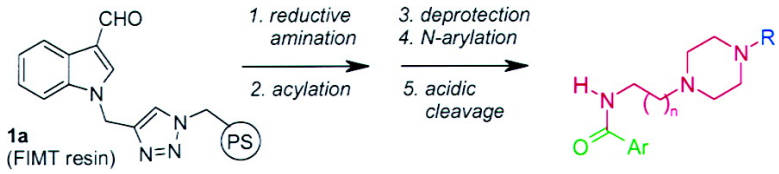
JOURNAL OF combinatorial CHEMISTRY

Article

Parallel Synthesis and Biological Screening of Dopamine Receptor Ligands Taking Advantage of a Click Chemistry Based BAL Linker

Laura Bettinetti, Stefan Lber, Harald Hbner, and Peter Gmeiner

J. Comb. Chem., **2005**, 7 (2), 309-316• DOI: 10.1021/cc049860s • Publication Date (Web): 25 January 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 7 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Parallel Synthesis and Biological Screening of Dopamine Receptor Ligands Taking Advantage of a Click Chemistry Based BAL Linker

Laura Bettinetti, Stefan Löber, Harald Hübner, and Peter Gmeiner*

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, Schuhstrasse 19, D-91052, Erlangen, Germany

Received August 30, 2004

The click-chemistry-derived formyl indolyl methyl triazole (FIMT) resin **1a** was evaluated for the parallel solid-phase synthesis of a series of BP-897-type arylcarboxamides. By application of a five-step sequence (including loading by reductive amination, subsequent amide coupling, deprotection, palladium-catalyzed *N*-arylation, and acidic cleavage), a focused library of putative dopamine D3 receptor ligands was constructed. The final products revealed good to excellent purity and were screened for binding at monoaminergic G-protein-coupled receptors when selected library members proved to show excellent binding affinity, especially toward the dopamine D3 receptor subtype.

Introduction

Aryl carboxamides frequently serve as key pharmacophoric elements in drugs. There are numerous well-established protocols for the synthesis of this functional group in solution; however, in terms of rationalization and automation in the drug design process, solid-phase organic syntheses (SPOS)-based procedures are often benefiting. Thus, different concepts of efficient solid-phase organic (SPO) amide synthesis were established recently, including the capture and release[1] and the backbone amide linker (BAL) strategy.[2] The latter utilizes the carboxamide functionality as the point of attachment to the resin linker. In detail, a building block with a primary amino function is immobilized by reductive amination of a resin functionalized with an electron-rich arylcarbaldehyde. After *N*-acylation, the resulting carboxamide can be readily liberated under acidic conditions. As an arylcarbaldehyde moiety, various alkoxy-substituted benzaldehydes and 3-formylindole were established.[3] Barany and co-workers[4] applied the BAL concept for the preparation of C-terminally modified and cyclic peptides, as well as nonpeptidic compounds. During the last years, the versatility of BAL linkage has been largely proved, especially in solid-phase peptide syntheses (SPPS).[5]

Taking advantage of the click chemistry strategy, we elaborated on several functionalized resins, including the polystyrene-based formyl indolyl methyl triazole (FIMT) derivative **1a**,[6] when the 1,3-dipolar cycloaddition of alkynes and azides—recently designated as a click reaction[7]—proved to be an efficient and high-yielding process for the immobilization of the functional linker unit.

In conjunction with a program to design superpotent dopamine D3 receptor partial agonists and antagonists,[8] we envisaged to use our BAL resin **1a** for the parallel synthesis of a series of *N*-arylpiperazinoalkyl-substituted arylcarboxamides when we chose the CNS active drug candidate BP 897 (Scheme 1), which is known for its benefiting effects on cocaine-seeking behavior,[9] as a lead compound.

Our plan of synthesis involved structural variations of the nature of both aromatic moieties and the length of the chain connecting the aryl carboxamide and the basic amino function in the central part of the molecular scaffold. Thus, we established a three-dimensional SPOS protocol, starting with the attachment of *N*-protected aminoalkylpiperazines by reductive amination. After coupling with activated arylcarboxylic acid derivatives and *N*-deprotection, a further diversification was planned, exploiting the Buchwald−Hartwig *N*-arylation methodology. Although the palladium-mediated SPO synthesis of arylamines is well-established,[10] only few examples that involve polymer-bound amines are described.[11]

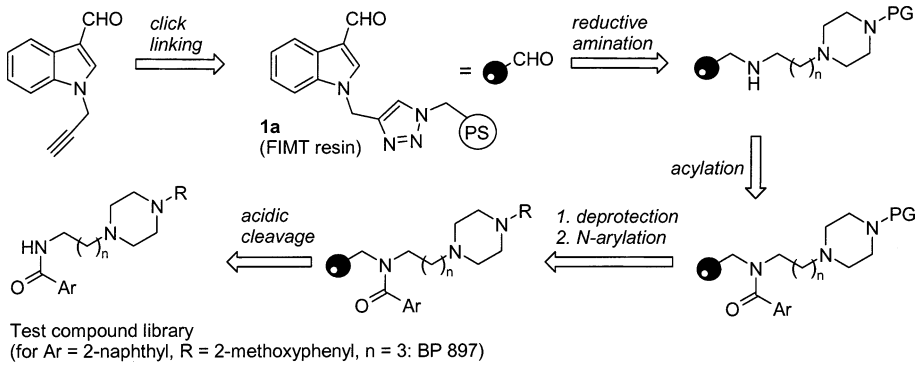
Results and Discussion

Linker Selection. To ascertain the value of our BAL handle **1a** to execute the parallel synthesis in the most efficient way, in regard to the purities and yields of the desired products and to investigate whether the attachment of the first building block by reductive amination is superior to a simple S_N2 displacement, we performed comparative model reactions with the 3-formylindolylmethyl-substituted polystyrene (**1b**),[12] the well-established Rink chloride (**1c**), and Wang bromide (**1d**) resins, respectively (Scheme 2). In detail, immobilization of *N*-aminopropyl-*N*′-(2-methoxyphenyl)-piperazine was done by nucleophilic substitution (for **1c** and **1d**) or reductively when $NaBH(OAc)_3$ was used (for **1b**). Substitution of **1c** with the primary amine was accomplished by following the procedure described by Garigipati,[13] whereas the use of a Hünig base turned out to be dispensable, because of the presence of 4 equiv of tertiary amine within the nucleophile. Subsequent acylation with pyrazolo[1,5-*a*]pyridine-3-carboxylic acid activated by HOAt/DIC and trifluoroacetic acid (TFA)-induced cleavage (2% for **1b** and **1c** and 95% for **1d**) in dichloromethane (DCM)

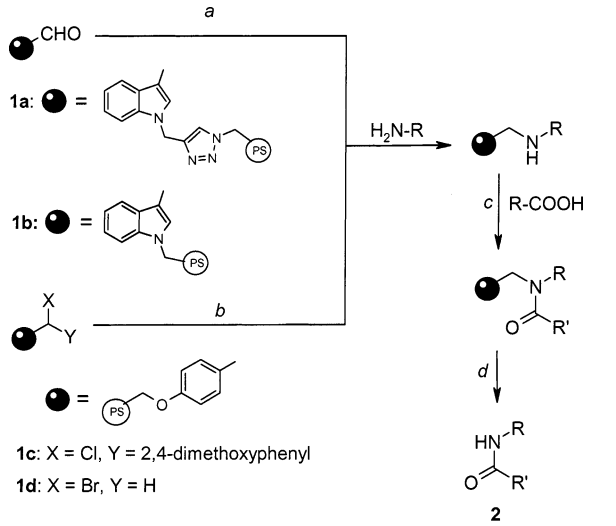
* Author to whom correspondence should be addressed. Phone: +49-9131-8522584. Fax: +49-9131-8522585. E-mail address: gmeiner@pharmazie.uni-erlangen.de.

