Biologically Active Compounds through Catalysis: Efficient Synthesis of *N*-(Heteroarylcarbonyl)-*N*′-(arylalkyl)piperazines

Kamal Kumar,[a] Dirk Michalik,[a] Ivette Garcia Castro,[a] Annegret Tillack,[a] Alexander Zapf,[a] Michael Arlt,[b] Timo Heinrich,[b] Henning Böttcher,[b] and Matthias Beller*[a]

Abstract: A practical route for the synthesis of new biologically active 5-HT_{2A} receptor antagonists has been developed. In only three catalytic steps, this class of central nervous system (CNS) active compounds can be synthesized efficiently with high diversity. As the initial step, an *anti*-Markovnikov addition of amines to styrenes provides an easy route to *N*-(arylalkyl)piperazines, which constitute the core structure of the active molecules. Here, base-catalyzed hydroamination reactions of styrenes with benzylated piperazine proceeded in high yield even at room temperature. After catalytic debenzylation, the free amines were successfully carbonylated with different aromatic and heteroaromatic halides and carbon monoxide to yield the desired compounds in good to excellent yields. The two key reactions, base-catalyzed hydroamination of styrenes and palladium-catalyzed aminocarbonylation of haloarenes/heterocycles, showed tolerance towards various functional groups, thereby demonstrating the potential to synthesize a wide variety of new derivatives of this promising class of pharmaceuticals.

Keywords: amphetamines · carbonylation · homogeneous catalysis · hydroamination · palladium

Introduction

The synthesis of new biologically active molecules is an important element in the development of innovative drugs for human and animal disorders. In general, drug development is dominated by the use of stoichiometric organic transformations. Although catalytic reactions, such as palladium-catalyzed coupling reactions,[1] have in recent years been receiving increasing attention from medicinal chemists, catalysis is still somewhat underrated with regard to drug development. This is rather surprising when one considers the overall importance of catalysis in chemistry; over 90% of all chemicals produced worldwide are made with the aid of catalysis. The reasons for the lesser use of catalytic technologies in drug development are various. Clearly, the commercial availability of catalysts and ligands, which is often not guaranteed for new catalysts or novel reactions, plays an important role.[2] Catalytic reactions are also often significantly influenced by small variations in reaction conditions or the substrate structure, thus making it difficult for pharmaceutical chemists to use such reactions in a general manner. Optimization of catalytic systems is most commonly carried out on comparably simple model systems, so the results obtained are often difficult to apply for more complicated lead structures, often bearing a variety of functional groups. Importantly, medicinal chemists also try to avoid the use of air- and water-sensitive organometallic complexes. Nevertheless, catalysis offers a number of possibilities for improved drug development. Catalytic routes to a desired active compound are often shorter in terms of reaction steps, providing the product in a faster and more economic manner. More importantly, catalytic reactions offer unusual modifications of given lead structures, thereby allowing the synthesis of potential drugs not easily accessed by stoichiometric organic transformations. In addition, a short catalytic route might be more easily scaled up than a longer traditional route if larger scale production of a certain molecule is required.

To explore the opportunities of homogeneous catalysis for drug development, we started a program on the synthesis of potentially active amphetamine analogues using catalysis as a tool box. As an interesting target we envisioned the serotonin (5-HT)-receptor subtype 2A, for which phenethylpiperazines (Figure 1) can be strong ligands.[3] Different derivatives of this class of compounds are suitable for the treat-

[a] Dr. K. Kumar, Dr. D. Michalik, Dr. I. Garcia Castro, Dr. A. Tillack, Dr. A. Zapf, Prof. Dr. M. Beller
Leibniz-Institut für Organische Katalyse an der Universität Rostock e.V.
Buchbinderstrasse 5–6, 18055 Rostock (Germany)
Fax: (+49) 381–46693–24
E-mail: matthias.beller@ifok.uni-rostock.de

[b] Dr. M. Arlt, Dr. T. Heinrich, Dr. H. Böttcher
Merck KGaA, Frankfurter Strasse 250
64293 Darmstadt (Germany)

