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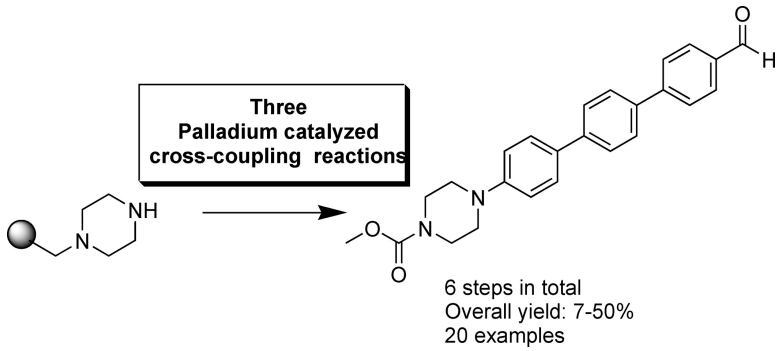

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Solid-Phase Synthesis of *N*-Bi- and *N*-Terarylpiperazines via Three Different and Consecutive Palladium-Catalyzed Cross-Coupling Reactions

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Novel nonsymmetrical *N*-bi- and *N*-terarylpiperazines were synthesized on solid phase via three consecutive palladium-catalyzed cross-coupling reactions in which C−N, C−B, and C−C bonds are formed consecutively.

Introduction

In recent years, a large number of diverse chemical transformations have been transferred from liquid phase to solid phase, enabling the design and synthesis of larger libraries consisting of small, nonpeptidic and "drug-like" compounds.[1] Palladium-catalyzed transformations, such as C−C or C−N bond formations, were among the first transformations applied on solid phase during the renaissance period of solid phase chemistry in the early 1990s following the pioneering work of Merrifield, Leznoff, Frechet, and Rapoport in the 1970s.[2] Palladium-catalyzed reactions on solid phase have since then found many applications in the discovery of novel biologically active compounds.[3]

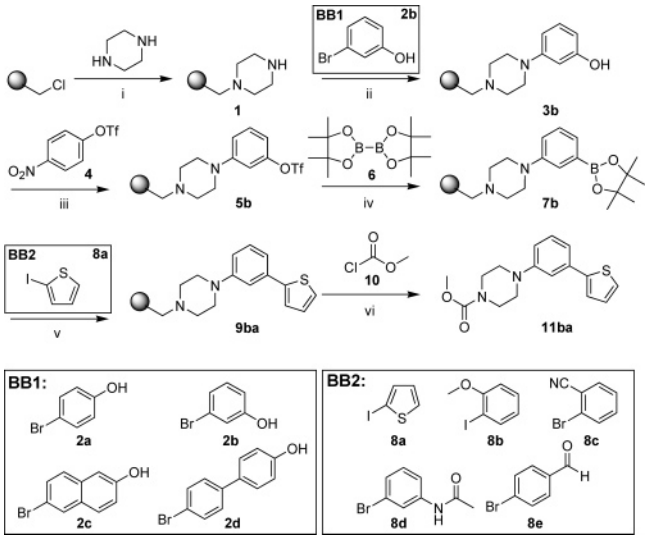
The combination of a piperazinyl moiety with an aryl or hetaryl moiety (often in close proximity to each other) has been found to be a structural key element in the architecture of many biologically active compounds. Recently, we have reported a general solid-phase synthesis of substituted *N*-phenylpiperazines via iron-assisted nucleophilic aromatic substitution on solid phase.[4] A number of *N*-monoarylated piparazines are known as ligands for G-protein-coupled receptors, such as nefazodone[5] used in the treatment of depression as well as N,N′-diarylated piperazines, such as the antifungal drug itraconazole.[6] However, *N*-biphenyl piperazines[7] are rare in the literature, and to the best of our knowledge, *N*-terphenyl piperazines are unknown.

In the following, we describe an efficient solid-phase approach for the synthesis of nonsymmetrical *N*-bi- and *N*-terarylpiperazines using three consecutive Palladium-catalyzed coupling steps.

Results and Discussion

Merrifield resin was used as a solid support in the solid-phase synthesis outlined in Scheme 1. The first diversifying element was introduced by attachment of symmetrical, secondary diamines, as exemplified with piperazine, resulting in the resin-bound piperazine **1**.[4,8]

Scheme 1[a]



[a] (i) 10.0 equiv. piperazine, 5.4 equiv. *N*-methylmorpholine (NMM), THF/DMF (1:1), 60 °C, 16 h; (ii) 15.0 equiv. BB1 (**2a**), 20 mol % Pd_2dba_3, 30 mol %, P(*o*-tol)$_3$, 40.0 equiv. *t*-BuOK, $PhCH_3$, 90 °C, 24 h; (iii) 2.5 equiv. **4**, 2.5 equiv. K_2CO_3, 50 °C, 2−3 days; (iv) 2.5 equiv. **6**, 10 mol % $PdCl_2(dppf)$*CH_2Cl_2, 5 mol % dppf, dry dioxane, 90 °C, 24 h; (v) 6.0 equiv. BB2 (**8a**), 10 mol % $Pd(PPh_3)_4$, 6.0 equiv. K_2CO_3, DMF/THF 1/1, 60 °C, 1d; (vi) ClCOOMe**,** CH_2Cl_2, 0 °C for 30 min, then room temperature for 16 h.

The second point of diversity was introduced by a Palladium-catalyzed aromatic amination reaction. Four diverse hydroxyaryl bromides **2a**−**d** (BB1) were coupled with **1** under modified Buchwald/Hartwig[9] conditions, resulting in the four resin-bound hydroxyarylpiperazines **3a**−**d** (Scheme 1).

In the third step, resin-bound hydroxyarylpiperazines **3a**−**d** were converted to the resin-bound trifluoromethanesulfonic acid esters **5a**−**d** by reaction with trifluoromethanesulfonic acid 4-nitrophenyl ester **4** under mild conditions. The triflation reagent **4**[10] was recently reported to be much more convenient to handle in comparison to classical triflation reagents, such as bis(trifluoromethanesulfonic)anhydride.[11] In addition, the triflation progress could be monitored visually, since intensely yellow *p*-nitrophenol was formed. However, triflation with **4** proceeded slowly on solid phase, and completion of the reaction required ∼3 days reaction time (compared to solution phase: 1−4 h[10]).