10.1021/cc049860s CCC: $30.25
Published on Web 01/25/2005

Scheme 1. Plan of Synthesis for a Solid-Phase-Supported Approach to Dopamine D3 Receptor Ligands



Scheme 2. Test Reactions for Linker Selection

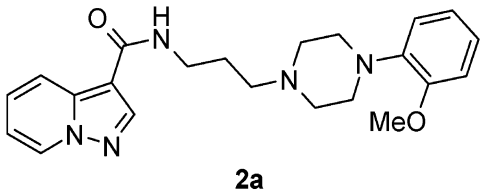


[a] $NaBH(OAc)_3$, DCM, RT, 24 h. [b]For **1c**: DCM, RT, 24 h; for **1d**: DMF, RT, 24 h. [c]HOAt, DIC, DCM−DMF. [d]For **1a** and **1b**: 2% TFA in DCM, RT, 4 h; for **1c**: 2% TFA in DCM, RT, 2 h; for **1d**: 95% TFA in H_2O, RT, 24 h.

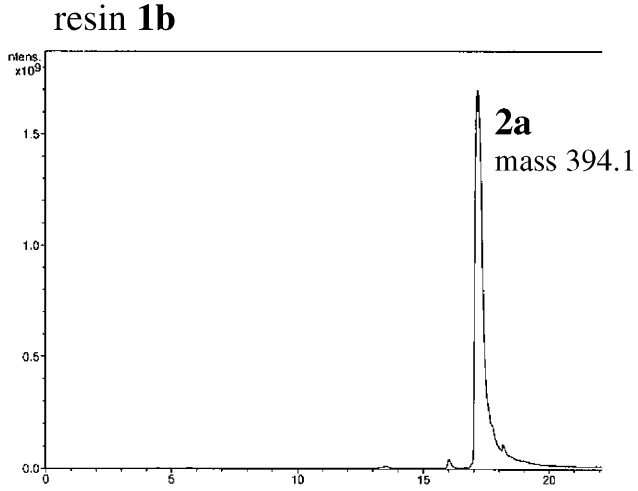
resulted in the formation of the arylcarboxamide **2a**. Liquid chromatography/mass spectroscopy (LC/MS) analysis, using **2a** prepared in solution-phase synthesis[8] as a reference, clearly displayed the superiority of the carbaldehyde-based BAL strategy (Figure 1). In our system, pure **2a** showed a retention time of 17.2 min, when the APCI-MS detection attributed an M+1 peak of 394.1. The synthesis supported by the Rink resin **1c** provided the product **2a** only as a minor component. The main product had an M+1 peak of 346.1 that was assignable to *N*-{4-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-2,2,2-trifluor-acetamide, expressing an incomplete *N*-acylation, which was obviously due to steric hindrance at the bulky benzhydrylamine when being reacted with the HOAt/DIC-activated aromatic carboxylate. The Wang resin (**1d**)-derived cleavage mixture revealed a higher portion of **2a**, even though contaminated with side products. On the other hand, 3-formylindolylmethyl-substituted polystyrene (**1b**) provided only one product being identical with the standard by means of retention time and mass spectra, indicating the superior properties of the formylindole-type resins.

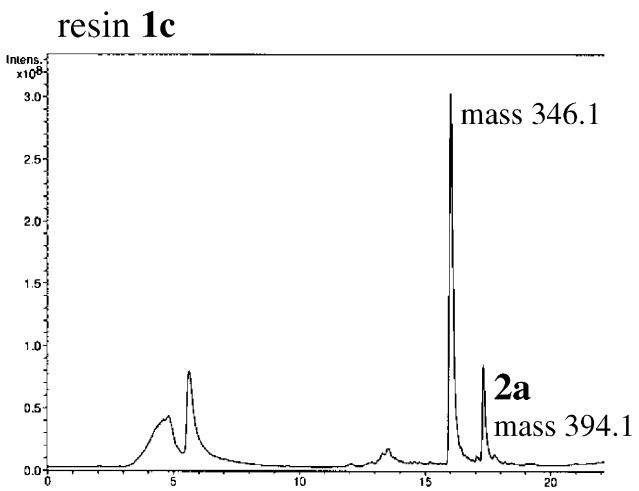
To investigate the reliability of the method when attaching various scaffolds, we compared **1b** to our novel click-chemistry-derived linker **1a**. Thus, we elaborated the synthesis of a model library of the eight arylcarboxamides **2b**−**i** when both resins were subjected to reductive amination using propylamine, cyclohexylamine, benzylamine, and 1-benzylpiperidin-4-ylamine and subsequent acylation using naphthalene-2-carboxylic acid and pyrazolo[1,5-*a*]pyridine-2-carboxylic acid as potentially pharmacophoric scaffolds. After cleavage by 2% TFA in DCM, high-performance liquid chromatography (HPLC) analysis showed that both resins generated the desired products in good to excellent purities (Table 1). Interestingly, the aminopiperidine-derived products **2h** and **2i** revealed significantly higher purities when being synthesized on an FIMT support. The click linker **1a** revealed the best overall performance, with regard to efficiency and robustness, thus, corroborating our plan of synthesis.

Library Generation. Based on our experiences gained with the model library, we established a parallel synthesis approach that enabled us to generate a series of putatively bioactive BP 897 analogues with three points of diversity and purities that were sufficient for the direct submission to the biological analyses without further purification (Scheme 3). Because we planned to extend the chemical description space of the library members by varying the arene substituent on the piperazine moiety, it was necessary to use an *N*-protecting group to avoid regioselectivity problems during the reductive alkylation of the amine moiety. Because *tert*-butyloxycarbonyl (BOC) piperazine is known as a commercially available, low-cost building block, we chose *tert*-butyl carbamate protection, being aware that the combination with the acid-labile BAL resin would not allow the common HCl- or TFA-mediated BOC cleavage. In fact, successful immobilization of *N*-aminobutyl-*N*′-*tert*-butyloxycarbonyl piperazine (scaffold **A1**) and its aminopentyl homologue **A2** in the presence of $NaBH(OAc)_3$ was monitored by infrared (IR) spectroscopy when we observed the substitution of the carbaldehyde-derived C═O band at 1655 cm^{-1} by a strong C═O absorption that was caused by the carbamate functionality at 1690 cm^{-1}. After HOAt/DIC-promoted amide coupling with the building blocks **B**{*1*−*7*}, selective removal of the BOC protecting group was investigated when we tried to take advantage of Burgess' methodology, using trimethylsilyl triflate in the presence of 2,6-lutidine.[14] In fact, we observed complete *N*-deprotection after 30 min at room temperature (RT), giving access to the secondary amine function that was envisioned to be arylated in the following step. Evaluation of a series of cross-coupling conditions for a palladium-mediated C−N bond formation, according to



2a





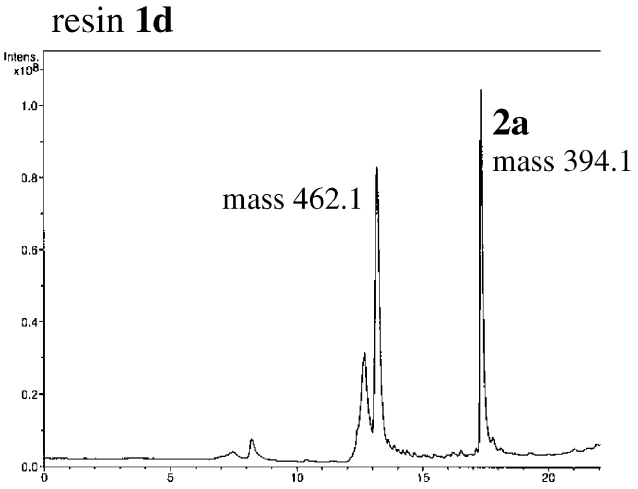


Figure 1. LC/MS analyses. Total ion current (TIC) chromatogram of crude *N*-{4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butyl}-pyrazolo-[1,5-*a*]pyridine-3-carboxamide **2a** obtained from resins **1b**−**d**.

