	97	43
32	A5B2C2	521.3	520.68	98	46	**60**	A10B2C2	448.0	447.6	95	38
33	A5B2C3	570.5	569.55	94	44	**61**	A10B2C3	496.90	496.50	81	41

members from the A3 series were determined. Results are shown in Table 4.

In general, when looking at the D3 receptor, the (2,3-dichlorophenyl)piperazine residue induces higher affinities, as compared to the (2-methoxyphenyl)piperazine moiety. Apparently, in this series, strong D3 binding requires an unsubstituted benzyl residue, a propyl chain on the triazole ring, or both. In this series, the analogue **37** displayed the highest affinity. In the case of α1 receptor, extremely high affinities were obtained for some receptor ligands, exhibiting binding values in subnanomolar range. The highest affinity was obtained for the compounds **40** (K_i = 56 pM), **29**, and **42** (both K_i = 58 pM). Apparently, α1 binding requires a methoxyphenylpiperizine moiety connected to a methyl-substituted triazole ring via a C4 or C5 atom spacer. For 5-HT receptors, none of the tested compounds was significantly active.

Summary

In summary, we applied the click chemistry-derived FAMT linker for a parallel solid-supported synthesis. A library of 60 test compounds revealing three points of diversity was generated by a four-step BAL-based strategy including reductive amination, acylation, 1,3-dipolar cycloaddition, and TFA-induced cleavage. The target compounds were screened for neuroreceptor binding employing eight different GPCRs, whereas high-affinity dopamine D3 and α1-receptor binders were identified. The library members **29**, **40**, and **42** revealed K_i values for the α1 receptor in the medium picomolar range.

Experimental Section

General. Polystyrene resins were purchased from Nova-Biochem. SPOS was performed manually in an Advanced Chemtech PLS synthesizer equipped with PTFA reactors or in a Heidolph Synthesis I equipped with PFA vessels. Absolute solvents were purchased from Acros. Commercially available starting material was used without further purification. IR spectra were registered on a Jasco model 410 FT-IR instrument using a film of substance on a NaCl pill or via KBr pellet. ^{1}H NMR (360 MHz) spectra were determined on a Brucker AM 360 or a Brucker AVANCE spectrometer in solution. COSY and NOE spectra (600 MHz) spectra were determined in solution using instrument Brucker AVANCE 600. LC/MS analyses were conducted in an Agilent Binary Gradient System in combination with ChemStation Software (MeOH/0.1 N aq HCOOH 10/90−90/10) and UV detection at 254 nm using a Zorbax SB-C8 (4.6 mm × 150 mm, 5 μm) with a flow rate of 0.5 mL/min. Mass detection was pointed out with a Brucker Esquire 2000 ion-trap mass spectrometer using an APC ionization source. MS spectra were recorded on a Finnigan MAT TSQ 70 spectrometer. Flash chromatography was done using silica gel (40−63 μm) as stationary phase. TLC analyses were done on Merck 60 F_{254} glass plates and analyzed by UV light (254 nm) or by iodine vapor.

Receptor binding data were generated by measuring the ability of the compounds to compete with [^{3}H]spiperone for the cloned human dopamine receptor subtypes $D2_{long}$, $D2_{short}$, D3, and D4 expressed in Chinese hamster ovary cells (CHO).[5a,13] Affinities to D1 were determined by using