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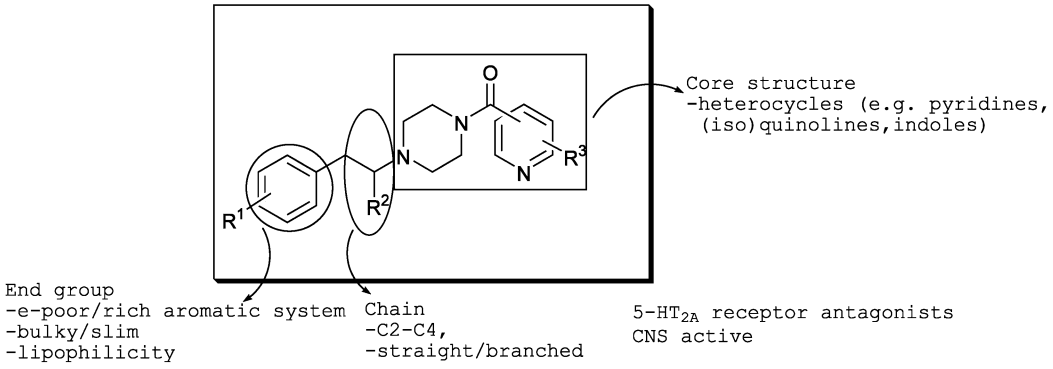
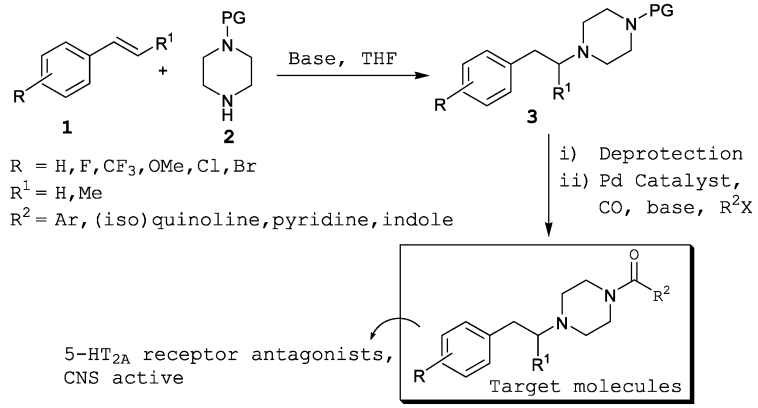


Figure 1. Target molecules and possible variations.

ment of a wide variety of diseases, such as psychosis, schizophrenia, depression, neural disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as nervous bulimia and anorexia, premenstrual syndromes, and for positive influencing of compulsive behavior (obsessive-compulsive disorder, OCD).[4]

In general, the synthesis of 5-HT_{2A} receptor antagonist molecules as shown in Figure 1 and similar molecules involves more than five reaction steps and the use of rather expensive raw materials.[3,4] Overall yields of the desired products are in the range of <30–$50\,\%$. Clearly, derivatives of this class of molecules can be easily synthesized if the corresponding (arylethyl)piperazines and (hetero)arylcarboxylic acids are available. Unfortunately, the known routes for the synthesis of (arylethyl)piperazines involve several reaction steps[5] and only a few of the desired carboxylic acids of the heterocycles are commercially available and so have to be synthesized by longer reaction sequences.[6]



Scheme 1. Catalytic route to biologically active amphetamine analogues.

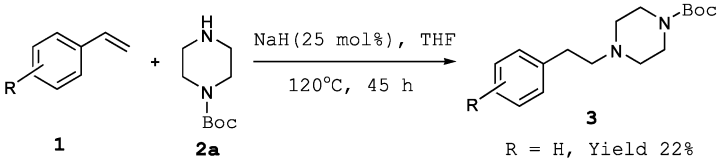
In the past, pharmacologically interesting *N*-(2-arylethyl)-piperazines[7] were synthesized by treatment either of *N*-benzylpiperazines with β-haloethylbenzenes or of substituted phenethylamines with *N*,*N*-bis(β-chloroethyl)amines.[8] Thus, the described syntheses started with halogenated substrates, producing a considerable amount of salt by-products. Also, from a pharmacological point of view, the known syntheses have some limitations for variation of the overall structures of these molecules. For example, the diversity of heterocycles in the core structure is limited to commercially available carboxylic acids. In addition, variations of the ethylene spacer unit are not easily achieved.

We imagined a shorter and more flexible approach to 5-HT_{2A} receptor antagonists based on our expertise in amination reactions of olefins[9] and carbonylation of aryl halide derivatives,[10] as shown in Scheme 1. We recently reported on the base-catalyzed hydroamination (BCH) of aryl olefins as a new synthetic route to amphetamines.[11] The presence of the *N*-(2-arylalkyl)piperazine unit as a core part of 5-HT_{2A} receptor antagonists encouraged us to exploit the BCH of substituted styrenes as a first step towards the target molecules. The *anti*-Markovnikov addition of monoprotected piperazine would provide the core structure for these molecules in one step. Subsequent deprotection and palladium-catalyzed carbonylation of the free amines with different aryl or heteroaryl halides should give the desired products in a short and efficient synthetic route (Scheme 1).