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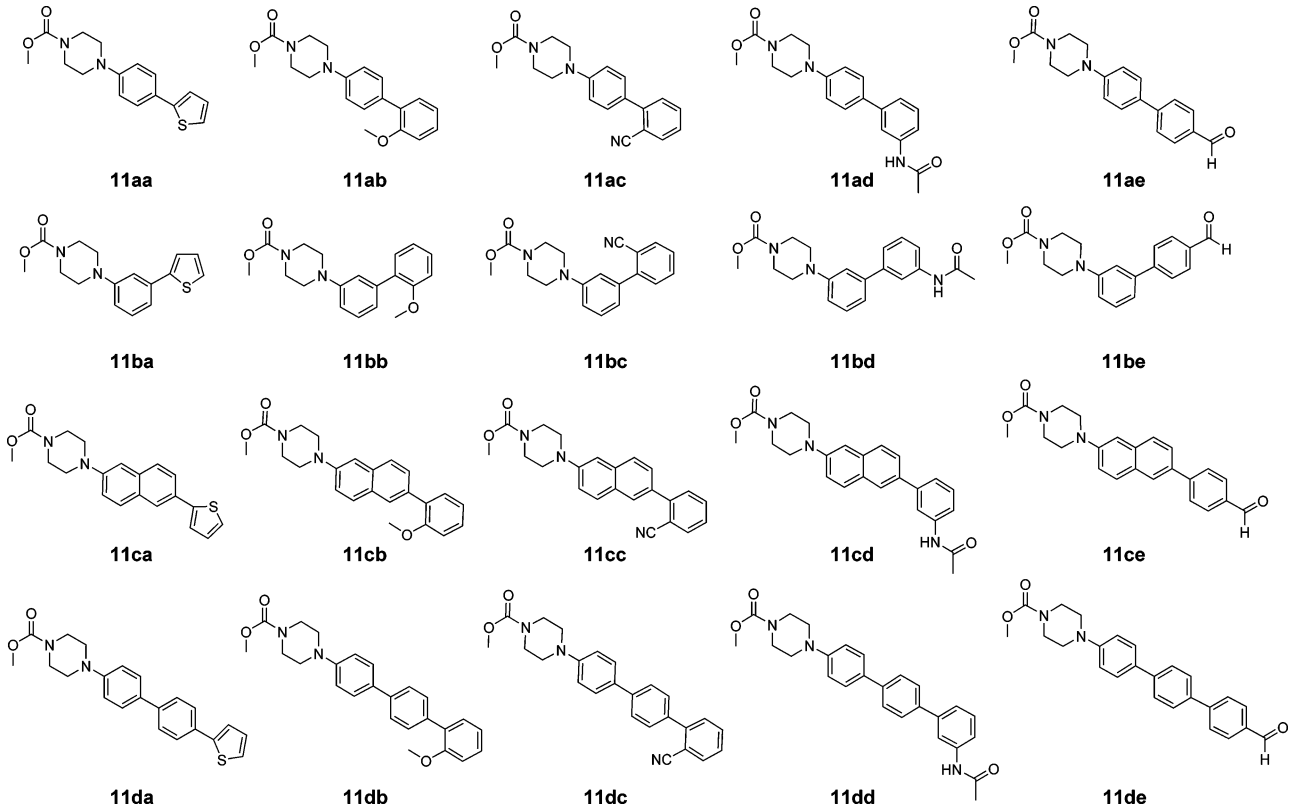
Chart 1. Overview of Synthesized Bi-and Terarylpiperazines



The activation of the hydroxy groups by conversion into triflate groups paved the way for the next Palladium-catalyzed step. To increase the flexibility of the synthesis strategy and to benefit from the large pool of commercially available aryl bromides/iodides, the resin-bound triflates **5a**−**d** were converted under Palladium-catalysis with bis-(pinacolato)diboron, **6**, into the corresponding resin-bound pinacol boronic esters **7a**−**d**.[12]

In the next step, the third point of diversity was introduced by conversion of the resin-bound boronic esters **7a**−**d** via coupling with five different (commercially available) aryl bromides and iodides **8a**−**e** (BB2) into the resin-bound bi- and terarylpiperazines **9aa**−**de** using Suzuki−Miyaura[13] conditions.

Finally, the fourth point of diversity was introduced by cleavage of the resin-bound bi- and terarylpiperazines **9aa**−**de** with chloroformates,[4,14] exemplified with methyl chloroformate **10** (Scheme 1), resulting in the carbamates **11aa**−**de** (Chart 1).

To obtain measurable yields after cleavage, each compound was cleaved from ∼1 g of resins **9aa**−**de**. The cleaved carbamates **11aa**−**de** (after removal of solvent) were analyzed by liquid chromatography/mass spectroscopy (LC/MS) and subsequently purified by column chromatography, recrystallization, or both. During purification, particularly *N*-terarylpiperazines, **11da**−**11de** were found to have very low solubility in common organic solvents. Overall yields (six steps) and purities of crude cleavage products are reported in Table 1. Overall yields are based on the loading of the initially used Merrifield resin (1.2 mmol/g), and purities are determined by LC/MS [UV detection (254 nm) and evaporative light-scattering detection (ELSD)]. In addition, Table 1 includes the yields of purified products.

Table 1. Analytical Results of Cleaved Products

entry	cleaved product	LC/MS−UV crude %	LC/MS-ELSD crude %	% yield[a] crude	% yield[a] purified[b]
1	**11aa**	33	86	70	15
2	**11ab**	52	93	53	7
3	**11ac**	54	85	61	9
4	**11ad**	64	77	54	8
5	**11ae**	86	92	62	12
6	**11ba**	93	97	92	52
7	**11bb**	95	99	88	40
8	**11bc**	89	92	85	45
9	**11bd**	96	97	83	46
10	**11be**	89	99	89	43
11	**11ca**	74	97	90	48
12	**11cb**	79	98	91	44
13	**11cm**	97	97	79	41
14	**11cd**	93	99	83	41
15	**11ce**	91	98	89	46
16	**11da**	73	94	81	38
17	**11db**	74	98	84	35
18	**11dc**	94	95	70	37
19	**11dd**	97	100	79	45
20	**11de**	85	94	87	45

[a] Yields = overall yields after six steps. [b] Purification by column chromatography and/or recrystallization.

The purity of crude products based on LC/MS-ELSD trace seems to be generally overestimated. This indicates that the main impurities are either volatile or possess UV extinction coefficients significantly lower than those of the product. Consequently, the following discussion will be based on yields and LC/MS−UV purities of crude products.

Excellent yields and purities were obtained for all compounds for which 3-bromophenol **2b**, 6-bromo-naphthalen-

2-ol **2c**, and 4′-bromobiphenylol **2d** were used in the first Palladium-catalyzed step (Buchwald/Hartwig aromatic amination reaction) (entries 6−20, Table 1). The overall yields (6 steps) for these 15 crude products (>70%) and LC/MS−UV purities (>73%) indicate that each chemical transformation in the reaction sequence has proceeded in average with a yield higher than 94%. However, for crude products for which 4-bromophenol **2a** was used in the first Palladium-catalyzed step (entries 1−5, Table 1) the overall yields (>53%) and LC/MS−UV purities (>33%) are significantly lower, indicating that the cross-coupling with resin-bound piperazine **1** and **2a** did not go to completion. Attempts to perform cross-couplings between **1** and 2-bromo phenol failed.