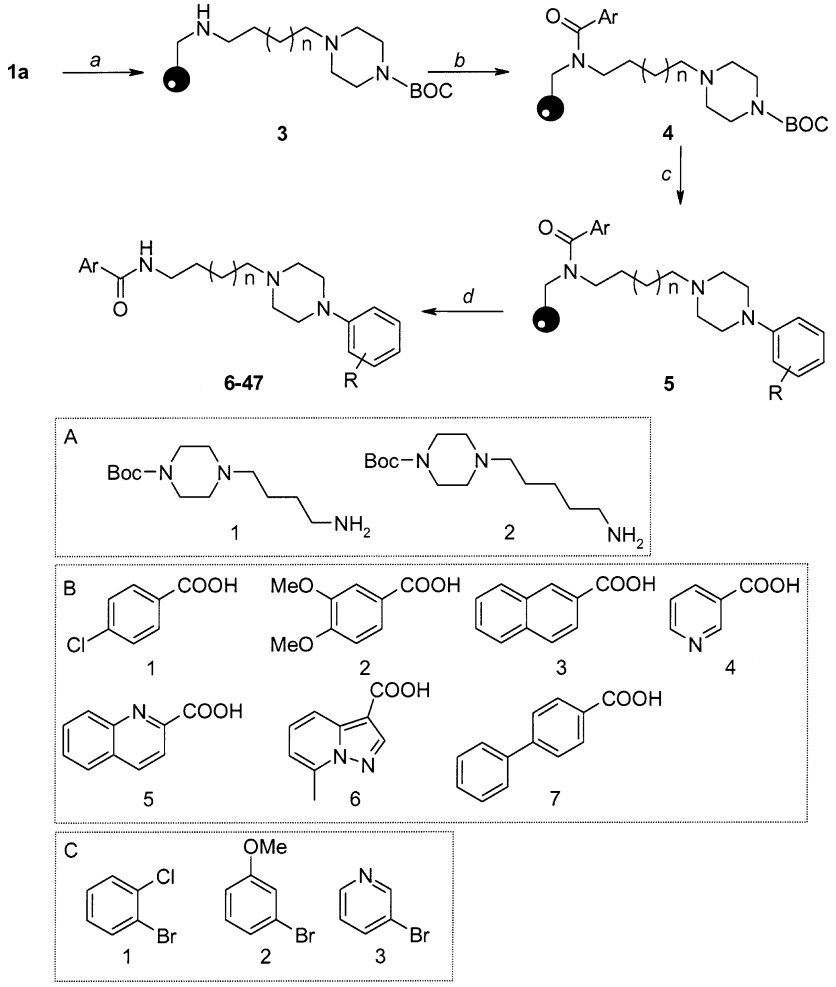
Table 1. Purities and Yields of the Model Library **2b**−**i** Supported by Resins **1a** and **1b**

		1a		**1b**	
	compound	purity (%)	yield (%)	purity (%)	yield (%)
R′= 2-naphthyl					
R = propyl	**2b**	97	40	92	25
R = cyclohexyl	**2d**	89	30	87	36
R = benzyl	**2f**	98	44	100	43
R = *N*-benzylpiperidin-4-yl	**2h**	92	50	58	15
R′= 2-pyrazolo[1,5-*a*]pyridyl					
R = propyl	**2c**	96	26	94	27
R = cyclohexyl	**2e**	85	39	96	38
R = benzyl	**2g**	99	36	93	30
R = *N*-benzylpiperidin-4-yl	**2i**	91	27	60	15

Buchwald and Hartwig's methodology, led to a catalyst system that was composed of $Pd_2(dba)_3$ and BINAP.[10] Using NaO*t*Bu as a base and toluene as a solvent, excellent purities were observed for the coupling of the bromoarene derivatives **C**{*1*−*3*}. Unfortunately, the yields were quite low, because of the necessity to transfer the reactions from polytetrafluoroethylene (PTFE) vessels to glass reactors and vice versa. Finally, smooth cleavage by TFA (2%) in DCM afforded the desired test compounds **6**−**47** in acceptable yields (Table 2). Note that the target compounds revealed an average purity of >85% when only two library members displayed purities of <70% (64% for **13**, 69% for **22**, and 66% for **25**). According to the LC/MS data, the existence of side products was usually due to an incomplete Buchwald coupling.

Screening. The biological screening of compounds **6**−**47** was done without further purification in concentrations of 10 μM, 100 nM, and 1 nM when dissolved in the respective assay buffer. Table 3 shows the binding affinities of **6**−**47** toward the dopamine receptors D1, $D2_{long}$, $D2_{short}$, D3, and D4 and the adrenergic α_1 subtype at concentrations of 100 nM. None of them was able to substantially displace the radioligands from the D1, $D2_{long}$, $D2_{short}$, and D4 receptors.[15] Nevertheless, the screening with the D3 subtype resulted in many hits. The most promising displacement properties (>85%) were observed for **6**{A1,B1,C1}, **9**{A1,B2,C1}, **12**{A1,B3,C1}, **21**{A1,B6,C1}, and **24**{A1,B7,C1}. Library member **26** displayed high selectivity but was not investigated further, because the D3 ligand displacement was <85%. After purification by column chromatography, determination of the Ki values of the selected hits proved **6**, **9**, **12**, **21**, and **24** as high-affinity binders at the D3 subtype, when the biphenyl carboxamide **24** turned out to be extraordinarily potent, revealing a Ki value of 0.28 nM and the best selectivity over the α_1 receptor within this subset

Scheme 3. Solid-Phase-Supported Synthesis of the Test Compounds **6**−**47**



[a] A{*1*−*2*}, $NaBH(OAc)_3$, DCM, RT, 21 h. [b]B{*1*−*7*}, HOAt, DIC, DCM/DMF, RT, 48 h. [c](i) TMSOTf, 2,6-lutidine, DCM, RT, 2 × 30 min; (ii) C{*1*−*3*}, $Pd_2(dba)_3$, BINAP, NaO*t*Bu, toluene, 80 °C, 60 h. [d]2% TFA/DCM, RT, 2 h.

(Table 4). Thus, combination of the biphenyl moiety with the 2-chloropiperazine substructure and a chain length of four led to a D3 receptor ligand (**24**) that was superior to the naphthalene-derived lead BP 897 (Ki = 1.4 nM).