Results and Discussion

The first reaction step in the planned sequence is a catalytic hydroamination[12] of substituted styrenes with a monoprotected piperazine derivative. This reaction is $100\,\%$ atom-economic and much more elegant than the sometimes troublesome nucleophilic substitution of β-(haloethyl)benzenes. While base-catalyzed hydroamination of aliphatic olefins did not proceed to any significant extent, the activating aryl substituent makes styrenes more suitable substrates for this reaction.[13] Pre-catalysts used for this reaction include metallic sodium, CsOH, and alkali metal amides, which can be formed in situ from *n*BuLi, Na_2Np, or KO*t*Bu. In general, primary and secondary amines add to styrene to form the corresponding secondary and tertiary amine products at temperatures $>100\,°C$.

Initially we attempted the reaction between styrene and mono-*N*-*tert*-butoxycarbonyl-protected (Boc-protected) piperazine (**2a**), due to the easy cleavage of the Boc group afterwards. In the presence of catalytic amounts of *n*BuLi, however, only low yields (<5%) of *N*-Boc-*N*′-2-phenethylpiperazine were obtained. As shown in Scheme 2, the use of

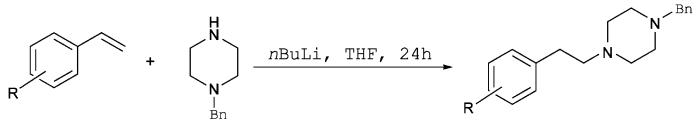


Scheme 2. Base-catalyzed hydroamination of aryl olefins with *N*-Boc-piperazine.

NaH as pre-catalyst gave a better yield of **3** (22%). However, no further improvement in the product yield could be obtained with styrene or substituted styrenes such as 4-chloro- and 3-(trifluoromethyl)styrene, despite significant variations in the reaction conditions (temperature: room temperature up to 120°C; catalyst: 5–20 mol%; amine/olefin ratio 2:1 to 1:2).

To avoid side reactions of the Boc protecting group, which is not stable under the basic conditions at high temperature, we used *N*-benzylpiperazine for the hydroamination reaction. Here, use of a catalytic amount (0.1 equiv) of *n*BuLi in THF was effective, yielding *N*-benzyl-*N*′-phenethylpiperazine (**4a**) in 94% yield (Table 1, entry 1). In addition, different substituted styrenes with electron-donating and -withdrawing functionalities—such as 3- and 4-chlorostyrene, 3- and 4-methylstyrene, 4-methoxystyrene, 2- and 3-bromostyrene, and 3-(trifluoromethyl)styrene—were successfully hydroaminated to the substituted *N*-benzyl-*N*′-(2-arylethyl)piperazines (**4a–j**) (Table 1, entries 1–15).

Table 1. Base-catalyzed hydroamination of aryl olefins at high temperature.[a]



Entry	R	Olefin/amine	*n*BuLi [mol%]	*T* [°C]	Conv.[b] [%]	Product (Yield[c] [%])
1	H	1:1	10	120	94	**4a** (94)
2[d]	4-Cl	1:1	10	65	92	**4b** (38)
3	4-Cl	1:1	20	120	92	**4b** (65)
4[d]	4-Me	1:1	10	65	91	**4c** (75)
5	4-Me	1:1	20	120	98	**4c** (95)
6[d]	4-OMe	1:1	10	65	98	**4d** (71)
7	4-OMe	1:1	20	120	96	**4d** (92)
8[d]	4-F	1:1	10	65	28	**4e** (15)
9[e]	4-F	1:1	20	70	50	**4e** (11)
10	4-F	1:3	20	120	66	**4e** (57)
11	3-Cl	1.5:1	10	120	96	**4f** (88)
12[d]	3-Me	1:1	10	65	91	**4g** (75)
13[d]	3-Br	1:1	10	65	89	**4h** (40)
14	3-CF_3	1:1	10	120	80	**4i** (60)
15[d]	2-Br	1:1	10	65	90	**4j** (30)

[a] Reaction conditions: **2** (2.2 mmol), olefin in THF (5 mL) in a pressure tube. [b] Determined by GC with hexadecane as internal standard (based on **2**). [c] Yield of isolated product. [d] Automated parallel synthesis. [e] 48 h.