Test experiments revealed that *t*-BuOK was required in very large excess (40 equiv) in toluene (as slurry at 90 °C) to achieve efficient cross-couplings. Since this large excess of *t*-BuOK is not completely soluble in toluene at this temperature (solubility: 2.27 g *t*-BuOK in 100.0 g toluene at 25−26 °C [15]), it is not obvious why this large excess of the base (∼30.0 g in 150 mL toluene) was required. Similar observations were reported by Ward and Farina in the solid-phase synthesis of *N*-diarylamines.[9a] The cross-couplings of resin-bound aryl bromides with diverse anilines required in their case 10−20 equiv of *t*-BuONa. A plausible explanation might be deduced by the recent work of Revell and Ganesan.[16] A significant acceleration of Palladium-catalyzed cross-coupling reactions (Suzuki−Miyaura) on solid phase was reported by the use of the ionic liquid, 1-butyl-3-methylimidazolonium tetrafluoroborate ([bmim][BF_4]) as cosolvent (at least 10%). It was concluded that the solvent effect due to the dissolving power of the polar medium must be an important factor for the acceleration (in addition to the possibility of the formation of *N*-heterocyclic carbene complexes). Particularly, the last report could give a hint for the need for such a high concentration of *t*-BuOK. Very recently (after this work was completed), Buchwald et al. reported an improved procedure for the cross-coupling of amines with aryl halides containing hydroxy, amide, or enolizable keto groups by use of bulky, electron-rich ligands and lithium bis(trimethylsilyl)amide as base.[17]

Conclusions

We have demonstrated the solid-phase synthesis of novel nonsymmetrical *N*-bi- and *N*-terarylpiperazines using three consecutive Palladium-catalyzed cross-coupling reactions in which C−N, C−B, and C−C bonds are formed consecutively. The synthesis strategy clearly demonstrates the power of Palladium-catalyzed reactions in combination with the advantages of solid phase, enabling the synthesis of unsymmetrical substituted target molecules by modular assembly.

Experimental Section

All reactions were carried out under positive pressure of nitrogen. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Dioxane, toluene, and tetrahydrofuran (THF) were distilled under N_2 from sodium/benzophenone immediately prior to use. DMF was dried over molecular sieve (4 Å) prior to use. Potassium acetate was dried in vacuo at 100 °C for 2 days. Thin-layer chromatography (TLC) was performed on Merck 60 F_{254} 0.25-μm silica gel plates. ^{1}H NMR and ^{1}H-decoupled/^{13}C NMR spectra were recorded at 500.13 and 125.67 MHz, respectively, on a Bruker Avance DRX 500 instrument. Unless otherwise noted, compounds were measured in deuterated methylene chloride (99.8%). Chemical shifts for ^{1}H NMR are reported in parts per million with TMS as internal reference. Chemical shifts for ^{13}C NMR are reported in parts per million relative to chemical shifts of deuterated solvents. Coupling constants (*J* values) are in hertz. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, dd = double doublet, and m = multiplet. LC−MS data were obtained on a PE Sciex API150EX equipped with a heated nebulizer source operating at 425 °C. The LC pumps were Shimadzu 8A series running with a Waters C-18 4.6 × 50 mm, 3.5-μm column. Solvent A, 100% water + 0.05% trifluoroacetic acid; solvent B, 95% acetonitrile 5% water + 0.035% trifluoroacetic acid. Gradient (2 mL/min): 10−100% B in 4 min, 10% B for 1 min. Total time including equilibration, 5 min. Injection volume, 10 μL from a Gilson 215 liquid handler. High-resolution mass spectra (HR-MS) were performed at the University of Odense (Southern Denmark) (Department of Chemistry) with a 4.7-T Ultima Fourier transform mass spectrometer. Elemental analyses were performed at the University of Vienna, Department of Physical chemistry (Vienna, Austria), with a Perkin-Elmer 2.400 CHN elemental analyzer. Merrifield resin was purchased from Rapp Polymere GmbH (Tübingen, Germany) (H 1001; loading, 1.20 mmol/g; 100−200 mesh; cross-linked with 1% divinylbenzene). The triflation reagent, **4**, 4-nitrophenyltrifluoromethanesulfonate, was prepared by literature methods.[10] All other reagents and catalysts used are commercially available.

(Piperazin-1-yl)methyl Polystyrene 1. A suspension of Merrifield resin (200.0 g, 240.0 mmol), piperazine (207 g, 2.3 mol, 10.0 equiv) and *N*-methylmorpholine (128.0 g, 1.3 mol, 5.4 equiv) in 2 L of THF/DMF (1:1) was gently stirred for 16 h at 60 °C. The resin was filtered and washed with THF (2 × 500 mL), methanol (1 × 500 mL), DMF (1 × 500 mL), water (2 × 500 mL), methanol (2 × 500 mL), THF (2 × 250 mL), methanol (1 × 500 mL), and methylene chloride (3 × 500 mL) and dried in vacuo at 50 °C for 16 h. An almost colorless resin was obtained, which was calculated to have a loading of 1.13 mmol/g, assuming the reaction went to completion.

Palladium-Catalyzed Aromatic Amination (Buchwald/Hartwig Reaction): [4-(2-Hydroxynaphthlen-6-yl)piperazin-1-yl]methyl Polystyrene 3c. The procedure for a typical experiment follows. A suspension of resin **1** (10.2 g, 11.5 mmol), 6-bromonaphthalen-2-ol **2c** (38.4 g, 172.1 mmol, 15 equiv), tris(dibenzylideneacetone)dipalladium(0) (1.04 g, 1.14 mmol, 0.2 equiv), tri-*o*-tolylphosphane (1.05 g, 3.44 mmol, 0.3 equiv), and sodium *t*-butoxide (44.1 g, 458.9 mmol, 40 equiv) in dry toluene (150 mL) was gently stirred for 24 h at 90 °C. The resin was collected by filtration and washed with water (1 × 500 mL), methanol (3 × 300 mL), methylene chloride (3 × 300 mL), DMF (2 × 300 mL),

water (1 × 300 mL), methanol (3 × 300 mL), THF (2 × 300 mL), methanol (1 × 300 mL), and methylene chloride (3 × 300 mL). After drying in vacuo at 50 °C for 16 h, a dark brown resin was obtained, which was calculated to have a loading of 0.97 mmol/g, assuming the reaction went to completion. The resins **3a** (1.03 mmol/g), **3b** (1.03 mmol/g), and **3d** (0.95 mmol/g) were prepared according to the procedure above.

Activation by Triflation: {4-[6-(Trifluoromethylsulfonyloxy)naphthalen-2-yl]piperazin-1-yl}methyl Polystyrene 5c. The procedure for a typical experiment follows. A suspension of resin **3b** (12.0 g, 11.6 mmol), 4-nitrophenyl trifluoromethanesulfonate (7.9 g, 29.1 mmol, 2.5 equiv) and fine powdered potassium carbonate (4.0 g, 28.9 mmol, 2.5 equiv) in dry DMF (150 mL) was gently stirred for 3 days at 50 °C. The resin was collected by filtration and washed with DMF (2 × 300 mL), methylene chloride (3 × 300 mL), methanol (1 × 300 mL), THF (2 × 300 mL), methanol (1 × 300 mL), and methylene chloride (3 × 300 mL). After drying in vacuo at 40 °C for 16 h, an orange-brown resin was obtained which was calculated to have a loading of 0.84 mmol/g, assuming the reaction went to completion. The resins **5a** (0.90 mmol/g), **5b** (0.90 mmol/g), and **5d** (0.84 mmol/g) were prepared according to the procedure above.