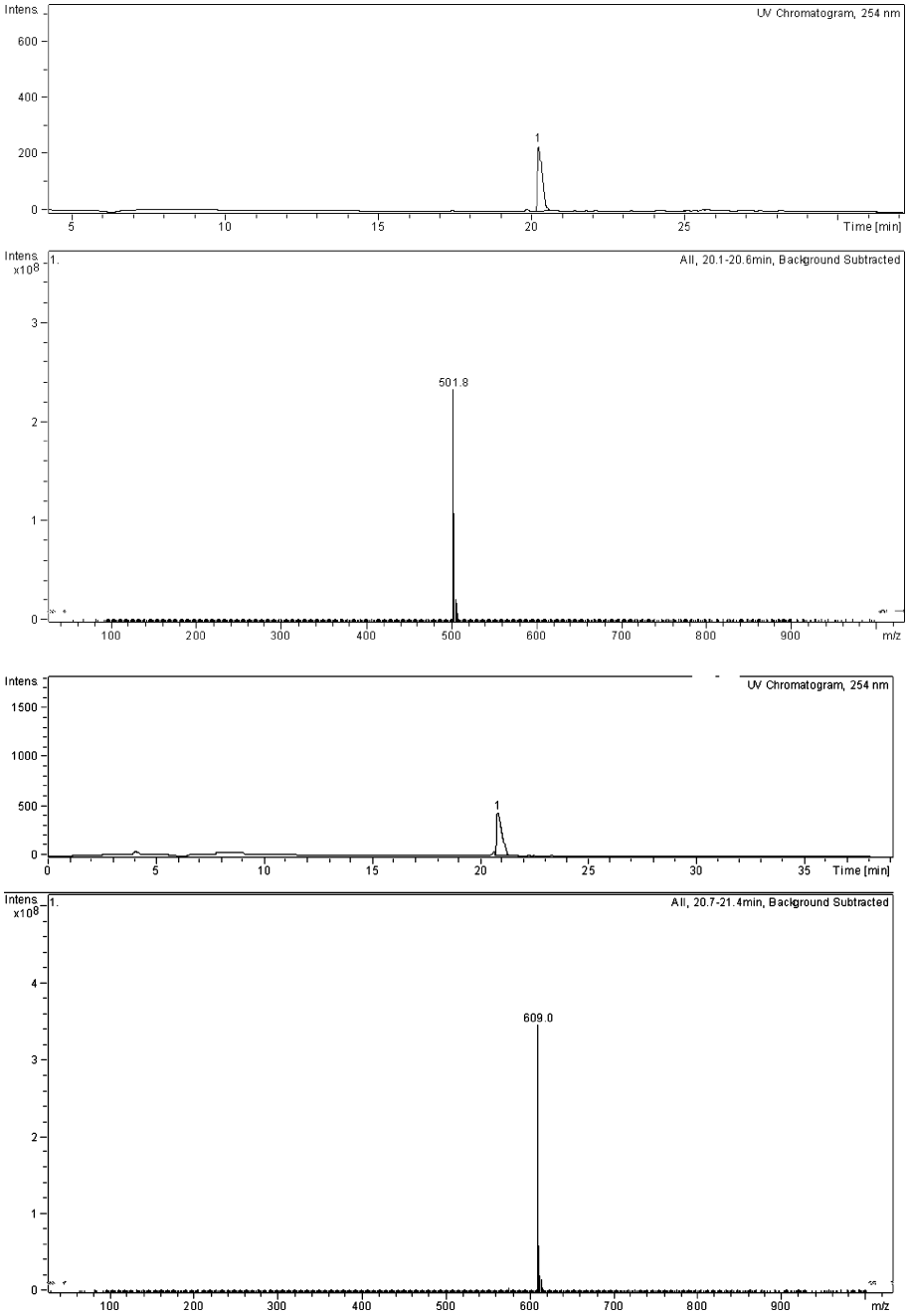


Figure 1. LC/MS chromatograms of the library members **14** (top) and **39** (bottom).

porcine striatal membranes and the D1 selective radioligand [^{3}H]SCH 23390. The measure of binding to the α1 receptor and serotonin receptor subtypes $5HT_{1A}$ and $5HT_2$ was done with porcine cortical membranes and the radioligands [^{3}H]-prazosin, [^{3}H]8-OH-DPAT, and [^{3}H]ketanserin, respectively. Screenings were performed at concentrations of 10 μM, 100 nM, and 1 nM of the tested compounds. K_i values are derived from dose−response curves using eight different concentrations (from 0.01 to 100 000 nM) in triplicate, using the equation of Cheng and Prussoff.[14]

Preparation from Amines A1−A2. These amines were readily prepared by N-alkylation of *o*-methoxyphenylpiperazine or 2,3-dichlorphenyl piperazine with phthaloyl alkyl bromides and subsequent hydrazinolysis following the methodology described by Glennon et al.[15] Characterization of the intermediates and final products was done according to the procedure reported earlier.[5a]

2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethylamine (A2). MS *m*/*z* 273 (M^+). IR (NaCl) ν (cm^{-1}): 3423, 2941, 2821, 1638, 1576, 1448, 1240. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.32−1.48 (bs, 2H), 2.54 (t, J = 6.1 Hz, 2H), 2.62−2.74 (m, 4H), 2.86 (t, J = 6.1 Hz, 2H), 3.05−3.16 (m, 4H), 6.98 (dd, J = 6.3, 3.1 Hz, 1H), 7.15−7.2 (m, 2H).

Preparation from Amine A3−A9. These amines were prepared from 1-(2-methoxyphenyl)-piperazine or 1-(2,3-dichlorphenyl)-piperazine by alkylation with the respective bromoalkyl nitrile and subsequent reduction by using $LiAlH_4$ as is described in the literature.[15] The intermediates were used without further purification. Characterization of the

Table 3. Relative Displacements of Radioligand at 100 nM Concentration

no.	series	D1	$D2_L$	$D2_S$	D3	D4	α1	$5HT_{1A}$	$5HT_2$	no.	series	D1	$D2_L$	$D2_S$	D3	D4	α1	$5HT_{1A}$	$5HT_2$
5	A1B1C1	0	0	7	17	3	57	31	9	**31**	A5B2C1	36	25	35	79	10	89	72	5
6	A1B1C2	6	1	1	1	12	53	45	5	**32**	A5B2C2	17	8	22	56	13	94	59	10
7	A1B1C3	0	2	3	14	6	55	59	6	**33**	A5B2C3	17	15	25	69	22	90	48	3
8	A1B2C1	1	5	14	11	77	50	21	0	**34**	A6B1C1	14	25	27	88	4	70	51	30
9	A1B2C2	5	12	8	10	18	51	19	0	**35**	A6B1C2	10	8	18	68	8	72	39	18
10	A1B2C3	0	4	3	11	11	54	12	3	**36**	A6B1C3	4	12	29	53	0	47	18	20
11	A2B1C1	0	2	2	0	0	3	2	0	**37**	A6B2C1	37	41	46	95	15	69	42	15
12	A2B1C2	6	11	12	35	15	42	nd	nd	**38**	A6B2C2	16	7	3	66	3	55	38	8
13	A2B1C3	0	7	13	30	6	30	28	6	**39**	A6B2C3	0	12	25	55	6	34	18	3
14	A2B2C1	1	7	1	19	3	58	22	0	**40**	A7B1C1	9	54	58	56	18	98	56	12
15	A2B2C2	6	7	16	30	12	12	18	0	**41**	A7B1C2	12	51	53	29	20	96	76	18
16	A2B2C3	0	1	0	8	9	10	19	1	**42**	A7B1C3	25	68	82	78	50	98	66	12
17	A3B1C1	0	9	11	9	68	68	80	5	**43**	A7B2C1	17	81	88	87	35	100	73	11
18	A3B1C2	8	11	10	6	19	77	83	9	**44**	A7B2C2	10	42	51	36	24	98	35	1
19	A3B1C3	12	10	15	16	29	71	72	0	**45**	A7B2C3	11	61	70	66	39	94	31	0
20	A3B2C1	4	2	7	16	11	71	17	0	**46**	A8B1C1	3	39	46	1	83	66	30	18
4c	A3B2C2	7	14	14	17	18	75	8	9	**47**	A8B1C2	6	33	52	74	26	89	14	23
21	A3B2C3	4	2	1	7	23	73	0	0	**48**	A8B1C3	6	19	35	61	9	54	3	8
22	A4B1C1	0	7	5	39	12	51	21	2	**49**	A8B2C1	7	17	31	69	2	56	36	3
23	A4B1C2	0	2	19	23	11	59	28	0	**50**	A8B2C2	10	16	15	38	7	42	0	4
24	A4B1C3	3	0	7	23	5	23	15	0	**51**	A8B2C3	0	16	22	39	3	23	9	11
25	A4B2C1	0	5	12	34	7	33	10	0	**4a**	A10B1C1	8	9	14	32	8	41	6	3
26	A4B2C2	12	8	14	43	17	41	13	14	**58**	A10B1C2	0	2	1	0	0	2	3	0
27	A4B2C3	2	1	0	8	0	22	0	0	**4b**	A10B1C3	0	7	1	1	1	7	4	7
28	A5B1C1	9	14	15	47	6	82	72	12	**59**	A10B2C1	2	11	0	3	8	15	11	0
29	A5B1C2	8	16	13	28	15	91	89	12	**60**	A10B2C2	0	2	5	7	0	19	6	2
30	A5B1C3	14	14	33	68	24	93	98	0	**61**	A10B2C3	5	0	0	0	38	7	25	3