Typically we applied 0.1 equivalents of base pre-catalyst at 65–120°C, although in some cases better yields of the desired products were obtained in the presence of 0.2 equivalents of base.

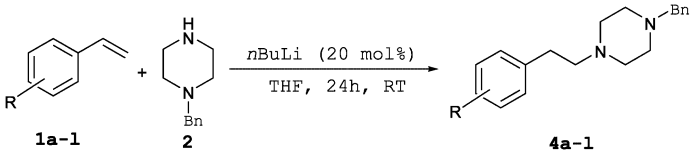
To speed up synthesis, we considered automation a promising approach. Automated and parallel synthesis and screenings of reaction parameters have become valuable methods in drug development.[14,15] Sample preparation (addition of reactant stock solutions), reaction processing (heating, mixing), and workup (cooling, dilution, analysis) steps were performed in an ACT-Vantage system. We used 12- and 48-well reactors and several modules providing the liquid handling. In these reactions a GC/MS system was used for analysis of the products. Both the automated and the manual synthesis of the *N*-(2-arylethyl)piperazines (**4**) gave similar yields.

With the exceptions of 2- and 3-bromostyrene and 4-fluorostyrene (Table 1, entries 8–10, 13, 15), all other starting materials gave the corresponding products in sufficient to very good yields (60–95%). In some cases a difference between the degree of conversion and the isolated product yield was observed. Here, base-catalyzed oligomerization and polymerization of the olefin had mainly occurred. Because of its expected pharmacological properties, we were especially interested in the corresponding *N*-(4-fluorophenethyl)piperazine (**4e**), and so we studied this reaction in more detail. Increasing the amount of *n*BuLi to 0.2 equiv could not enhance the yield of this product (Table 1, entry 9). However, when the amine was used in excess (olefin to amine in 1:3 ratio), **4e** was obtained in 57% yield (Table 1, entry 10). Surprisingly, even better yields of **4e** (87%) were observed when the reaction was performed in the presence of 0.2 equiv of base pre-catalyst at room temperature (Table 2, entry 5). This is one of the few examples of efficient olefin hydroamination at room temperature.[16] Because of the success of the lower reaction temperature we performed a number of further experiments at room temperature. As demonstrated in Table 2, in most cases similar or even better yields were achieved.

In addition to the reactions shown in Table 2, 1,2-dihydronaphthalene (**5**) and allylbenzene (**7**) were also successfully hydroaminated with *N*-benzylpiperazine and the use of 0.2 equivalents of pre-catalyst in THF solution at room temperature. Previous studies had revealed that it is possible to isomerize allylbenzene to give β-methylstyrene under the reaction conditions required for base-catalyzed hydroamination.[17] The reaction therefore generates branched amphetamine derivatives, which considerably broadens the structural diversity of our synthetic route. Here, hydroamination of allylbenzene proceeded regioselectively (>99%) to yield *N*-benzyl-*N*′-(2-phenylpropyl)piperazine (**8**) in good yield (88%; Scheme 3).

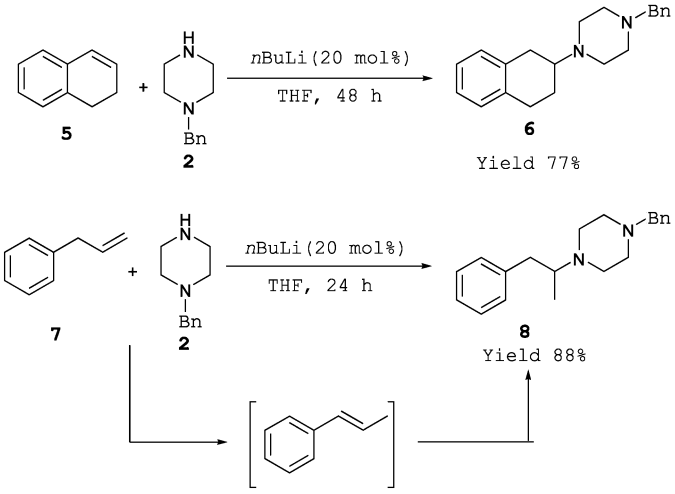
The next step in our reaction sequence was the deprotection of the *N*-benzyl-*N*′-(2-arylethyl)piperazines. Debenzylation was performed with 10 mol% of Pearlman's catalyst ($Pd(OH)_2$, 20 wt% on carbon) under hydrogen atmosphere

Table 2. Base-catalyzed hydroamination reactions of aryl olefins at room temperature.[a]