Palladium-Catalyzed Aromatic Borolanation (Miyaura Reaction): {4-[6-(4,4,5,5-Tetramethyl-1,3,2dioxaborolan-2-yl)naphthalen-2-yl]piperazin-1-yl}methyl Polystyrene 7c. The procedure for a typical experiment follows. A suspension of resin **5c** (12.4 g, 10.7 mmol), 4,4,5,5,4′,4′,5′,5′-octamethyl[2,2′]bi[1,3,2dioxaborolanyl] (6.8 g, 26.8 mmol, 2.5 equiv), anhydrous potassium acetate (8.4 g, 85.5 mmol), 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloride, methylene chloride adduct (874.0 mg, 1.07 mmol, 0.1 equiv), and 1,1′-bis(diphenylphosphino)ferrocene (296.0 mg, 0.53 mmol, 0.05 equiv) in freshly distilled dioxane was gently stirred for 24 h at 90 °C. The resin was collected by filtration and washed with DMF (2 × 300 mL), methylene chloride (3 × 300 mL), methanol (1 × 300 mL), THF (2 × 300 mL), methanol (1 × 300 mL), and methylene chloride (3 × 300 mL) and dried in vacuo at 40 °C for 16 h. The resins **7a**, **7b**, and **7d** were prepared according to the procedure above.

Palladium-Catalyzed Biaryl Formation (Suzuki Reaction): {4-[6-(Thiophene-2-yl)naphthalen-2-yl]piperazin-1-yl}methyl Polystyrene 9ca. The procedure for a typical experiment follows. To a mixture of 2-iodothiophene (1.2 g, 5.5 mmol) in THF (10 mL) and an aqueous solution of potassium carbonate (2 M, 2.8 mL, 5.6 mmol) was added DMF (∼10 mL) until a homogeneous solution was obtained. Resin **7c** (1.05 g, 0.92 mmol) and tetrakis(triphenylphosphine)palladium(0) (104.0 mg, 0.09 mmol, 0.1 equiv) were added, and the mixture was gently stirred for 24 h at 60 °C. The resin was collected by filtration and washed with DMF (2 × 300 mL), methylene chloride (3 × 300 mL), methanol (1 × 300 mL), THF (2 × 300 mL), methanol (1 × 300 mL), and methylene chloride (3 × 300 mL) and dried in vacuo at 40 °C for 16 h. The resins **9aa**, **9ba**, **9da** (using 2-iodothiophene), **9ab**−**db** (using 2-iodoanisol), **9ac**−**dc** (using 2-bromobenzonitril), **9ad**−**dd** [using *N*-(3-Bromo-phenyl)-acetamide] and **9ae**−**de** (using 4-bromobenzaldehyde) were prepared analogously according to the procedure above.

Cleavage from Solid Support: 4-(6-Thiophen-2-yl-naphthalen-2-yl)piperazine-1-carboxylic Acid Methyl Ester 11ca. The procedure for a typical experiment follows. Resin **9ca** (1.0 g, loading max: 0.92 mmol) was treated at 0 °C with 20 mL methylene chloride/methyl chloroformate (20:1). After 30 min, the suspension was slowly warmed to room temperature and additionally stirred for 16 h. The resin was filtered and washed with methylene chloride (3 × 10 mL), methanol (1 × 10 mL), methylene chloride (1 × 10 mL), and methanol (1 × 10 mL). The filtrates were combined and removed from the solvents and volatile byproducts to obtain a brown residue (299 mg, 92%) as crude product (LC−MS purities: 74% UV, 97% ELSD; $R_t = 3.64$). After purification by flash chromatography (heptane/ethyl acetate 5:1), 158 mg (49%) of a colorless solid was obtained (LC−MS purities: 99% UV, 100% ELSD). mp 196−199 °C (acetone/hexane); ^{1}H NMR δ 3.35 (broad t, 4H, $J = 4.7$), 3.76 (s, 3H), 3.76 (broad m, 4H), 7.17 (m, 1H), 7.32 (broad s, 1H), 7.36 (d, 1H, $J = 4.7$), 7.40 (broad d, 1H, $J = 4.2$), 7.47 (d, 1H, $J = 3.8$), 7.77 (m, 2H), 7.83 (broad d, 1H, $J = 9.0$), 8.02 (s, 1H); ^{13}C NMR δ 44.1 (broad), 50.9 (broad), 53.3, 112.5 (broad), 120.7, 123.8, 124.5, 125.4, 125.7, 128.3, 128.9, 130.9, 134.5, 145.3, 149.9 (broad), 156.5; HRMS [M + 1] calcd for $C_{20}H_{20}N_2O_2S$, 353.1318; found 353.1305. Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 68.06; H, 5.72; N, 8.03; S, 8.87. The final compounds **11aa**, **11ba**, **11ab**−**db**, **11ac**−**dc**, **11ad**−**dd**, and **11ae**−**de** were cleaved analogously according to the procedure above.

4-(4-Thiophen-2-yl-phenyl)piperazine-1-carboxylic Acid Methyl Ester 11aa. This compound was cleaved from resin **9aa** (1.0 g, loading max: 0.96 mmol/g). A brown residue (206 mg, 71%) as crude product (LC−MS purities: 33% UV, 86% ELSD; $R_t = 3.08$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 43 mg (15%) of a colorless solid was obtained (LC−MS purities: 98% UV, 94% ELSD). mp 176−177 °C (acetone/hexane); ^{1}H NMR δ 3.25 (broad t, 4H, $J = 4.9$), 3.72 (broad t, 4H, $J = 4.9$), 3.75 (s, 3H), 7.07 (broad d, 2H, $J = 7.5$), 7.32 (dd, 1H, $J_1 = J_2 = 5.4$), 7.27 (d, 2H, $J = 4.2$), 7.58 (d, 2H, $J = 8.9$); ^{13}C NMR δ 44.1 (broad), 50.3 (broad), 53.3, 117.8, 122.8, 124.6, 127.5, 128.7, 144.9, 150.4 (broad), 156.4; HRMS [M + 1] calcd for $C_{16}H_{18}N_2O_2S$, 303.1162; found 303.1163. Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26; S, 10.60. Found: C, 63.57; H, 6.00; N, 9.35; S, 10.48.

4-(3-Thiophen-2-yl-phenyl)piperazine-1-carboxylic Acid Methyl Ester 11ba. This compound was cleaved from resin **9ba** (1.0 g, loading max: 0.96 mmol/g). A brown residue (271 mg, 93%) as crude product (LC−MS purities: 88% UV, 98% ELSD; $R_t = 3.01$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 153 mg (53%) of a slightly yellow solid was obtained (LC−MS purities: 93% UV, 97% ELSD). mp (without recrystallization) 87−88 °C; ^{1}H NMR δ 3.24 (broad t, 4H, $J = 5.2$), 3.69 (broad t, 4H, $J = 5.2$), 3.75 (s, 3H), 6.94 (broad d, 1H, $J = 7.5$), 7.13 (m, 1H), 7.20 (broad d, 1H, $J = 7.5$), 7.23

(broad s, 1H), 7.31 (d, 1H, $J = 8.0$), 7.34 (d, 1H, $J = 4.2$), 7.36 (d, 1H, $J = 3.3$); ^{13}C NMR δ 44.4 (broad), 50.2 (broad), 53.2, 114.9, 116.7, 118.9 (broad), 123.9, 125.5, 128.7, 130.4, 136.1, 145.4, 152.4 (broad), 156.5; HRMS [M + 1] calcd for $C_{16}H_{18}N_2O_2S$, 303.1162; found 303.1157. Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26; S, 10.60. Found: C, 63.26; H, 6.14; N, 9.26; S, 10.13.