Summary

Utilizing the FIMT resin **1a**, which is readily available via a click-chemistry-based immobilization, a BAL strategy has been developed for the parallel synthesis of dopaminergic aryl carboxamides. A library of 42 test compounds, revealing three points of diversity, was generated by a five-step SPOS approach, including intermediate BOC deprotection and palladium-mediated *N*-arylation of polymer-bound amines. Receptor binding studies indicated excellent D3 receptor affinity for five library members when the biphenyl carboxamide **24** revealed a Ki value of 0.28 nM substantially exceeding the binding properties of the drug candidate BP 897.

Experimental Section

General. Polystyrene resins were purchased from Novabiochem. Absolute solvents (over molecular sieves) and starting materials obtained from commercial source were used without further purification. Solid-phase syntheses were performed manually in a Heidolph Instruments Synthesis 1 and an AdvancedChemtech PLS synthesizer equipped with PFA or PTFA reaction vessels, respectively. Reactions and resin washes were conducted at ambient temperature, unless otherwise stated. Analytical HPLC was performed using a Nucleosil RP18 column (4.6 mm ID × 250 mm, 7 μm) in CH_3CN/0.1 N aqueous HCOOH (1/1) at a flow rate of 1.0 mL/min and in combination with UV detection at 254 nm. Mass spectra were recorded on a FINNIGAN MAT TSQ 70 spectrometer. LC/MS analyses were conducted using an Agilent binary gradient system in combination with ChemStation software (MeOH/0.1 N aqueous HCOOH 50/50−90/10) and ultraviolet (UV) detection at 254 nm. At this point, a Zorbax SB-C8 (4.6 mm ID × 250 mm, 5 μm) column was used, with a flow rate of 0.5 or 0.8 mL/min. The mass detection was noted with a Bruker Esquire 2000 ion-trap mass spectrometer using an APCI ionization source. ^{1}H NMR (360 MHz) and ^{13}C NMR (90 MHz) spectra were recorded in solution using a Bruker AM 360 instrument. IR spectra were registered on a Jasco model FT/IR 410 instrument, using a film of substance on a NaCl pill or via a KBr pellet. Melting points were determined on a BÜCHI apparatus. CHN elementary analyses were done at the Department of Organic Chemistry (Friedrich Alexander University). Flash chromatography was performed using Silica Gel 60 (40−63 μm). For thin layer chromatography

Table 2. Composition, Physicochemical Data, Purity, and Crude Yield of the Test Compounds **6**−**47**

compound	mass	molecular weight, MW	purity[a] (%)	crude yield (%)	t_R
6{A1,B1,C1}	406.5	406.37	79	14	17.6
7{A1,B1,C2}	402.3	401.95	90	9	22.6
8{A1,B1,C3}	373.2	372.91	92	23	5.5
9{A1,B2,C1}	432.5	431.97	96	30	3.6
10{A1,B2,C2}	428.3	427.56	73	20	14.1
11{A1,B2,C3}	399.2	398.52	97	28	3.0
12{A1,B3,C1}	422.4	421.98	93	20	24.7
13{A1,B3,C2}	418.3	417.56	64	37	23.8
14{A1,B3,C3}	389.2	388.52	95	14	20.3
15{A1,B4,C1}	373.4	372.91	82	15	10.2
16{A1,B4,C2}	369.2	368.49	92	13	7.6
17{A1,B4,C3}	340.2	339.45	90	13	2.6
18{A1,B5,C1}	423.5	422.97	98	21	19.2
19{A1,B5,C2}	419.3	418.55	76	14	16.7
20{A1,B5,C3}	390.4	389.51	88	22	3.4
21{A1,B6,C1}	426.4	425.97	88	35	22.4
22{A1,B6,C2}	422.2	421.55	69	21	21.2
23{A1,B6,C3}	393.3	392.52	100	26	3.0
24{A1,B7,C1}	448.3	448.02	73	34	24.6
25{A1,B7,C2}	444.2	443.60	66	20	23.9
26{A1,B7,C3}	415.2	414.56	95	32	20.3
27{A2,B1,C1}	420.5	420.39	87	24	17.2
28{A2,B1,C2}	416.4	415.97	90	20	16.1
29{A2,B1,C3}	387.3	386.93	100	21	10.3
30{A2,B2,C1}	446.5	445.99	90	32	15.1
31{A2,B2,C2}	442.3	441.58	78	30	13.7
32{A2,B2,C3}	413.3	412.54	94	21	8.1
33{A2,B3,C1}	436.4	436.00	81	35	17.5
34{A2,B3,C2}	432.3	431.58	90	31	16.6
35{A2,B3,C3}	403.2	402.54	99	27	12.0
36{A2,B4,C1}	387.3	386.93	95	18	13.9
37{A2,B4,C2}	383.2	382.51	79	10	12.0
38{A2,B4,C3}	354.3	353.47	88	12	3.1
39{A2,B5,C1}	437.5	436.99	82	15	17.2
40{A2,B5,C2}	433.3	432.57	79	11	16.1
41{A2,B5,C3}	404.2	403.53	96	15	11.4
42{A2,B6,C1}	440.4	439.99	84	28	16.2
43{A2,B6,C2}	436.2	435.57	85	20	15.0
44{A2,B6,C3}	407.2	406.54	83	13	9.7
45{A2,B7,C1}	462.5	462.04	87	28	18.5
46{A2,B7,C2}	458.3	457.62	78	23	17.7
47{A2,B7,C3}	429.3	428.58	100	28	13.8

[a] Using LC/MS.

(TLC), Merck 60 F_{254} aluminum plates were used and analyzed by UV light (254 nm) or by iodine vapor.

Biological screening was performed at concentrations of 10 μM, 100 nM, and 1 nM of the test compounds. Receptor binding data were generated by measuring their ability to compete with [^{3}H]spiperone for the cloned human dopamine receptor subtypes $D2_{long}$, $D2_{short}$, D3, and D4.4 stably expressed in Chinese hamster ovary (CHO) cells. D1 and α_1 receptor affinities were determined utilizing porcine striatal membranes and the D1 selective radioligand [^{3}H]-SCH 23390 and [^{3}H]prazosine and porcine cortical membranes, respectively.[15]

Abbreviations used in this paper are as follows: abs, absolute; eq, equivalent; h, hours; min, minutes; RT, room temperature; sat, saturated; DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran; HOAt, 1-hydroxy-7-azabenzotriazole; DIC, *N*,*N*′-diisopropylcarbodiimide; TFA, trifluoroacetic acid; TMSOTf, trimethylsilyltriflate; $Pd_2(dba)_3$, tris(dibenzylidenacetone)-dipalladium(0); and BINAP, racemic (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Resin 1a. Merrifield resin (5.0 g, 1.3 mmol/g) was reacted with NaN_3 (2.1 g, 32.5 mmol) in dimethyl sulfoxide (DMSO) (40 mL) at 80 °C for 53 h. After being cooled to RT, sequential filtration and washing with methanol (MeOH) (5 × 30 mL), DCM (5 × 30 mL), and Et_2O (2 × 30 mL) gave azidomethyl polystyrene (IR: 2096 cm^{-1}). *N*-(2-Propynyl)-indole-3-carbaldehyde (6.0 g, 32.5 mmol), CuI (25 mg, 0.13 mmol), DIPEA (8 mL), and THF (40 mL) were added into the reactor and agitated at 40 °C. After 63 h, the IR signal of the azido group had completely disappeared and the resin was collected by filtration and subsequently washed with pyridine (5 × 30 mL), MeOH (5 × 30 mL), and DCM (5 × 30 mL). Drying of the residue in a vacuum gave resin **1a**, showing an IR signal for the aldehyde C═O at 1654 cm^{-1}.