Entry	R	Olefin/ amine	Conv.[b] [%]	Product (Yield[c] [%])
1	H	2:1	82	**4a** (80)
2	4-Cl	2:1	99	**4b** (60)
3	4-Me	2:1	99	**4c** (96)
4	4-OMe	2:1	100	**4d** (99)
5	4-F	2:1	98	**4e** (87)
6	3-Cl	2:1	94	**4f** (85)
7	3-Me	2:1	80	**4g** (47)
8	3-Br	2:1	90	**4h** (41)
9	3-CF_3	2:1	78	**4i** (69)
10	2-Br	1:1	88	**4j** (59)
11	[d]	2:1	96	**4k** (94)
12	4-Ph	2:1	98	**4l** (98)

[a] Reaction conditions: **2** (2.2 mmol), olefin in THF (5 mL) in a pressure tube. [b] Determined by GC with hexadecane as internal standard (based on **2**). [c] Yield of isolated product. [d] 2-Vinylnaphthalene was used.



Scheme 3. Base-catalyzed hydroamination of 1,2-dihydronaphthalene and base-catalyzed isomerization/hydroamination of allylbenzene at room temperature.

in the presence of 10 mol% Et_3N at 40 °C.[18] On small scales (2–4 mmol), deprotection proceeded with excellent yields (>99%) under 1 bar of hydrogen in 7 h. On larger scales (>9 mmol; Table 3, entry 5), however, reactions had to be run for 15 h under 10 bar of H_2 to obtain complete cleavage of the benzyl group. After filtration of the reaction mixture over celite and evaporation of the solvent the analytically pure free amines were obtained (**9a–f**, Table 3).

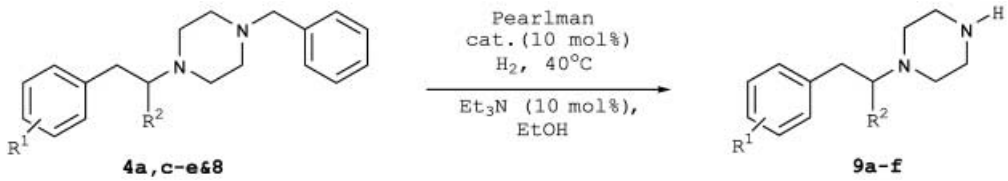
Next, we studied the aminocarbonylation of aromatic halides with *N*-benzylpiperazine as a model system closely resembling **9**. On the basis of our recently reported alkoxycarbonylation of *N*-heteroaryl chlorides[19] we used 1 mol% of $Pd(PhCN)_2Cl_2$ in the presence of 3 mol% 1,1′-bis(diphenylphosphino)ferrocene (dppf) as catalyst system. 2-Bromonaphthalene and various haloheteroarenes were carbonylated in excellent yields at 10–25 bar of CO pressure in toluene at 130 °C (Table 4). When the CO pressure was reduced, some quantities of directly aminated products were observed in the reaction mixture.

Chloropyridines (Table 4, entries 2 and 3) and 1-chloroisoquinoline (Table 4, entry 4) yielded exclusively the aminocarbonylated product. 2,5-Dichloropyridine (Table 4, entry 3) reacted with *N*-benzylpiperazine selectively at the 2-position. Interestingly, 5-bromoindole (Table 4, entry 6) gave the corresponding 5-piperazinylcarbonylindole in >99% yield. *To the best of our knowledge, this is one of the rare examples of a palladium-catalyzed coupling reaction involving unprotected haloindoles.* Clearly, this is an efficient route to this class of molecules, which otherwise need protection and deprotection steps for their synthesis. It is interesting to note that compounds **10a–f**, apart from being models for 5-HT_{2A} receptor antagonists, are also interesting building blocks for other drugs containing piperazinyl moieties.

Finally, we performed the carbonylation of different halopyridines, halo(iso)quinolines, and haloindoles with *N*-(2-arylethyl)piperazines **9**. Because of the biological activity expected of the products, most of the reactions were performed with *N*-[2-(4-fluorophenyl)ethyl]piperazine and *N*-(2-phenethyl)piperazine. Selected experiments are shown in Table 5.