4-(4′-Thiophen-2-yl-biphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11da. This compound was cleaved from resin **9da** (1.0 g, loading max: 0.90 mmol/g). Due to low solubility of this compound, the resin needed to be intensively washed with chloroform (10 × 20 mL) after cleavage. A brown solid residue (283 mg, 83%) as crude product (LC−MS purities: 73% UV, 94% ELSD; $R_t = 3.93$) was obtained. After washing with acetone and recrystallization from chloroform/diethyl ether, 134 mg (39%) of a slightly yellow, microcrystalline solid was obtained (LC−MS purities: 95% UV, 98% ELSD). mp (chloroform/diethyl ether) >268 °C (decomposition); ^{1}H NMR δ 3.38 (broad m, 4H), 3.77 (s, 3H), 3.92 (broad m, 4H), 6.94 (broad d, 1H, $J = 7.5$), 7.13 (m, 1H), 7.20 (broad d, 1H, $J = 7.5$), 7.23 (broad s, 1H), 7.15 (dd, 1H, $J_1 = 4.7$, $J_2 = 3.3$), 7.37 (dd, 1H, $J_1 = 5.2$, $J_2 = 1.4$), 7.43 (dd, 1H, $J_1 = 3.8$, $J_2 = 1.4$), 7.44 (broad s, 2H), 7.65 (d, 2H, $J = 8.5$), 7.70 (d, 2H, $J = 8.5$), 7.74 (d, 2H, $J = 8.5$); ^{13}C NMR δ 43.2 (broad), 52.7 (broad), 53.5, 119.4 (broad), 124.0, 125.8, 127.0, 127.9, 128.7, 129.0, 134.1, 139.7, 144.6, 156.3; HRMS [M + 1] calcd for $C_{22}H_{22}N_2O_2S$, 379.1475; found 379.1465. Anal. Calcd for $C_{22}H_{22}N_2O_2S$: C, 69.81; H, 5.86; N, 7.40; S, 8.47. Found: C, 68.79; H, 5.88; N, 7.31; S, 8.20.

4-(2′-Methoxybiphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11ab. This compound was cleaved from resin **9ab** (1.0 g, loading max: 0.94 mmol/g). A brown residue (167 mg, 54%) as crude product (LC−MS purities: 52% UV, 85% ELSD; $R_t = 2.85$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 153 mg (53%) of a slightly yellow oil was obtained (LC−MS purities: 87% UV, 93% ELSD); ^{1}H NMR δ 3.12 (broad m, 4H), 3.59 (broad m, 4H), 3.61 (s, 3H), 3.71 (s, 3H), 6.89 (d, 1H, $J = 8.9$), 6.91 (t, 1H, $J = 7.1$), 6.95 (broad s, 2H), 7.19 (d, 1H, $J = 7.5$), 7.20 (t, 1H, $J = 6.4$), 7.37 (broad d, 2H, $J = 8.5$); ^{13}C NMR δ 44.2 (broad), 50.6 (broad), 53.2, 56.2, 112.0, 117.1 (broad), 121.5, 129.0 (broad), 130.9, 131.1, 131.2, 150.2 (broad), 156.5, 157.4; HRMS [M + 1] calcd for $C_{19}H_{22}N_2O_3$, 327.1703; found 327.1701. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.73; H, 6.78; N, 8.61.

4-(2′-Methoxybiphenyl-3-yl)piperazine-1-carboxylic Acid Methyl Ester 11bb. This compound was cleaved from resin **9bb** (1.0 g, loading max: 0.94 mmol/g). A brown residue (275 mg, 89%) as crude product (LC−MS purities: 75% UV, 98% ELSD; $R_t = 2.76$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 124 mg (40%) of a colorless oil was obtained (LC−MS purities: 95% UV, 99% ELSD). ^{1}H NMR δ 3.22 (broad t, 4H, $J = 4.9$), 3.69 (broad m, 4H), 3.73 (s, 3H), 3.84 (s, 3H), 6.98 (broad s, 1H), 7.05 (m, 2H), 7.08 (broad s, 1H), 7.41 (broad s, 1H), 7.34 (m, 2H), 7.38 (t, 1H, $J = 8.0$); ^{13}C NMR δ 44.4 (broad), 50.6 (broad), 53.2, 56.2, 112.1, 116.2, 119.1, 121.5, 122.7 (broad), 129.4, 131.4, 131.6, 140.5, 151.7 (broad), 156.5, 157.3; HRMS [M + 1] calcd for $C_{19}H_{22}N_2O_3$, 327.1703; found 327.1692. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 69.92; H, 6.79; N, 8.58. Found: C, 68.19; H, 6.80; N, 8.16.

4-[6-(2-Methoxyphenyl)naphthalen-2-yl]piperazine-1-carboxylic Acid Methyl Ester 11cb. This compound was cleaved from resin **9cb** (1.0 g, loading max: 0.89 mmol/g). A brown solid residue (316 mg, 94%) as crude product (LC−MS purities: 79% UV, 98% ELSD; $R_t = 3.45$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 154 mg (46%) of a colorless solid was obtained (LC−MS purities: 97% UV, 97% ELSD). mp (acetone/heptane) 116−118 °C; ^{1}H NMR δ 3.34 (broad t, 4H, $J = 4.9$), 3.77 (s, 3H), 3.78 (broad m, 4H), 3.87 (s, 3H), 7.08 (d, 1H, $J = 7.5$), 7.11 (dd, 1H, $J_1 = 7.5$, $J_2 = 1.0$), 7.33 (broad s, 2H), 7.39 (td, 1H, $J_1 = 7.2$, $J_2 = 2.0$), 7.45 (dd, 1H, $J_1 = 7.5$, $J_2 = 1.9$), 7.67 (dd, 1H, $J_1 = 8.5$, $J_2 = 1.9$), 7.78 (d, 1H, $J = 8.5$), 7.83 (d, 1H, $J = 8.9$), 7.90 (s, 1H); ^{13}C NMR δ 44.3 (broad), 50.9 (broad), 53.32, 56.3, 112.2, 120.3, 121.6, 126.9, 128.4, 129.3; 129.4, 129.9, 131.4, 131.6, 134.1, 135.3 (broad), 148.9 (broad), 156.5, 157.6; HRMS [M + 1] calcd for $C_{23}H_{24}N_2O_3$, 377.1860; found 377.1866. Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.41; H, 6.38; N, 7.57.

4-(2″-Methoxy[1,1′;4′,1″]terphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11db. This compound was cleaved from resin **9db** (1.0 g, loading max: 0.88 mmol/g). Due to low solubility of this compound, the resin needed to be intensively washed with chloroform (10 × 20 mL) after cleavage. A brown solid residue (308 mg, 87%) as crude product (LC−MS purities: 74% UV, 98% ELSD; $R_t = 3.64$) was obtained. After washing with acetone and recrystallization from chloroform/acetone, 128 mg (36%) of a slightly yellow, microcrystalline solid was obtained (LC−MS purities: 83% UV, 97% ELSD). mp (chloroform/acetone) 199−200 °C; ^{1}H NMR δ 3.27 (broad t, 4H, $J = 4.9$), 3.72 (broad m, 4H), 3.75 (s, 3H), 3.87 (s, 3H), 7.07 (m, 2H), 7.13 (broad s, 2H), 7.38 (m, 2H), 7.60 (d, 2H, $J = 8.5$), 7.65 (m, 4H); ^{13}C NMR δ 44.2 (broad), 50.3 (broad), 53.2, 56.2, 112.1, 117.8 (broad), 121.6, 126.7, 128.4, 129.4, 130.7, 131.0, 131.3, 137.9, 139.8, 156.5, 157.4; HRMS [M + 1] calcd for $C_{25}H_{26}N_2O_3$, 403.2016; found 403.2000. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.40; H, 6.44; N, 7.05.