Table 4. K_i Values of Selected Library Members[a]

		K_i values (nM)						
		[^{3}H]SCH 23990	[^{3}H]spiperone				[^{3}H] prazosin	[^{3}H] 8-HO-DPAT
no.	building blocks	pD1	hD2L	hD2S	hD3	hD3	pα1	p5-HT1
17	A3B1C1	nd	nd	nd	nd	nd	nd	30
18	A3B1C2	nd	nd	nd	nd	230	nd	31
19	A3B1C3	nd	nd	nd	nd	66	nd	27
28	A5B1C1	3000	230	370	68	970	0.14[b]	32
29	A5B1C2	800	55	76	29	280	0.058[b]	26
30	A5B1C3	410	62	53	32	91	0.077[b]	35
31	A5B2C1	530	57	51	11	300	0.12[b]	52
32	A5B2C2	360	43	66	13	130	0.087[b]	40
33	A5B2C3	140	22	25	3.5	76	0.15[b]	nd
34	A6B1C1	200	39	20	4.3	280	1.4[b]	nd
37	A6B2C1	170	14	15	2.4	220	5.5	nd
40	A7B1C1	570	9.4	11	16	160	0.056[b]	41
41	A7B1C2	2500	17	21	87	270	0.10	50
42	A7B1C3	350	4.9	5.7	15	42	0.058[b]	62
43	A7B2C1	330	3.2	3.0	7.8	26	0.10	34
44	A7B2C2	580	7.7	8.2	22	66	0.23	nd
45	A7B2C3	260	5.3	6.9	7.4	40	0.38	nd
46	A8B1C1	500	10	11	8.5	250	4.6	nd
47	A8B1C2	4200	9.1	32	34	290	4.4	nd

[a] Derived from two to eight independent experiments, each done in triplicate. [b] High-affinity binding site.

intermediates and final products was in agreement with those reported in the literature.[5a,17]

2-[4-(2,3-Dichlorphenyl)piperazin-1-yl]propionitrile. MS *m*/*z* 283 (M^+). IR (NaCl) ν (cm^{-1}): 2945, 2882, 2825, 2248, 1577, 1449, 1240, 1135, 958, 782. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 2.59 (t, J = 6.8 Hz, 2H), 2.71−2.77 (m, 4H), 2.81 (t, J = 6.8 Hz, 2H), 3.07−3.15 (m, 4H), 6.98 (ddd, J = 6.9, 2.7, 2.4 Hz, 1H), 7.17−7.21 (m, 2H).

2-[4-(2-Methoxyphenyl)piperazin-1-yl]butyronitrile. MS *m*/*z* 259 (M^+). IR (NaCl) ν (cm-1): 2942, 2819, 2247, 1500, 1452, 1241,1139, 1025, 753. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.89 (q, J = 6.9 Hz, 2H), 2.48 (t, J = 7.1 Hz, 2H), 2.55 (t, J = 6.6 Hz, 2H), 2.68−2.70 (m, 4H), 3.08−3.25 (m, 4H), 3.89 (s, 3H), 6.89 (d, J = 7.7 Hz, 1H), 6.94−7.10 (m, 3H).

2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyronitrile. MS *m*/*z* 297 (M^+). IR (NaCl) ν (cm^{-1}): 2945, 2821, 2246, 1577, 1449, 1242, 1134, 969. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.89 (q, J = 6.9 Hz, 2H), 2.48 (t, J = 7.1 Hz, 2H), 2.57 (t, J = 6.9 Hz, 2H), 2.63−2.69 (m, 4H), 3.06−3.11 (m, 4H), 6.96−7.0 (m, 1H), 7.14−7.20 (m, 2H).

2-[4-(2-Methoxyphenyl)piperazin-1-yl]pentanonitrile. MS *m*/*z* 273 (M^+). IR (NaCl) ν (cm^{-1}): 2940, 2877, 2814, 2244, 1592, 1500, 1450, 1300, 1240, 1137, 1026, 752. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.65−1.82 (m, 4H), 2.38−2.50 (m, 4H), 2.60−2.73 (m, 4H), 3.06−3.18 (m, 4H), 3.89 (s, 3H), 6.89 (dd, J = 7.9, 1.1 Hz, 1H), 6.92−7.06 (m, 3H).

2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentanonitrile. MS *m*/*z* 311 (M^+). IR (NaCl) ν (cm^{-1}): 2942, 2875, 2823, 2246, 1578, 1449, 1422, 1240. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.66−1.78 (m, 4H), 2.41−2.51 (m, 4H), 2.61−2.72 (m, 4H), 3.04−3.15 (m, 4H), 6.98 (dd, J = 6.3, 3.4 Hz), 7.14−7.21 (m, 2H).