Resin 1b. Merrifield resin (2.0 g, 1.1 mmol/g) was reacted with 3-[1-pyrrolidin-1-yl-methylidene]-3H-indole (1.3 g, 6.6 mmol) in DCM (50 mL) at 30 °C for 18 h. The suspension was filtered and the resin was washed with DCM (5 × 45 mL) and then treated with 0.2 N NaOH solution (15 mL) in DMF (35 mL) at RT for 2 h. After sequential filtration and washing with MeOH (3 × 40 mL), MeOH:H_2O = 1:1 (2 × 40 mL), MeOH (3 × 40 mL), DCM (2 × 40 mL), and then Et_2O (2 × 40 mL), the residue was dried in a vacuum to give resin **1b**,[12] showing an IR signal for the aldehyde C═O at 1662 cm^{-1}.

***N*-{4-[4-(2-Methoxyphenyl)-piperazin-1-yl]-propyl}-pyrazolo[1,5-*a*]pyridine-3-carboxamide (2a).** Immobilization: (a) Resin **1b** (100 mg, 1.36 mmol/g), $NaBH(OAc)_3$ (116 mg, 0.54 mmol) and a solution of *N*-aminopropyl-*N*′-(2-methoxyphenyl)-piperazine (140 mg, 0.57 mmol) in DCM (10 mL) were agitated for 24 h. The resin was filtered and washed with MeOH (3 × 5 mL), MeOH:0.1 N HC = 9/1 (3 × 5 mL), 2% NEt_3 in DCM(3 × 5 mL), and DCM (3 × 5 mL) and dried by suction. (b) Rink acid resin (300 mg, 0.43 mmol/g), PPh_3 (187 mg, 0.7 mmol), Cl_3CCCl_3 (168 mg, 0.7 mmol), and THF (10 mL) were shaken for 7 h to obtain Rink chloride **1c**. After washing with THF and acetone, the resin was shaken with a solution of *N*-aminopropyl-*N*′-(2-methoxyphenyl)-piperazine (130 mg, 0.52 mmol) in DCM (10 mL) for 24 h. After washing with DCM (3 × 5 mL), MeOH (3 × 5 mL), and DCM (3 × 5 mL), the resin was dried by suction. (c) Wang bromide resin **1d** (100 mg, 1.2 mmol/g) was pre-swollen with DCM (7 mL) for 1 h, filtered, and washed twice with DMF. Subsequently, a solution of *N*-aminopropyl-*N*′-(2-methoxyphenyl)-piperazine (121 mg, 0.48 mmol) in DMF (8 mL) was added and the reaction was shaken for 24 h. After washing with DMF (2 × 5 mL), MeOH (2 × 5 mL), DCM (2 × 5 mL), and hexane (2 × 5 mL), the resin was dried by suction.

1. Acylation of Immobilized Secondary Amines. The reaction vessels containing the previously described resins were filled with pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (4 equiv), HOAt (4 equiv), DIC (4.5 equiv), and a mixture of DCM:DMF = 9/1 (10 mL) and shaken for 24 h. After sequential filtration and washing with DMF (3 × 5 mL), MeOH (3 × 5 mL), and DCM (3 × 5 mL), the resins were dried by suction.

2. Cleavage. Cleavage was performed using 2% TFA in DCM (8 mL) at RT for 4 h (resin **1b** and **1c**) or 95% TFA

Table 3. Binding Affinities of **6**−**47** toward the Dopamine Receptors D1, $D2_{long}$, $D2_{short}$, D3, D4, and the Adrenergic α1 Subtype at Concentrations of 100 nM

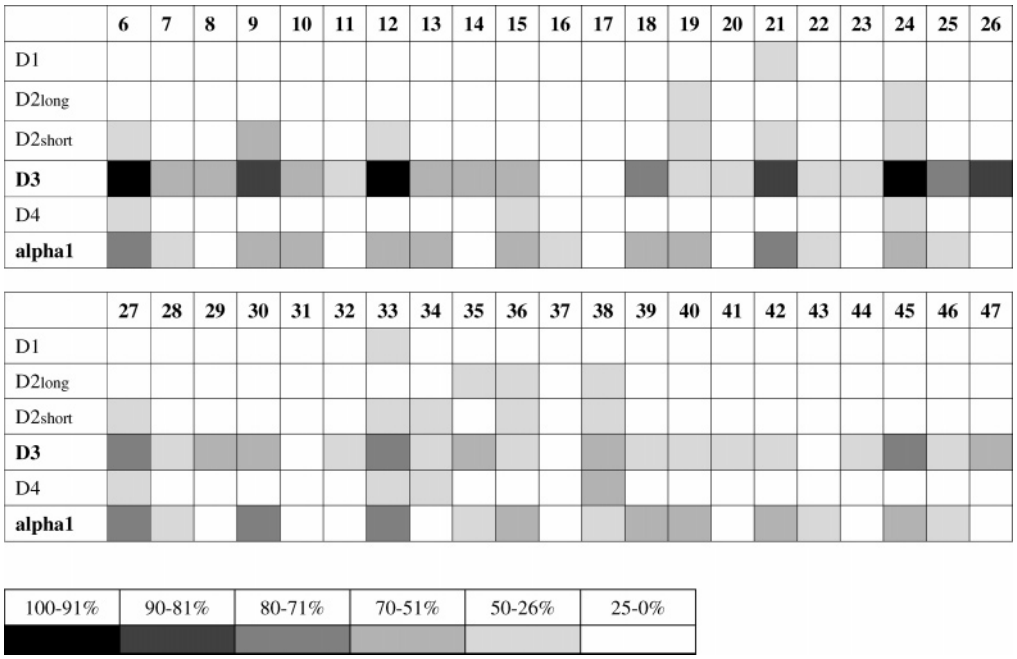


Table 4. Ki Values of the Hits **6**, **9**, **12**, **21**, and **24**

		Ki values (nM)					
		[^{3}H]SCH 23390	[^{3}H]spiperone				[^{3}H]prazosine
compound	purity (%)	pD1	$hD2_{long}$	$hD2_{short}$	hD3	hD4	pα1
6	>95	790	470	110	1.7	280	9.3
9	>95	3100	280	67	3.1	170	3.4
12	>95	400	460	94	1.0	200	6.0
21	>95	240	230	47	3.7	36	3.3
24	>95	360	130	30	0.28	240	11
BP 897		760	210	210	1.4	39	5.0

in water (8 mL) at RT for 24 h (resin **1d**). The cleavage solutions were separately collected and washed alternately with MeOH (2 × 5 mL) and DCM (2 × 5 mL); the solvents were evaporated and the residue was treated with saturated $NaHCO_3$ and extracted with DCM to obtain crude **2a**, which was analyzed using LC/MS.