4-(2′-Cyanobiphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11ac. This compound was cleaved from resin **9ac** (1.0 g, loading max: 0.94 mmol/g). A brown solid residue (167 mg, 51%) as crude product (LC−MS purities: 54% UV, 85% ELSD; $R_t = 2.85$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 22 mg (7%) of a colorless oil (LC−MS purities: 87% UV, 93% ELSD) was obtained. ^{1}H NMR δ 3.46 (broad t, 4H, $J = 5.2$), 3.67 (s, 3H), 3.74 (broad t, 4H, $J = 5.2$), 7.42−7.47 (m, 2H), 7.63 (td, 1H, $J_1 = 7.5$, $J_2 = 1.4$), 7.66 (d, 2H, $J = 8.9$), 7.73 (dt, 1H, $J_1 = 7.1$, $J_2 < 1.0$), 7.92 (d, 2H, $J = 8.9$); ^{13}C NMR δ 41.7 (broad), 53.8, 55.8, 112.1, 118.6, 122.7, 129.3, 130.9, 131.7, 133.9, 134.6, 141.1, 143.1, 143.9, 156.0; HRMS [M + 1] calcd for $C_{19}H_{19}N_3O_2$,

322.1550; found 322.1556. Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07. Found: C, 70.89; H, 6.04; N, 12.20.

4-(2′-Cyanobiphenyl-3-yl)piperazine-1-carboxylic Acid Methyl Ester 11bc. This compound was cleaved from resin **9bc** (1.0 g, loading max: 0.94 mmol/g). A brown residue (262 mg, 85%) as crude product (LC−MS purities: 91% UV, 99% ELSD; $R_t = 2.81$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 124 mg (40%) of a colorless solid was obtained (LC−MS purities: 89% UV, 92% ELSD). mp (diethyl ether/heptane) 111−112 °C; ^{1}H NMR δ 3.28 (broad t, 4H, $J = 4.9$), 3.71 (broad m, 4H), 3.74 (s, 3H), 7.12 (broad d, 2H, $J = 7.5$), 7.19 (broad s, 1H), 7.45 (t, 1H, $J = 8.0$), 7.50 (t, 1H, $J = 7.5$), 7.58 (d, 1H, $J = 7.5$), 7.70 (t, 1H, $J = 7.8$), 7.81 (d, 1H, $J = 7.5$); ^{13}C NMR δ 44.3 (broad), 50.3 (broad), 53.2, 112.1, 117.7, 118.2, 119.4, 121.7 (broad), 128.4, 130.3, 130.7, 133.5, 134.4, 140.1, 146.4, 151.7 (broad), 156.5; HRMS [M + 1] calcd for $C_{19}H_{19}N_3O_2$, 322.1550; found 322.1540. Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07. Found: C, 71.22; H, 5.97; N, 12.74.

4-[6-(2-Cyanophenyl)naphthalen-2-yl]piperazine-1-carboxylic Acid Methyl Ester 11cc. This compound was cleaved from resin **9cc** (1.0 g, loading max: 0.90 mmol/g). A brown residue (271 mg, 81%) as crude product (LC−MS purities: 81% UV, 98% ELSD; $R_t = 3.22$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 140 mg (42%) of a colorless solid was obtained (LC−MS purities: 97% UV, 97% ELSD). mp (acetone/heptane) 147−148 °C; ^{1}H NMR δ 3.36 (broad t, 4H, $J = 4.9$), 3.75 (broad m, 4H), 3.76 (s, 3H), 7.32 (broad s, 1H), 7.43 (broad d, 1H, $J = 8.9$), 7.51 (t, 1H, $J = 7.5$), 7.67 (d, 2H, $J = 8.5$), 7.73 (t, 1H, $J = 7.8$), 7.84 (d, 1H, $J = 7.5$), 7.89 (m, 2H), 7.99 (s, 1H); ^{13}C NMR δ 44.3 (broad), 50.4 (broad), 53.3, 56.2, 111.6 (broad), 112.2, 119.5, 120.8, 127.7, 128.0, 128.2, 128.6, 129.3, 130.1, 131.0, 133.6, 134.4, 134.5, 135.1, 146.3, 149.9 (broad), 156.5; HRMS [M + 1] calcd for $C_{23}H_{21}N_3O_2$, 372.1707; found 372.1710. Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.40; H, 5.70; N, 11.11.

4-(2″-Cyano[1,1′;4′,1″]terphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11dc. This compound was cleaved from resin **9dc** (1.0 g, loading max: 0.88 mmol/g). Due to low solubility of this compound, the resin needed to be intensively washed with chloroform (10 × 20 mL) after cleavage. A brown solid residue (253 mg, 72%) as crude product (LC−MS purities: 84% UV, 98% ELSD; $R_t = 3.35$) was obtained. After washing with acetone and recrystallization from chloroform/acetone, 134 mg (38%) of a colorless, microcrystalline solid was obtained (LC−MS purities: 94% UV, 95% ELSD). mp (chloroform/acetone) 222−223 °C; ^{1}H NMR δ 3.30 (broad t, 4H, $J = 5.2$), 3.75 (broad m, 4H), 3.76 (s, 3H), 7.18 (broad d, 2H, $J = 5.2$), 7.51 (td, 1H, $J_1 = 7.5$, $J_2 = 1.4$), 7.61 (d, 1H, $J = 7.1$), 7.68 (m, 4H), 7.72 (td, 1H, $J_1 = 7.5$, $J_2 = 1.4$), 7.76 (d, 2H, $J = 8.5$), 7.83 (d, 1H, $J = 8.0$); ^{13}C NMR δ 44.1 (broad), 50.4 (broad), 53.3, 111.9, 117.9 (broad), 119.5, 127.4, 128.3, 128.6, 130.0, 130.8, 133.6, 134.5, 137.4, 141.6, 145.8, 156.4; HRMS [M + 1] calcd for $C_{25}H_{23}N_3O_2$, 398.1863; found 398.1878. Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.55; H, 5.83; N, 10.57. Found: C, 75.23; H, 5.80; N, 10.27.