4-(4-Phenyl-3,6-dihydro-2*H*-pyridin-1-yl)butyronitrile. MS *m*/*z* 226 (M^+). IR (NaCl) ν (cm^{-1}): 2921, 2808, 2774, 2738, 2244, 1494, 1445, 1379, 1137, 749, 695. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.94 (q, J = 7.1 Hz, 2H), 2.47−2.53 (t, J = 7.1 Hz, 2H), 2.50 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 6.9 Hz, 2H), 2.74 (t, J = 5.5 Hz, 2H), 3.19 (dd, J = 6.3, 2.7 Hz, 2H), 6.07−6.11 (m, 1H), 7.23−7.28 (m, 1H, phenyl), 7.32−7.45 (m, 4H).

3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propylamine A4. MS *m*/*z* 287 (M^+). IR (NaCl) ν (cm^{-1}): 3364, 2942, 2820, 1577, 1448, 1240, 1139, 964, 780. ^{1}H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.73 (q, J = 6.9 Hz, 2H), 1.90−2.0 (bs,

2H), 2.52 (t, $J = 7.1$ Hz, 2H), 2.62−2.72 (m, 4H), 2.83 (t, $J = 6.6$ Hz, 2H), 3.05−3.14 (m, 4H), 6.98 (dd, $J = 6.3$, 3.1 Hz, 1H), 7.13−7.19 (m, 2H).

4-(4-Phenyl-3,6-dihydro-2*H*-pyridin-1-yl)butylamine A9. MS *m*/*z* 230 (M^+). IR (NaCl) ν (cm^{-1}): 3331, 2928, 2860, 1610, 1571, 1465, 1445, 1308, 1139, 824, 744, 691. ^1H NMR ($CDCl_3$, 360 MHz), δ (ppm): 1.46−1.58 (m, 4H), 2.50 (t, $J = 7.4$ Hz, 2H), 2.58−2.65 (m, 2H), 2.74 (t, $J = 5.4$ Hz, 2H), 2.77 (t, $J = 6.9$ Hz, 2H), 3.19 (dd, $J = 6.1$, 2.7 Hz, 2H), 6.06−6.11 (m, 1H), 7.22−7.28 (m, 1H), 7.30−7.45 (m, 4H).

Preparation from Benzyl Azides C1−C3. These azides were prepared according with the procedure of Alvarez et al. and the spectroscopical data corresponded with that already reported.[18]

***p*-Methoxybenzyl Azide C2.** MS *m*/*z* 163 (M^+). IR (NaCl) ν (cm^{-1}): 2958, 2936, 2837, 2095, 1612, 1585, 1513, 1463, 1442, 1303, 1249, 1176, 1033, 846, 814.

***o*-Bromobenzyl Azide C3.** MS *m*/*z* 163 (M^+). IR (NaCl) ν (cm^{-1}): 2958, 2936, 2837, 2095, 1612, 1585, 1513, 1463, 1442, 1303, 1249, 1176, 1033, 846, 814.

Preparation of FAMT Resin 1. Merrifield resin (5 g, 1.1 mmol/g) was reacted with NaN_3 (1.07 g, 16.5 mmol, 3 equiv), in 40 mL of DMSO at 60 °C for 48 h. After being cooled at room temperature, the resulting resin was sequentially washed with H_2O (5 × 35 mL), MeOH (5 × 35 mL), CH_2Cl_2 (3 × 35 mL) and Et_2O (2 × 35 mL). The precursor 4,5-dimethoxy-2-(prop-2-yn-1-yloxy)benzaldehyde was added to the azidomethyl polystyrene (IR: 2090 cm^{-1}), together with CuI (0.02 g, 0.11 mmol, 0.1 equiv), in a mixture of THF/DIPEA 2:1 (25 mL), and the resin was shaken at 35 °C for 36 h (disappearance from the band at 2090 cm^{-1}); sequentially washed with pyridine (3 × 35 mL), MeOH (5 × 35 mL), CH_2Cl_2 (5 × 35 mL), and Et_2O (2 × 35 mL); and dried under high vacuum to afford FAMT resin (IR: 1680−1670 cm^{-1} for the C═O group).

Sequence Optimization. 1-Benzyl-4-aminopiperidine (3 equiv) or 3-[4-(2-methoxyphenyl)piperazin-1-yl]propylamine (3 equiv) in CH_2Cl_2 (10 mL) was added to FAMT linker (100 mg/tube), followed of $NaBH(OAc)_3$ (3 equiv), and the mixture was shaken at room temperature for 24 h. The resins were washed with MeOH (3 × 25 mL), CH_2Cl_2 (3 × 25 mL), and Et_2O (2 × 25 mL) and dried by suction. 2-Butynoic acid or 2-hexynoic acid (5 equiv), CH_2Cl_2 (5 mL), and DIC (0.08 mL, 0.55 mmol, 5 equiv) were added to the resin, and the mixture was shaken at room temperature for 7 h and washed with CH_2Cl_2 (3 × 20 mL). The acylation procedure was repeated one more time. Finally, the resin was washed with MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and Et_2O (3 × 20 mL) and dried by suction. IR spectra signals showed signals at 2200 cm^{-1} (C≡C) and 1630 cm^{-1} (C═O amide). Cycloaddition reactions were carried out after addition of the respective benzyl azide (20 equiv) to the resin (100 mg) by (a) heating in a microwave at 180 °C, 15 min in DMSO (1 mL) or (b) conventional heating at 150 °C for 36 or 48 h in DMF (1 mL). The resins were washed extensively with DMF (5 × 20 mL), MeOH (5 × 20 mL), DMF (5 × 20 mL), MeOH (5 × 20 mL), CH_2Cl_2 (5 × 25 mL), and Et_2O (3 × 20 mL). The products were cleaved from the resin by reaction with 2% TFA in CH_2Cl_2 (10 mL) at room temperature for 2 h. The resins were filtered and washed with CH_2Cl_2 (20 mL); the combined filtrates were collected and washed separately with $NaHCO_3$ solution, separated, and dried with Na_2SO_4; and the solvent was evaporated under vacuum. The products were dried under high vacuum overnight to afford **4a−c**, which were characterized by ^1H NMR. The purities were determined by HPLC.