Model Library (2b−i). To 0.135 mmol of resin (**1a** or **1b**) were added $NaBH(OAc)_3$ (115 mg, 0.54 mmol, 4 equiv) and a solution of propyl-, cyclohexyl-, benzyl-, or 1-benzylpiperidin-4-ylamine (4 equiv) in DCM (10 mL) and the reaction was shaken for 21 h. The resin was filtered and washed with MeOH (3 × 5 mL), MeOH:0.1 N HCl = 9/1 (3 × 5 mL), 2% NEt_3 in DCM (3 × 5 mL), and DCM (3 × 5 mL) and dried by suction. The reaction vessel was filled with 2-naphthyl- or 2-pyrazolo[1,5-a]pyridyl-carboxylic acid (4 equiv), HOAt (4 equiv), DIC (4.5 equiv) and a mixture of DCM:DMF = 9/1 (10 mL) and shaken for 24 h. After sequential filtration and washing with DMF (3 × 5 mL), MeOH (3 × 5 mL), and DCM (3 × 5 mL), the resins were dried by suction. The cleavage was done by 2% TFA in DCM (5 mL) for 2 h. The solution was collected and washed alternately with MeOH (2 × 5 mL) and DCM (2 × 5 mL), and the solvents were evaporated; the residues were treated with saturated $NaHCO_3$ and extracted with DCM, and the organic layers were dried (with $MgSO_4$) and evaporated to give **2b**−**i** (15% to 50%). The products were analyzed by an LC/MS system when UV detection (254 nm) was used to determine the purity.

Test Compound Library (6−47). Resin **1a** was loaded into 42 reaction vessels (100 mg, 0.1 mmol), which were treated with $NaBH(OAc)_3$ (115 mg, 0.54 mmol, 4 equiv) and a solution of **A**{*1*−*2*} (4 equiv) in DCM (5 mL) and then agitated for 21 h. The resins were filtered and washed with MeOH (3 × 5 mL), MeOH:0.1 N HCl = 9/1 (3 × 5 mL), 2% NEt_3 in DCM (3 × 5 mL), and DCM (3 × 5 mL) and dried by suction. After addition of **B**{*1*−*7*} (4 equiv), HOAt (4 equiv), DIC (4.5 equiv), and a mixture of DCM:DMF = 9/1 (5 mL), the vessels were shaken for 48 h. Sequential filtration and washing with DMF (3 × 5 mL), MeOH (3 × 5 mL), and DCM (3 × 5 mL) was followed by treatment with a solution of TMSOTf (1.0 mol/L) and 2,6-lutidine (1.5 mol/L) in DCM (2 mL) and agitation for 30 min. After washing twice with DCM (2 × 2 mL), an additional 2 mL of the TMSOTf/2,6-lutidine solution were added, followed by agitation for 30 min. After sequential filtration and washing with DCM, MeOH, DMF (5 mL, 5 × 1 min, then 3 × 5 min), 10% NEt_3 in DCM (2 × 5 mL), and DCM (2 × 5 mL), the resins were dried by suction and transferred from PTFE vessels into glass reactors. $Pd_2(dba)_3$ (4.8 mg, 5 mol %), BINAP (9.7 mg, 15 mol %), and NaO*t*Bu

(200 mg, 20 equiv) were added and the reactors were three times evacuated, filled with nitrogen, and a solution of **C**-{*1*−*3*} (6 equiv) in absolute toluene (2 mL) was added. The reaction was shaken at 80 °C for 60 h, then transferred back into the PTFE vessels and washed with MeOH:H_2O = 1/1 (3 × 5 mL), MeOH (3 × 5 mL), DMF (3 × 5 mL), and DCM (3 × 5 mL). The cleavage was done by 2% TFA in DCM (5 mL) for 2 h. The solution was collected and washed alternately with MeOH (2 × 5 mL) and DCM (2 × 5 mL), and the solvents were evaporated; the residues were treated with saturated $NaHCO_3$ and extracted with DCM, and the organic layers were dried (with $MgSO_4$) and evaporated to give **6**−**47** (9% to 37%). The products were analyzed using an LC/MS system, whereas UV detection (254 nm) was used to determine the purity.

***t*-Butyl 4-(4-amino-butyl)-piperazine-1-carboxylate (A1).** To a solution of *N*-BOC-piperazine (1.0 g, 5.4 mmol) and NEt_3 (1.1 g, 10.7 mmol) in *o*-xylene (25 mL) at 70 °C was added dropwise a solution of *N*-(4-bromobutyl)-phthalimide (1.52 g, 5.4 mmol) in *o*-xylene (10 mL). The mixture was stirred at 125 °C for 20 h and cooled to 0 °C. After filtration, the liquid was concentrated to obtain an orange thick oil that was purified by flash chromatography (hexane:EtOAc = 4/6) to yield *t*-butyl 4-[4-(2-phthalimido)-butyl]-piperazine-1-carboxylate as a yellow solid (1.96 g, 94%): mp 86 °C; EI-MS *m*/*z* 387 (M^+); IR (NaCl, cm^{-1}) 1772, 1712, 1695; ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 1.49−1.59 (m, 2H), 1.67−1.76 (m, 2H), 2.34−2.39 (m, 6H), 3.39−3.42 (m, 4H), 3.71 (t, J = 7.1 Hz, 2H), 7.68−7.74 (m, 2H), 7.81−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 24.1, 26.5, 28.4, 37.8, 52.9 (2 C; isochrones), 57.9, 79.5, 123.1, 132.1, 133.8, 154.7, 168.4; Anal. Calcd. for $C_{21}H_{29}N_3O_4$: C, 65.10; H, 7.54; N, 10.84. Found: C, 65.09; H, 7.44; N, 10.78.

To a solution of *tert*-butyl 4-[4-(2-phthalimido)-butyl]-piperazine-1-carboxylate (3.1 g, 8.0 mmol) in ethanol (EtOH) (70 mL) was added dropwise a solution of 80% hydrazine hydrate (0.64 g, 16 mmol) in EtOH (10 mL). The solution was refluxed for 7 h and then allowed to cool to RT. The obtained solid was removed by filtration, and the filtrate was subjected to evaporation. The purification was done by flash chromatography (DCM:MeOH:NEt_3 = 90/8/2), obtaining **A1** as a colorless oil (0.93 g, 45%): EI-MS *m*/*z* 257 (M^+); IR (NaCl, cm^{-1}) 3370, 1697; ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 1.48−1.55 (m, 4H), 2.32−2.38 (m, 6H), 2.71−2.75 (m, 2H), 3.40−3.43 (m, 4H).

***t*-Butyl 4-(5-Amino-pentyl)-piperazine-1-carboxylate (A2).** To a solution of *N*-BOC-piperazine (5.0 g, 27 mmol) and NEt_3 (5.4 g, 54 mmol) in *o*-xylene (120 mL) was added dropwise *N*-(5-bromopentyl)-phthalimide (7.96 g, 27 mmol) as a solution in *o*-xylene (20 mL) at 70 °C. The mixture was stirred at 125 °C for 37 h and cooled to 0 °C. After filtration the filtrate was concentrated to yield an orange thick oil, which was purified by flash chromatography (hexane:EtOAc = 7/3) to yield *tert*-butyl 4-[5-(2-phthalimido)-pentyl]-piperazine-1-carboxylate as a yellow solid (7.87 g, 73%): mp 109 °C; EI-MS *m*/*z* 401 (M^+); IR (NaCl, cm^{-1}) 1773, 1714, 1693; ^{1}H NMR ($CDCl_3$): δ 1.32−1.40 (m, 2H), 1.45 (s, 9H), 1.49−1.58 (m, 2H), 1.66−1.74 (m, 2H), 2.30−2.36 (m, 6H), 3.39−3.42 (m, 4H), 3.68 (t, J = 7.3 Hz, 2H), 7.69−7.72 (m, 2H), 7.82−7.85 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 24.7, 26.2, 28.1, 28.5, 37.8, 53.0 (2 C; isochrones), 58.4, 79.5, 123.1, 132.1, 133.8, 154.7, 168.4. Anal. Calcd. for $C_{22}H_{31}N_3O_4$: C, 65.81; H, 7.78; N, 10.47. Found: C, 65.28; H, 7.67; N, 10.35.