4-(3′-Acetylaminobiphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11ad. This compound was cleaved from resin **9ad** (1.0 g, loading max: 0.92 mmol/g). A brown residue (179 mg, 55%) as crude product (LC−MS purities: 64% UV, 77% ELSD; $R_t = 2.16$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 3:1), 28 mg (9%) of a colorless solid was obtained (LC−MS purities: 95% UV, 93% ELSD). mp (acetone/heptane) 198−199 °C; ^{1}H NMR δ 2.19 (s, 3H), 3.31 (broad t, 4H, $J = 4.7$), 3.76 (s, 3H), 3.83 (broad m, 4H), 7.29 (broad s, 1H), 7.34 (broad d, 2H, $J = 7.5$), 7.40 (t, 1H, $J = 8.0$), 7.51 (broad d, 2H, $J = 6.6$), 7.61 (d, 2H, $J = 8.9$), 7.78 (s, 1H); ^{13}C NMR δ 25.2, 43.5 (broad), 51.7 (broad), 53.4, 118.6, 119.2, 123.0, 128.8, 130.1, 139.6, 141.6, 156.3, 169.1; HRMS [M + 1] calcd for $C_{20}H_{23}N_3O_3$, 354.1812; found 354.1814. Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.92; H, 6.50; N, 11.78.

4-(3′-Acetylaminobiphenyl-3-yl)piperazine-1-carboxylic Acid Methyl Ester 11bd. This compound was cleaved from resin **9bd** (1.0 g, loading max: 0.92 mmol/g). A brown residue (277 mg, 85%) as crude product (LC−MS purities: 88% UV, 98% ELSD; $R_t = 2.18$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 3:1), 152 mg (47%) of a slightly brown foam was obtained (LC−MS purities: 96% UV, 97% ELSD). ^{1}H NMR δ 2.19 (s, 3H), 3.25 (broad t, 4H, $J = 4.9$), 3.71 (broad m, 4H), 3.75 (s, 3H), 7.04 (broad d, 1H, $J = 7.1$), 7.18 (broad d, 1H, $J = 7.1$), 7.24 (broad s, 1H), 7.38 (m, 3H), 7.58 (broad d, 1H, $J = 7.5$), 7.77 (broad s, 1H), 7.81 (broad s, 1H); ^{13}C NMR δ 25.1, 44.2 (broad), 50.7 (broad), 53.3, 56.2, 116.7, 116.9, 119.2, 119.6, 120.8 (broad), 123.5, 130.0, 130.4, 139.6, 142.7, 142.8, 151.6 (broad), 156.5, 169.2; HRMS [M + 1] calcd for $C_{20}H_{23}N_3O_3$, 354.1812; found 354.1827. Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.67; H, 6.53; N, 11.62.

4-[6-(3-Acetylaminophenyl)naphthalen-2-yl]piperazine-1-carboxylic Acid Methyl Ester 11cd. This compound was cleaved from resin **9cd** (1.0 g, loading max: 0.88 mmol/g). A brown residue (304 mg, 86%) as crude product (LC−MS purities: 72% UV, 94% ELSD; $R_t = 2.64$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 3:1), 149 mg (42%) of a colorless solid was obtained (LC−MS purities: 93% UV, 99% ELSD). mp (acetone/heptane) 234−235 °C; ^{1}H NMR δ 2.22 (s, 3H), 3.37 (broad t, 4H, $J = 4.7$), 3.77 (s, 3H), 3.83 (broad m, 4H), 7.48 (m, 4H), 7.55 (d, 1H, $J = 7.5$), 7.75 (d, 1H, $J = 8.5$), 7.85 (d, 1H, $J = 8.5$), 7.88 (d, 1H, $J = 9.4$), 7.92 (broad s, 1H), 8.01 (s, 1H); ^{13}C NMR δ 25.2, 43.8 (broad), 51.5 (broad), 53.4, 113.3 (broad), 119.1, 119.3, 120.4, 123.5, 126.1, 126.9, 128.4, 130.1, 130.3, 134.3, 137.5 (broad), 139.7, 142.4, 147.7 (broad), 156.4, 169.0; HRMS [M + 1] calcd for $C_{24}H_{25}N_3O_3$, 404.1969; found 404.1975. Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 68.19; H, 6.80; N, 8.16.

4-(3″-Acetylamino[1,1′;4′,1″]terphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11dd. This compound was cleaved from resin **9dd** (1.0 g, loading max: 0.86 mmol/g). Due to low solubility of this compound, the resin needed to

be intensively washed with chloroform (10 × 20 mL) after cleavage. A brown solid residue (302 mg, 82%) as crude product (LC−MS purities: 67% UV, 89% ELSD; $R_t = 2.85$) was obtained. After washing with acetone and recrystallization from chloroform/acetone, 172 mg (47%) of a slightly brown, microcrystalline solid was obtained (LC−MS purities: 97% UV, 100% ELSD). mp (chloroform/acetone) 288−289 °C/decomposition; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H), 3.20 (broad t, 4H, $J = 4.9$), 3.53 (broad t, 4H, $J = 4.9$), 3.63 (s, 3H), 7.05 (d, 2H, $J = 8.9$), 7.35 (d, 1H, $J = 8.0$), 7.38 (t, 1H, $J = 7.8$), 7.55 (d, 1H, $J = 8.0$), 7.61 (d, 2H, $J = 8.5$), 7.64 (d, 2H, $J = 8.0$), 7.71 (d, 2H, $J = 8.0$), 7.93 (broad s, 1H), 9.99 (broad s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.4, 43.6, 48.3, 52.7, 116.4, 117.4, 118.3, 121.5, 126.7, 127.3, 127.5, 129.6, 130.50, 138.5, 139.4, 140.3, 140.6, 150.6, 155.4, 168.8; HRMS [M + 1] calcd for $C_{26}H_{27}N_2O_3$, 430.2125; found 430.2125. Anal. Calcd for $C_{26}H_{27}N_2O_3$: C, 72.71; H, 6.34; N, 9.78. Found: C, 72.46; H, 6.36; N, 9.54.

4-(4′-Formylbiphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11ae. This compound was cleaved from resin **9ae** (1.0 g, loading max: 0.94 mmol/g). A brown residue (167 mg, 55%) as crude product (LC−MS purities: 45% UV, 65% ELSD; $R_t = 2.85$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 22 mg (7%) of a yellow solid was obtained (LC−MS purities: 86% UV, 92% ELSD). mp (acetone/heptane) 194−195 °C; ^{1}H NMR δ 3.41 (broad t, 4H, $J = 4.7$), 3.67 (s, 3H), 4.09 (broad t, 4H, $J = 5.2$), 7.68 (d, 2H, $J = 8.0$), 7.71 (d, 2H, $J = 8.5$), 7.81 (d, 2H, $J = 8.5$), 7.89 (d, 2H, $J = 8.5$), 9.98 (s, 1H); ^{13}C NMR δ 41.9 (broad), 55.2, 122.4, 128.5, 129.9, 131.0, 136.7, 141.6, 143.6, 145.7, 156.1, 192.3; HRMS [M + 1] calcd for $C_{19}H_{20}N_2O_3$, 325.1547; found 325.1540. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.32; H, 6.16; N, 8.42.