***N*-(1-Benzylpiperidin-4-yl)-1-benzyl-5-methyl-1,2,3-triazole-4-carboxamide 4a.** ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.55−1.67 (m, 2H), 1.95−2.05 (m, 2H), 2.10−2.21 (m, 2H), 2.50 (s, 3H), 2.75−2.90 (m, 2H), 3.49 (s, 2H), 3.87−4.02 (m, 1H), 5.55 (s, 2H), 7.05−7.17 (m, 3H), 7.27−7.87 (m, 8H).

***N*-(1-Benzylpiperidin-4-yl)-1-(2-bromo)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 4b.** ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm): 1.65−1.85 (m, 2H), 2.03−2.13 (m, 2H), 2.25−2.45 (m, 2H), 2.55 (s, 3H), 2.9−3.1 (m, 2H), 3.65 (bs, 2H), 3.95−4.1 (m, 1H), 5.6 (s, 2H), 6.69 (d, $J = 7.5$ Hz, 1H) 7.1−7.4 (m, 7H), 7.73 (d, $J = 7.2$ Hz).

***N*-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-1-(4-methoxybenzyl)-5-propyl-1,2,3-triazole-4-carboxamide 4c.** ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm): 0.93 (t, $J = 7.5$ Hz, 3H), 1.43−1.56 (m, 2H), 1.92−2.03 (m, 2H), 2.72−2.98 (m, 6H), 3.2−3.34 (m, 4H), 3.52−3.6 (m, 2H), 3.82 (s, 3H), 3.89 (s, 3H), 5.47 (s, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.92−7.09 (m, 4H), 7.16 (d, $J = 8.8$ Hz, 2H).

Library Synthesis of Benzyltriazole Carboxamides 4a−c and 5−61. FAMT resin **1** (0.8 mmol/g) was distributed in to 60 Teflon vessels (100 mg/tube), followed by addition of a solution of the corresponding primary amines A1−A10 (4 equiv) in CH_2Cl_2 (5 mL), and shaken for 30 min at room temperature. $NaBH(OAc)_3$ (0.093 g, 0.44 mmol, 4 equiv) was added, and the mixture was shaken again for 24 h. The resins were extensively washed with MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and Et_2O (3 × 20 mL) and dried by suction. To the amino-bound resins was added the corresponding acid B1 or B2 (5 equiv) and DIC (0.08 mL, 0.55 mmol, 5 equiv) in CH_2Cl_2 (5 mL). The mixture was shaken at room temperature for 7 h and washed with CH_2Cl_2 (3 × 20 mL), and the entire process of acylation was repeated. The resins finally were washed with MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and Et_2O (3 × 20 mL). For the cycloaddition, DMF (2 mL) was added to the acylated resins and the corresponding benzyl azide C1−C3 (10 equiv). The reactions were shaken at 150 °C for 48 h and washed extensively with DMF (5 × 20 mL), MeOH (5 × 20 mL), DMF (5 × 20 mL), MeOH (5 × 20 mL), CH_2Cl_2 (5 × 25 mL), and Et_2O (3 × 20 mL). Finally, the products were cleaved from the resin by reaction with 2% TFA in CH_2Cl_2 (10 mL) at room temperature for 2 h. Each resin was filtered and rinsed with CH_2Cl_2 (20 mL); the combined filtrates were collected and washed with $NaHCO_3$ saturated solution, separated, and dried with Na_2SO_4; and the solvent was evaporated under vacuum. The resultant products were dried under high vacuum overnight to afford the crude products. The products were analyzed by the LC/MS system with UV detection (254 nm) for the determination of the purity.

***N*-{2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl}-1-(2-bromo)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 13 (A2B1C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 2.55 (s, 3H), 2.62−3.15 (m, 6H), 3.18−3.34 (m, 4H), 3.69−3.82 (m, 2H), 5.64 (s, 2H), 6.75 (ddd, J = 7.3, 1.8 Hz, 1H), 7.01 (dd, J = 7.2, 2.1 Hz, 1H), 7.17−7.27 (m, 4H), 7.65 (ddd, J = 7.7, 1.4, 1.0 Hz, 1H).

***N*-{2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl}-1-(4-methoxy)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 14 (A2B2C2).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.94 (dd, J = 7.5, 7.2 Hz, 3H) 1.45−1.70 (m, 4H), 2.67−2.88 (m, 4H), 2.94 (t, J = 7.9 Hz, 2H), 3.12−3.22 (m, 4H), 3.59−3.71 (m, 2H), 3.82 (s, 3H), 5.48 (s, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.0 (ddd, J = 6.6, 2.8, 2.5 Hz, 1H), 7.16−7.21 (m, 4H).

***N*-{2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]ethyl}-1-(2-bromo)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 15 (A2B2C3).** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 0.91 (dd, J = 7.8, 7.2 Hz, 3H), 1.43−1.51 (m, 2H), 2.88 (t, J = 7.8 Hz, 2H), 3.12−3.20 (m, 2H), 3.25−3.34 (m, 2H), 3.38−3.42 (m, 2H), 3.45 (t, J = 6 Hz, 2H), 3.90−4.0 (m, 4H), 5.63 (s, 2H), 6.79 (d, J = 6.6 Hz, 1H), 6.98 (dd, J = 7.8, 1.2 Hz, 1H), 7.17−7.24 (m, 4H), 7.61 (d, J = 7.8 Hz, 1H), 8.03 (t, J = 6 Hz, 1H).