To a solution of *tert*-butyl 4-[5-(2-phthalimido)-pentyl]-piperazine-1-carboxylate (3.0 g, 7.5 mmol) in EtOH (30 mL) was added dropwise a solution of 80% hydrazine hydrate (0.45 g, 11.2 mmol) in EtOH (5 mL). The solution was heated at reflux temperature for 8 h and then allowed to cool to RT. The obtained solid was removed by filtration and the filtrate evaporated. The purification was accomplished by flash chromatography (DCM:MeOH:NEt_3 = 90/8/2), obtaining **A2** as a colorless oil (1.8 g, 89%): EI-MS *m*/*z* 272 (M^+); IR (NaCl, cm^{-1}) 3370, 1696; ^{1}H NMR ($CDCl_3$): δ 1.40−1.51 (m, 11H), 2.38−2.44 (m, 6H), 2.79 (t, J = 6.1 Hz, 2H), 3.41−3.44 (m, 4H), 3.68 (t, J = 7.3 Hz, 2H), 7.69−7.72 (m, 2H), 7.82−7.85 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 24.8, 26.7, 28.4, 33.5, 42.0, 53.1 (2 C; isochrones), 58.6, 79.5, 154.8.

7-Methyl-pyrazolo[1,5-*a*]pyridine-3-carboxylic acid (B6). To a mixture of 1-amino-2-methylpyridinium iodide[16] (2 g, 8.5 mmol) and K_2CO_3 (2.4 g, 17.4 mmol) in DMF (15 mL) was added dropwise propargylic acid ethyl ester (0.78 g, 9.3 mmol), and the mixture was stirred at RT for 24 h. The suspension was filtered, followed by evaporation of the solvent. The obtained residue was treated with Et_2O, and the organic layer washed three times with water, dried (with $MgSO_4$), and evaporated. The crude product was purified by flash chromatography (hexane:EtOAc = 9/1) to give pure ethyl 7-methyl-pyrazolo[1,5-*a*]pyridine-3-carboxylate as a light yellow solid (744 mg, 46%): mp 103 °C; EI-MS *m*/*z* 190 (M^+); IR (NaCl, cm^{-1}) 1709, 1639; ^{1}H NMR ($CDCl_3$): δ 2.79 (s, 3H), 3.91 (s, 3H), 6.81 (d, J = 7.1 Hz, 1H), 7.36 (dd, J = 8.9 Hz, 7 Hz, 1H), 8.08 (d, J = 8.9 Hz, 1H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 17.8, 51.1, 103.7, 113.2, 116.6, 127.4, 139.2, 141.3, 144.2, 164.0.

NaOH (16 g, 50% in water) was added to ethyl 7-methyl-pyrazolo[1,5-*a*]pyridine-3-carboxylate (700 mg, 3.7 mmol) and stirred for 1 h under reflux. After cooling to RT, EtOH (12 mL) was added and the mixture was refluxed for 30 min and allowed to cool to 0 °C. Concentrated HCl was slowly added to reach pH 3 when the obtained white solid was collected, washed with water, and dried over P_2O_5. Pure **B6** was added to a second crop of product, which was obtained by extraction of the filtrate with $CHCl_3$ (combined yield: 396 mg, 61%): mp 211 °C; EI-MS *m*/*z* 176 (M^+); IR (NaCl, cm^{-1}) 1661, 1640; ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H), 7.05 (br d, J = 6.8 Hz, 1H), 7.50 (dd, J = 8.9 Hz, 6.8 Hz, 1H), 8.00 (br d, J = 8.9 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 17.2, 103.8, 113.3, 115.8, 127.8, 139.0, 140.5, 144.0, 164.1. Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found C, 61.31; H, 4.60; N, 15.83.

***N*-{4-[4-(2-Chlorophenyl)-piperazin-1-yl]-butyl}-3,4-dimethoxybenzamide 6{A1,B2,C1}.** ^{1}H NMR ($CDCl_3$): δ 1.65−1.75 (m, 4H), 2.48 (t, J = 6.9 Hz, 2H), 2.64 (m, 4H), 3.06 (m, 4H), 3.45−3.50 (m, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 6.49 (br s, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.96 (ddd, J = 7.9 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.00 (dd, J = 8.2 Hz, 1.6 Hz, 1H),

7.20 (ddd, J = 8.2 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.25 (dd, J = 8.2 Hz, 2.0 Hz, 1H), 7.34 (dd, J = 7.9 Hz, 1.6 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H).

***N*-{4-[4-(2-Chlorophenyl)-piperazin-1-yl]-butyl}-naphthalene-2-carboxamide 12{A1,B3,C1}.** ^{1}H NMR ($CDCl_3$): δ 1.68−1.78 (m, 4H), 2.50 (t, J = 6.9 Hz, 2H), 2.64 (m, 4H), 3.01 (m, 4H), 3.55 (m, 2H), 6.85 (dd, J = 7.9 Hz, 1.6 Hz, 1H), 6.89 (br s, 1H), 6.94 (ddd, J = 7.9 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.15 (ddd, J = 7.9 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.33 (dd, J = 7.9 Hz, 1.6 Hz, 1H), 7.50−7.58 (m, 2H), 7.81−7.92 (m, 4H), 8.27 (br s, 1H).

***N*-{4-[4-(3-methoxyphenyl)-piperazin-1-yl]-butyl}-pyridine-3-carboxamide 16{A1,B4,C2}.** ^{1}H NMR ($CDCl_3$): δ 1.73−1.78 (m, 4H), 2.60−2.68 (br m, 2H), 2.74−2.82 (m, 4H), 3.24−3.28 (m, 4H), 3.50−3.55 (m, 2H), 3.79 (s, 3H), 6.43−6.53 (m, 3H), 7.15−7.21 (m, 2H), 7.34−7.39 (m, 4.9 Hz, 1H), 8.12−8.17 (m, 1H), 8.68−8.72 (m, 1H), 8.99−9.02 (br s, 1H).

***N*-{4-[4-(2-chlorophenyl)-piperazin-1-yl]-butyl}-7-methyl-pyrazolo[1,5-*a*]pyridine-3-carboxamide 21{A1,B6,C1}.** ^{1}H NMR ($CDCl_3$): δ 1.66−1.74 (m, 4H), 2.50 (t, J = 6.9 Hz, 2H), 2.66 (m, 4H), 3.08 (m, 4H), 3.53 (m, 2H), 6.18 (br s, 1H), 6.78 (d, J = 6.9 Hz, 1H), 6.95 (ddd, J = 7.9 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.02 (dd, J = 8.2 Hz, 1.6 Hz, 1H), 7.20 (ddd, J = 8.2 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.30 (dd, J = 8.9 Hz, 6.9 Hz, 1 H), 7.33 (dd, J = 7.9 Hz, 1.6 Hz, 1H), 8.18 (s, 1 H), 8.22 (d, J = 8.9 Hz, 1H).