4-(4′-Formylbiphenyl-3-yl)piperazine-1-carboxylic Acid Methyl Ester 11be. This compound was cleaved from resin **9be** (1.0 g, loading max: 0.94 mmol/g). A brown residue (276 mg, 91%) as crude product (LC−MS purities: 89% UV, 99% ELSD; $R_t = 2.76$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 134 mg (44%) of a yellow solid was obtained (LC−MS purities: 91% UV, 99% ELSD). mp (acetone/heptane) 139−140 °C; ^{1}H NMR δ 3.28 (broad t, 4H, $J = 5.2$), 3.72 (broad t, 4H, $J = 4.9$), 3.75 (s, 3H), 7.09 (broad d, 1H, $J = 7.5$), 7.24 (broad d, 1H, $J = 7.5$), 7.29 (broad s, 1H), 7.44 (t, 1H, $J = 8.0$), 7.80 (d, 2H, $J = 8.0$), 7.98 (d, 2H, $J = 8.5$), 10.09 (s, 1H); ^{13}C NMR δ 44.3 (broad), 50.4 (broad), 53.2, 116.6, 117.6, 120.5 (broad), 128.5, 130.6, 130.8, 136.3, 141.7, 148.0, 152.1 (broad), 156.5, 192.4; HRMS [M + 1] calcd for $C_{19}H_{20}N_2O_3$, 325.1547; found 325.1541. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.11; H, 6.26; N, 8.38.

4-[6-(4-Formylphenyl)naphthalen-2-yl]piperazine-1-carboxylic Acid Methyl Ester 11ce. This compound was cleaved from resin **9ce** (1.0 g, loading max: 0.90 mmol/g). A brown residue (309 mg, 91%) as crude product (LC−MS purities: 77% UV, 99% ELSD; $R_t = 3.35$) was obtained. After purification by flash chromatography (heptane/ethyl acetate 5:1), 158 mg (47%) of a yellow solid was obtained (LC−MS purities: 91% UV, 98% ELSD). mp (acetone/heptane) 178−179 °C; ^{1}H NMR δ 3.39 (broad t, 4H, $J = 4.9$), 3.77 (s, 3H), 3.39 (broad t, 4H, $J = 4.9$), 7.45 (broad s, 1H), 7.47 (broad d, 1H, $J = 4.9$), 7.81 (dd, 1H, $J_1 = 8.5$, $J_2 = 1.9$), 7.91 (m, 2H), 7.94 (d, 2H, $J = 8.5$), 8.01 (d, 2H, $J = 8.5$), 8.01 (d, 1H, $J = 1.9$), 10.10 (s, 1H); ^{13}C NMR δ 44.0 (broad), 51.1 (broad), 53.2, 112.8 (broad), 120.6, 126.5, 126.9, 128.3, 128.6, 130.3, 130.5, 130.9, 134.9, 136.0, 147.6, 148.6, 156.4 (broad), 192.4; HRMS [M + 1] calcd for $C_{23}H_{22}N_2O_3$, 375.1703; found 375.1722. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.98; H, 6.00; N, 7.33.

4-(4″-Formyl[1,1′;4′,1″]terphenyl-4-yl)piperazine-1-carboxylic Acid Methyl Ester 11de. This compound was cleaved from resin **9de** (1.0 g, loading max: 0.88 mmol/g). Due to low solubility of this compound, the resin needed to be intensively washed with chloroform (10 × 20 mL) after cleavage. A brown solid residue (316 mg, 89%) as crude product (LC−MS purities: 76% UV, 96% ELSD; $R_t = 3.66$) was obtained. After washing with acetone and recrystallization from chloroform/acetone, 164 mg (47%) of a yellow, microcrystalline solid was obtained (LC−MS purities: 85% UV, 94% ELSD). mp (chloroform/acetone) 256−260 °C; ^{1}H NMR δ 3.43 (broad m, 4H), 3.78 (s, 3H), 4.02 (broad m, 4H), 7.61 (m broad, 2H), 7.76 (d, 2H, $J = 5.2$), 7.77 (d, 2H, $J = 5.7$), 7.81 (d, 2H, $J = 8.5$), 7.87 (d, 2H, $J = 8.0$), 8.01 (d, 2H, $J = 8.5$), 10.10 (s, 1H); ^{13}C NMR δ 42.8 (broad), 53.3 (broad), 53.6, 120.5 (broad), 128.2, 128.6, 129.1, 130.9, 136.3, 139.6, 140.6, 146.4 (broad), 147.0, 156.2, 192.4; HRMS [M + 1] calcd for $C_{25}H_{24}N_2O_3$, 401.1860; found 401.1877. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 74.79; H, 6.08; N, 6.85.

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References and Notes

(1) (a) Dolle, R. E. *J. Comb. Chem.* **2000**, *3*, 477−517. (b) Willoughby, C. A.; Berk, S. C.; Rosauer, K. G.; Degrado, S.; Chapman, K. T.; Gould, S. L.; Springer, M. S.; Malkowitz, L.; Schleif, W. A.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Holmes, K.; Lineberger, J.; Carella, A.; Carver, G.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3137−3141. (c) Willoughby, C. A.; Hutchins, S. M.; Rosauer, K. G.; Dhar, M. J.; Chapman, K. T.; Chicchi, G. G.; Sadowski, S.; Weinberg, D. H.; Patel, S.; Malkowitz, L.; Di Salvo, J.; Pacholok, S. G.; Cheng, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 93−96. (d) Shaw, D.; Chicchi, G. G.; Elliott, J. M.; Kurtz, M.; Morrison, D.; Ridgill, M. P.; Szeto, N.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3031−3034.

(2) (a) Crowley, J. I.; Rapoport, H. *Acc. Chem. Res.* **1976**, *9*, 135−144. (b) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327−333. (c) Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492−496. (d) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149−2154.

(3) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885−939.

(4) Ruhland, T.; Bang, K. S.; Andersen, K. *J. Org. Chem.* **2002**, *67*, 5257−5268.

(5) (a) Madding, G. D.; Smith, D. W.; Sheldon, R. I.; Lee, B. *J. Heterocycl. Chem.* **1985**, *22*, 1121−1126. (b) Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. *J. Med. Chem.* **1997**, *40*, 1293−1315.
(6) Hepperle, M.; Eckert, J.; Gala, D.; Shen, L.; Anderson Evans, C.; Goodman, A. *Tetrahedron Lett.* **2002**, *43*, 3359−3363.
(7) Huang, Y.; Kegeles, L. S.; Bae, S.-A.; Hwang, D.; Roth, B. L.; Savage, J. E.; Laruelle, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1375−1377.
(8) (a) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 3413−3415. (b) Bräse, S.; Schroen, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1071−1073.
(9) (a) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37* (39), 6993−6996. (b) Yang, B. H.; Buchwald, S. L.; *J. Organomet. Chem.* **1999**, *576*, 125−146. (c) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181−7184.
(10) Zhu, J.; Bigot, A.; Tran Huu Dau, M. E. *Tetrahedron Lett.* **1997**, *38*, 1181−1182.
(11) Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett.* **2002**, *4*, 4717−4718.
(12) (a) Tempest, P. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7607−7608. (b) Piettre, S. R.; Baltzer, S. *Tetrahedron Lett.* **1997**, *38*, 1197−1200.
(13) (a) Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 8, 6331−6332. (b) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169−5171.
(14) Conti, P.; Demont, D.; Cals, J.; Ottenheijm, H. C. J.; Leysen, D. *Tetrahedron Lett.* **1997**, *38*, 2915−2918.
(15) *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1995; Vol. 6, p 4189.
(16) Revell, J. D.; Ganesan, A.; *Org. Lett.* **2002**, *4*, 3071−3073.
(17) Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885−2888.

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