***N*-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-1-(4-methoxy)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 18 (A3B1C2).** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 1.84−1.87 (m, 2H), 2.52 (s, 3H), 2.55−2.62 (m, 2H), 2.65−2.78 (m, 4H), 3.11−3.23 (m, 4H), 3.55 (ddd, J = 12, 6.6, 6 Hz, 2H), 3.81 (s, 3H), 3.89 (s, 3H), 5.44 (s, 2H), 6.85−6.90 (m, 3H), 6.92−7.04 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H).

***N*-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-1-(2-bromo)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 21 (A3B2C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.95 (dd, J = 7.5, 7.2 Hz, 3H), 1.47−1.57, (m, 2H), 2.16−2.25 (m, 2H), 2.89−2.97 (m, 2H), 3.10−3.45 (m, 6H), 3.48−3.81 (m, 6H), 3.89 (s, 3H, OCH_3), 5.67 (s, 2H), 6.82 (dd, J = 7.5, 1.8 Hz, 1H), 6.91−7.01 (m, 3H), 7.10−7.16 (m, 1H), 7.21−7.28 (m, 2H), 7.59−7.67 (m, 2H).

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}-1-benzyl-5-methyl-1,2,3-triazole-4-carboxamide 22 (A4B1C1).** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 2.10−2.14 (m, 2H), 2.52 (s, 3H), 2.92−3.30 (m, 4H), 3.33−3.50 (m, 4H), 3.56−3.80 (m, 4H), 5.53 (s, 2H), 7.03 (dd, J = 7.9, 1.8 Hz, 1H), 7.17−7.28 (m, 4H), 7.35−7.44 (m, 3H), 7.48−7.56 (m, 1H).

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}-1-(4-methoxy)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 23 (A4B1C2).** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 1.79−1.88 (m, 2H), 2.52 (s, 3H), 2.58−2.64 (m, 2H), 2.66−2.75 (m, 4H), 3.11−3.21 (m, 4H), 3.57 (dd, J = 12, 6 Hz, 2H), 3.81 (s, 3H), 5.45 (s, 2H), 6.87 (d, J = 8.4 Hz, 2H), 7.05−7.09 (m, 1H), 7.11−7.14 (m, 2H), 7.16−7.20 (m, 2H).

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}-1-(2-bromo)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 24 (A4B1C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 2.15−2.27 (m, 2H), 2.55 (s, 3H,), 3.10−3.20 (m, 2H), 3.25−3.58 (m, 4H), 3.41−3.50 (m, 2H), 3.56−3.64 (m, 2H), 3.78−3.86 (m, 2H,), 5.65 (s, 2H), 6.77 (dd, J = 7.5, 1.8 Hz, 1H), 7.02 (dd, J = 7.9, 1.8 Hz, 1H), 7.21−7.29 (m, 3H), 7.66 (dd, J = 7.5, 1.4 Hz, 1H).

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}-1-(2-bromo)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 27 (A4B2C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.95 (dd, J = 7.5, 7.2 Hz, 3H), 1.46−1.56, (m, 2H), 2.16−2.26 (m, 2H), 2.90−2.95 (m, 2H), 3.07−3.19 (m, 2H), 3.25−3.40 (m, 4H), 3.41−3.50 (m, 2H), 3.56−3.64 (m, 2H), 3.75−3.83 (m, 2H), 5.67 (s, 2H), 6.83 (dd, J = 7.2, 1.4 Hz, 1H), 7.02 (dd, J = 7.9, 1.4 Hz, 1H), 7.20−7.29 (m, 3H), 7.65 (ddd, J = 7.7, 1.4, 1.0 Hz, 2H).

***N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1-benzyl-5-methyl-1,2,3-triazole-4-carboxamide 38 (A5B1C1).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.63−1.82 (m, 4H), 2.53 (s, 3H), 2.56−2.68 (m, 2H), 2.73−2.93 (m, 4H), 3.10−3.29 (m, 4H), 3.46−3.55 (m, 2H), 3.89 (s, 3H), 5.53 (s, 2H), 6.89 (dd, J = 7.9, 1.4 Hz, 1H), 6.93−6.98 (m, 2H), 7.0−7.07 (m, 1H), 7.16−7.21(m, 2H), 7.33−7.42 (m, 4H).

***N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1-(4-methoxy)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 29 (A5B1C2).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.68−1.87 (m, 4H), 2.54 (s, 3H), 2.80−2.90 (m, 2H), 2.98−3.15 (m, 4H), 3.22−3.35 (m, 4H), 3.47−3.53 (m, 2H), 3.82 (s, 3H), 3.89 (s, 3H), 5.45 (s, 2H), 6.87−6.99 (m, 5H), 7.03−7.10 (m, 1H), 7.13−7.19 (m, 2H), 7.34−7.40 (m, 1H).

***N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1-(2-bromo)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 30 (A5B1C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.69−1.78 (m, 2H), 1.79−1.90 (m, 2H), 2.55 (s, 3H), 2.82−2.96 (m, 2H), 3.0−3.20 (m, 4H), 3.24−3.38 (m, 4H), 3.52 (ddd, J = 13.1, 6.8, 6.4 Hz, 2H), 3.89 (s, 3H), 5.61 (s, 2H), 6.73 (dd, J = 7.5, 1.8 Hz, 1H), 6.88−6.92 (m, 1H), 6.95−6.98 (m, 2H), 7.04−7.10 (m, 1H), 7.20−7.27 (m, 2H), 7.38−7.44 (m, 1H), 7.65 (dd, J = 7.5, 1.4 Hz, 1H).