***N*-{4-[4-(2-chlorophenyl)-piperazin-1-yl]-butyl}-biphenyl-4-carboxamide 24{A1,B7,C1}.** ^{1}H NMR ($CDCl_3$): δ 1.66−1.75 (m, 4H), 2.49 (t, J = 6.7 Hz, 2H), 2.64 (m, 4H), 3.04 (m, 4H), 3.49−3.54 (m, 2H), 6.74 (br s, 1H), 6.92−6.98 (m, 2H), 7.13−7.18 (m, 1H), 7.34 (dd, J = 7.9 Hz, 1.6 Hz, 1H), 7.37−7.40 (m, 1H), 7.43−7.47 (m, 2H), 7.58−7.60 (m, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H).

***N*-{5-[4-pyridin-3-yl-piperazin-1-yl]-pentyl}-4-chlorobenzamide 29{A2,B1,C3}.** ^{1}H NMR ($CDCl_3$): δ 1.40−1.48 (m, 2H), 1.54−1.71 (m, 4H), 2.39−2.44 (m, 2H), 2.59−2.62 (m, 4H), 3.20−3.24 (m, 4H), 3.43−3.49 (m, 2H), 6.15 (br s, 1H), 7.15−7.18 (m, 2H), 7.38−7.42 (m, 2H), 7.69−7.73 (m, 2H), 8.09−8.11 (m, 1H), 8.30 (br s, 1H).

***N*-{5-[4-pyridin-3-yl-piperazin-1-yl]-pentyl}-naphthalene-2-carboxamide 35{A2,B3,C3}.** ^{1}H NMR ($CDCl_3$): δ 1.43−1.52 (m, 2H), 1.58−1.76 (m, 4H), 2.41−2.45 (m, 2H), 2.60−2.63 (m, 4H), 3.21−3.23 (m, 4H), 3.51−3.56 (m, 2H), 6.39 (br s, 1H), 7.14−7.16 (m, 2H), 7.50−7.58 (m, 2H), 7.81−7.92 (m, 4H), 8.08−8.10 (m, 1H), 8.27 (br s, 1H), 8.29 (br s, 1H).

***N*-{5-[4-(2-chloro-phenyl)-piperazin-1-yl]-pentyl}-pyridine-3-carboxamide 36{A2,B4,C1}.** ^{1}H NMR ($CDCl_3$): δ 1.43−1.50 (m, 2H), 1.63−1.71 (m, 4H), 2.46−2.51 (m, 2H), 2.70 (m, 4H), 3.10 (m, 4H), 3.47−3.53 (m, 2H), 6.26 (br s, 1H), 6.97 (ddd, J = 7.9 Hz, 7.4 Hz, 1.6 Hz, 1H), 7.04 (dd, J = 8.1 Hz, 1.5 Hz, 1H), 7.22 (ddd, J = 8.1 Hz, 7.4 Hz, 1.5 Hz, 1H), 7.35 (dd, J = 7.9 Hz, 1.4 Hz, 1H), 7.49 (dd, J = 7.9 Hz, 4.9 Hz, 1H), 8.12 (br d, J = 7.9 Hz, 1H), 8.72 (br d, J = 4.9 Hz, 1H), 8.97 (br s, 1H).

***N*-{5-[4-pyridin-3-yl-piperazin-1-yl]-pentyl}-biphenyl-4-carboxamide 47{A2,B7,C3}.** ^{1}H NMR ($CDCl_3$): δ 1.41−1.50 (m, 2H), 1.56−1.73 (m, 4H), 2.40−2.44 (m, 2H), 2.59−2.62 (m, 4H), 3.21−3.24 (m, 4H), 3.47−3.53 (m, 2H), 6.27 (br s, 1H), 7.14−7.18 (m, 2H), 7.36−7.41 (m, 1H), 7.44−7.49 (m, 2H), 7.59−7.62 (m, 2H), 7.65 (br d, J = 8.5 Hz, 2H), 7.84 (br d, J = 8.5 Hz, 2H), 8.09 (dd, J = 3.9 Hz, 1.8 Hz, 1H), 8.31 (br s, 1H).

References and Notes

(1) Kischning, A.; Monenschein, H.; Wittenberg, R. *Chem.—Eur. J.* **2000**, *6* (24), 4445−4450.

(2) Alsina, J.; Jensen, K. J.; Albericio, F.; Barany, G. *Chem.—Eur. J.* **1999**, *5* (10), 2787−2795.

(3) (a) Swayze, E. E. *Tetrahedron Lett.* **1997**, *38* (49), 8465−8468. (b) Fivush, A. M.; Willson, T. M. *Tetrahedron Lett.* **1997**, *38* (41), 7151−7154. (c) Estep, K. G.; Neipp, C. E.; Stephens Stramiello, L. M.; Adam, M. D.; Allen, M. P.; Robinson, S.; Roskamp, E. J. *J. Org. Chem.* **1998**, *63*, 5300−5301.

(4) Jensen, K. J.; Alsina, J.; Songester, M. F.; Vágner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441−5452.

(5) (a) Alsina, J.; Yokum, T. S.; Albericio, F.; Barany, G. *J. Org. Chem.* **1999**, *64* (24), 8761−8769. (b) Guillaumie, F.; Kappel, J. C.; Kelly, N. M.; Barany, G.; Jensen, K. J. *Tetrahedron Lett.* **2000**, *41*, 6131−6135. (c) Alsina, J.; Yokum, T. S.; Albericio, F.; Barany, G. *Tetrahedron Lett.* **2000**, *41*, 7277−7280. (d) Boas, U.; Brask, J.; Christensen, J. B.; Jensen, K. J. *J. Comb. Chem.* **2002**, *4*, 223−228. (e) Gu, W.; Silverman, R. B. *Org. Lett.* **2003**, *5* (4), 415−418. (f) Shannon, S. K.; Peacock, M. J.; Kates, S. A.; Barany, G. *J. Comb. Chem.* **2003**, *5*, 860−868. (g) Forns, P.; Sevilla. S.; Erra, M.; Ortega, A.; Fernández, J.-C.; de la Figuera, N.; Fernández-Forner, D.; Albericio, F. *Tetrahedron Lett.* **2003**, *44*, 6907−6910.

(6) Löber, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5* (10), 1753−1755.

(7) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(8) (a) Bettinetti, L.; Schlotter, K.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594−4597. (b) Boeckler, F.; Leng, A.; Mura, A.; Bettinetti, L.; Feldon, J.; Gmeiner, P.; Ferger, B. *Biochem. Pharmacol.* **2003**, *66*, 1025−1032.

(9) Pilla, M.; Perachon, S.; Sautel, F.; Garrido, F.; Mann, A.; Wermuth, C. G.; Schwartz, J.-C.; Everitt, B. J.; Sokoloff, P. *Nature* **1999**, *400*, 371−375.

(10) (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174. (c) Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Halides and Related Reactions. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002; Chapter III.3.2, pp 1051−1096.

(11) (a) Weigand, K.; Pelka, S. *Org. Lett.* **2002**, *4* (26), 4689−4692. (b) Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1999**, *40*, 5837−5840.

(12) Yan, B.; Nguyen, N.; Liu, L.; Holland, G.; Raju, B. *J. Comb. Chem.* **2000**, *2*, 66−74.

(13) Garigipati, R. S., K. *Tetrahedron Lett.* **1997**, *38*, 6807−6810.

(14) Zhang, A. J.; Russel, D. H.; Zhu, J.; Burgess, K. *Tetrahedron Lett.* **1998**, *39*, 7439−7442.

(15) Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756−762.

(16) Gösl, R.; Meuwsen, A. *Organic Synthesis*; Wiley: New York, 1963; Vol. 43, pp 1−3.

CC049860S