***N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1-benzyl-5-propyl-1,2,3-triazole-4-carboxamide 31 (A5B2C1).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.92 (dd, J = 7.5, 7.2 Hz, 3H) 1.43−1.55 (m, 2H), 1.63−1.74 (m, 4H), 2.5 (t, J = 6.8 Hz, 2H), 2.64−2.78 (m, 4H), 2.92 (t, J = 7.9 Hz, 2H), 3.10−3.21 (m, 4H), 3.46−3.53 (m, 2H), 3.89 (s, 3H), 5.48 (s, 2H), 6.89 (dd, J = 7.9, 1.4 Hz, 1H), 6.92−7.05 (m, 3H), 7.18−7.22 (m, 2H), 7.34−7.42 (m, 4H).

***N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1-(4-methoxy)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 32 (A5B2C2).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.93 (dd, J = 7.5, 7.2 Hz, 3H) 1.44−1.55 (m, 2H), 1.64−1.75 (m, 4H), 2.47−2.52 (m, 2H), 2.65−2.79 (m, 4H), 2.93 (t, J = 7.9 Hz, 2H), 3.08−3.21 (m, 4H), 3.46−3.52 (m, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 5.47 (s, 2H), 6.86−6.92 (m, 3H), 6.93−7.05 (m, 3H), 7.13−7.18 (dd, J = 6.4, 2.1 Hz, 2H).

***N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1-(2-bromo)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 33 (A5B2C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.95 (dd, J = 7.5, 7.2 Hz, 3H), 1.48−1.59, (m, 2H), 1.67−1.79 (m, 2H), 2.50−2.59 (m, 2H), 2.69−2.82 (m, 4H), 2.91−3.0 (m, 2H), 3.12−3.22 (m, 4H), 3.47−3.56 (m, 2H), 3.89 (s, 3H), 5.61 (s, 2H), 6.77 (ddd, J = 7.5, 2.1, 1.4 Hz, 1H), 6.89 (dd,

J = 7.9, 1.0 Hz, 1H), 6.92−7.06 (m, 3H), 7.19−7.28 (m, 2H), 7.39−7.45 (m, 1H), 7.65 (ddd, J = 7.7, 1.4, 1.0 Hz, 1H).

***N*-{5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}-1-benzyl-5-methyl-1,2,3-triazole-4-carboxamide 34 (A6B1C1).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.63−1.80 (m, 4H), 2.47−2.55 (bs, 5H), 2.62−2.77 (m, 4H), 3.07−3.20 (m, 4H), 3.46−3.55 (m, 2H), 5.53 (s, 2H), 7.0 (ddd, J = 6.4 Hz, 3.2 Hz, 2.8 Hz, 1H), 7.16−7.21 (m, 4H), 7.33−7.45 (m, 4H).

***N*-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}-1-(4-methoxy)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 35 (A6B1C2).** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 1.66−1.83 (m, 4H), 2.52 (s, 3H), 2.63−2.97 (m, 6H), 3.15−3.33 (m, 4H), 3.49 (dd, J = 12.6, 6.6 Hz, 2H), 3.81 (s, 3H), 5.45 (s, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 7.8 Hz, 1H), 7.12−7.15 (m, 2H), 7.16−7.22 (m, 2H), 7.37−7.40 (m, 1H).

***N*-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}-1-benzyl-5-propyl-1,2,3-triazole-4-carboxamide 37 (A6B2C1).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.92 (t, J = 7.5 Hz, 3H), 1.43−1.55 (m, 2H), 1.68−1.74 (m, 4H), 2.48−2.58 (m, 2H), 2.65−2.77 (m, 4H), 2.89−2.96 (m, 2H), 3.09−3.18 (m, 4H), 3.47−3.53, (m, 2H), 5.55 (s, 2H), 7.0 (dd, J = 6.4, 3.2 Hz, 1H), 7.16−7.22 (m, 4H), 7.34−7.39 (m, 3H).

***N*-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}-1-benzyl-5-methyl-1H-1,2,3-triazole-4-carboxamide 40 (A7B-1C1).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.42−1.51 (m, 2H), 1.62−1.73 (m, 4H), 2.53 (s, 3H), 2.53−2.62 (m, 2H), 2.72−2.89 (m, 4H), 3.13−3.24 (m, 4H), 3.47 (dd, J = 13.3, 6.8 Hz, 2H), 3.89 (s, 3H), 5.55 (s, 2H), 6.89 (ddd, J = 7.9, 1.4, 1.0 Hz, 1H), 6.92−7.07 (m, 3H), 7.16−7.21 (m, 2H), 7.34−7.41 (m, 3H).

***N*-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}-1-(4-methoxy)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 41 (A7B1C2).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.45−1.54 (m, 2H), 1.65−1.74 (m, 2H), 1.82−1.93 (m, 2H), 2.53 (s, 3H), 3.11 (dd, J = 8.6, 7.9 Hz, 2H), 3.15−3.27 (m, 2H), 3.29−3.42 (m, 2H), 3.46, (ddd, J = 13.3, 6.8, 6.4 Hz, 2H), 3.52−3.61 (m, 2H), 3.69−3.79 (m, 2H), 3.84 (s, 3H), 3.90 (s, 3H), 5.46 (s, 2H), 6.90 (d, J = 9 Hz, 2H), 6.93 (dd, J = 8.2, 1.0 Hz, 1H), 6.97−7.06 (m, 2H), 7.11−7.18 (m, 3H), 7.38−7.42 (m, 1H).

***N*-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}-1-(2-bromo)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 42 (A7B1C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.44−1.54 (m, 2H), 1.64−1.77 (m, 4H), 2.55 (s, 3H), 2.58−2.67 (m, 2H), 2.80−2.93 (m, 4H), 3.14−3.27 (m, 4H), 3.49 (m, 2H), 3.89 (s, 3H), 5.61 (s, 2H), 6.71 (dd, J = 7.5, 1.8 Hz, 1H), 6.88−6.92 (m, 1H), 6.94−7.0 (m, 2H), 7.02−7.07 (m, 1H), 7.20−7.29 (m, 2H), 7.65 (dd, J = 7.9, 1.4 Hz, 1H).

***N*-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}-1-benzyl-5-propyl-1,2,3-triazole-4-carboxamide 43 (A7B2C1).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.92 (dd, J = 7.5, 7.2 Hz, 3H), 1.41−1.53 (m, 4H), 1.58−1.75 (m, 4H), 2.45 (dd, J = 7.9, 7.2 Hz, 2H), 2.63−2.73 (m, 4H), 2.89−2.96 (m, 2H), 3.09−3.19 (m, 4H), 3.46 (ddd, J = 13.1, 7.2, 6.8 Hz, 2H), 3.89 (s, 3H), 5.45 (s, 2H), 6.89 (ddd, J = 7.9, 1.4, 1.0 Hz, 1H), 6.92−6.95 (m, 1 H), 6.96−6.98 (m, 1H), 6.99−7.05 (m, 1H), 7.18−7.22 (m, 2H), 7.34−7.39 (m, 3 H).

***N*-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}-1-(4-methoxy)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 44 (A7B2C2).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.94 (dd, J = 7.5, 7.2 Hz, 3H), 1.42−1.55 (m, 4H), 1.60−1.73 (m, 4H), 2.47−2.56 (m, 2H), 2.69−2.82 (m, 4H), 2.93 (t, J = 7.9 Hz, 2H), 3.10−3.23 (m, 4H), 3.46 (ddd, J = 13.1, 7.2, 6.8 Hz, 2H), 3.83 (s, 3H), 3.89 (s, 3H), 5.48 (s, 2H), 6.87−6.92 (m, 3H), 6.93−7.06 (m, 3H), 7.16 (d, J = 8.6 Hz, 2H), 7.24−7.28 (m, 1H).

***N*-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}-1-(2-bromo)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 45 (A7B2C3).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 0.94 (dd, J = 7.5, 7.2 Hz, 3H), 1.44−1.59, (m, 4H), 1.66−1.80 (m, 4H), 2.69−2.80 (m, 2H), 2.91−3.08 (m, 6H), 3.20−3.32 (m, 4H, piperazine), 3.48 (ddd, J = 13.3, 7.2, 6.4 Hz, 2H), 3.89 (s, 3H), 5.62 (s, 2H), 6.78 (dd, J = 7.2, 1.8 Hz, 1H), 6.88−6.92 (d, 1H), 6.93−7.0 (m, 2H), 7.03−7.09 (m, 1H), 7.19−7.29 (m, 2H), 7.66 (ddd, J = 7.7, 1.8, 1.4 Hz, 1H).

***N*-{5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentyl}-1-benzyl-5-methyl-1,2,3-triazole-4-carboxamide 46 (A8B1C1).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.45−1.55 (m, 2H), 1.65−1.74 (m, 2H), 1.76−1.87 (m, 2H), 2.52 (s, 3H), 2.86−2.96 (m, 2H), 3.05−3.28 (m, 4H), 3.29−3.39 (m, 4H), 3.47 (dd, J = 12.9, 6.8 Hz, 2H), 5.53 (s, 2H), 7.01 (dd, J = 7.9, 1.8 Hz, 1H), 7.17−7.27 (m, 4H), 7.34−7.41 (m, 3H).

***N*-{5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentyl}-1-(4-methoxy)benzyl-5-methyl-1,2,3-triazole-4-carboxamide 47 (A8B1C2).** ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 1.42−1.52 (m, 2H), 1.60−1.73 (m, 4H), 1.77−1.86 (m, 2H), 2.53 (bs, 5H), 2.71−2.85 (m, 4H), 3.09−3.321 (m, 4H), 3.43−3.50 (m, 2H), 3.82 (s, 3H), 5.46 (s, 2H), 6.89 (d, J = 9 Hz, 2H), 6.99 (ddd, J = 7.0, 2.8, 2.5 Hz, 1H), 7.13−7.20 (m, 4H).

***N*-{5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentyl}-1-benzyl-5-propyl-1,2,3-triazole-4-carboxamide 49 (A8B2C1).** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 0.88 (dd, J = 7.8, 7.2 Hz, 3H), 1.40−1.49 (m, 4H), 1.57−1.69 (m, 4H), 2.44−2.52 (m, 2H), 2.60−2.83 (m, 4H), 2.89 (t, J = 7.8 Hz, 2H), 3.04−3.15 (m, 4H), 3.43 (ddd, J = 13.5, 7.2, 6.6 Hz, 2H), 5.51 (s, 2H), 6.96 (dd, J = 7.2, 2.4, Hz, 1H), 7.12−7.18 (m, 4H), 7.21−7.25 (m, 1H, NH), 7.30−7.36 (m, 3H).

***N*-{5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentyl}-1-(4-methoxy)benzyl-5-propyl-1,2,3-triazole-4-carboxamide 50 (A8B2C2).** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm): 0.92 (t, J = 7.2, 3H), 1.42−1.52 (m, 4H), 1.57−1.71 (m, 4H), 2.42−2.52 (m, 2H), 2.60−2.77 (m, 4H), 2.92 (t, J = 7.8 Hz, 2H), 3.05−3.16 (m, 4H), 3.45 (dd, J = 13.2, 6.6 Hz, 2H), 3.81 (s, 3H), 5.45 (s, 2H), 6.88 (d, J = 9 Hz, 2H), 6.98 (dd, J = 7.2, 1.4 Hz, 1H), 7.11−7.19 (m, 4H), 7.23−7.27 (m, 1H).

Acknowledgment. The authors wish to thank Dr. H. H. M. Van Tol (Clarke Institute of Psychiatry, Toronto), Dr. J.-C. Schwartz, and Dr. P. Sokoloff (INSERM, Paris), as well as J. Shine (The Garvan Institute of Medical Research, Sydney), for providing dopamine D4, D3, and D2 receptor-expressing cell lines, respectively. This work was supported by the Deutsche Forschungsgemeinschaft (DFG).

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CC050127Q