All tested heteroaryl halides and 4-(trifluoromethyl)bromobenzene gave the desired product in practical, often very

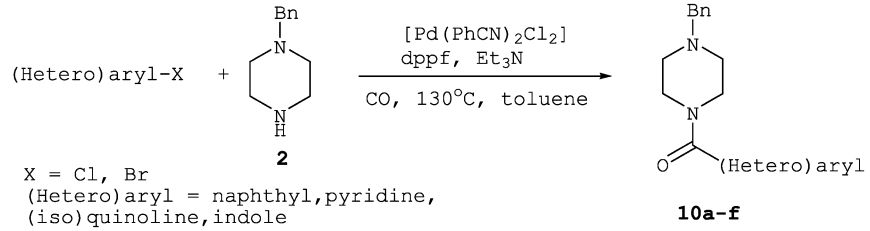
Table 3. Debenzylation of *N*-benzyl-*N*′-(2-arylethyl)piperazines.

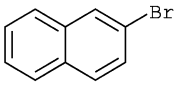
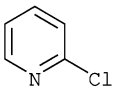
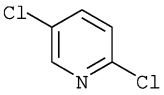
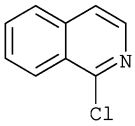
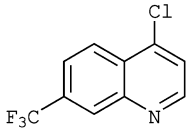
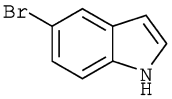


Entry	R^1	R^2	Time [h]	Conv. [%]	Product (yield[a] [%])
1[b]	H	H	7.0	100	**9a** (95)
2[b]	3-Me	H	7.0	100	**9b** (>99)
4[b]	4-Me	H	7.0	100	**9c** (>99)
5[c]	4-OMe	H	15.0	100	**9d** (98)
6[b]	4-F	H	7.0	100	**9e** (95)
7[b]	H	Me	6.5	100	**9f** (86)

[a] Yield of isolated product. [b] 1.0–3.0 mmol scale reactions, 2–4 bar H_2. [c] 9.0 mmol scale reaction, 10 bar H_2.

Table 4. Aminocarbonylation of (hetero)aromatic halides with *N*-benzylpiperazine.[a]



Entry	(Hetero)Aryl-X	Time [h]	pCO [bar]	Conv.[b] [%]	Product (yield[b] [%])
1		20	10	100	**10a** (96)
2		20	25	100	**10b** (99)
3		20	10	100	**10c** (95)
4		20	25	100	**10d** (99)
5		20	25	100	**10e** (85)
6		20	25	100	**10f** (>99)

[a] Reaction conditions: (Hetero)aryl-X (1.2 equiv), *N*-benzylpiperazine (2–3 mmol), Et_3N (1.2 equiv), $[Pd(PhCN)_2Cl_2]$ (1 mol%), dppf (3 mol%), toluene (10 mL), 130°C in an autoclave (25 mL). [b] Determined by GC with hexadecane as internal standard.

good, yields. However, in contrast to the model system we observed competitive amination of the heteroaryl halide in some carbonylation reactions (especially of 1-chloroisoquinoline). As in the model system, 4-bromo- and 5-bromoindole reacted well with amines to yield the carbonylated adducts exclusively, with no amination products observed. In general, *N*-(2-arylalkyl)piperazines with an ethylene bridge reacted with higher yields than the corresponding derivatives with a propylene bridge.

It is important to note that a significant number of the synthesized compounds showed strong binding to the 5-HT_{2A} receptor. In particular, **11g** and **11h** (Table 5; entries 7, 8) proved to be very potent ligands. In binding experiments, **11g** showed a sub-nanomolar and **11h** a single-digit nanomolar affinity, respectively.[20]

Conclusion

A short and practical route to biologically interesting amphetamine analogues has been developed with catalysis as a tool box. In three catalytic steps, different 5-HT_{2A} receptor antagonists have been synthesized in good to excellent yields. The developed strategy is an interesting alternative to previous routes to this class of compounds and can be used to synthesize new active agents, which may otherwise be difficult to access. As the first reaction step, base-catalyzed hydroamination of styrenes with *N*-benzylpiperazine provides the core structure of the desired compounds. Interestingly, hydroamination proceeds smoothly even at room temperature, thus minimizing side reactions of reactive substituents. Subsequent removal of the benzyl group and palladium-catalyzed aminocarbonylation of different haloarenes with the free (arylalkyl)piperazines gives the desired target molecules in good overall yields.

Experimental Section

General: Starting materials were used as received from commercial suppliers. THF was dried over sodium. Toluene (over molecular sieves) was used as received from Fluka. Hydroamination reactions were performed in threaded ACE pressure tubes, and in a parallel ACT-Vantage synthesizer, with 12- and 48-well ARES reactors, respectively. For aminocarbonylation reactions, two types of autoclaves—160 mL (with magnetic stirring) and 25 mL (with electromechanical stirring)—were used.

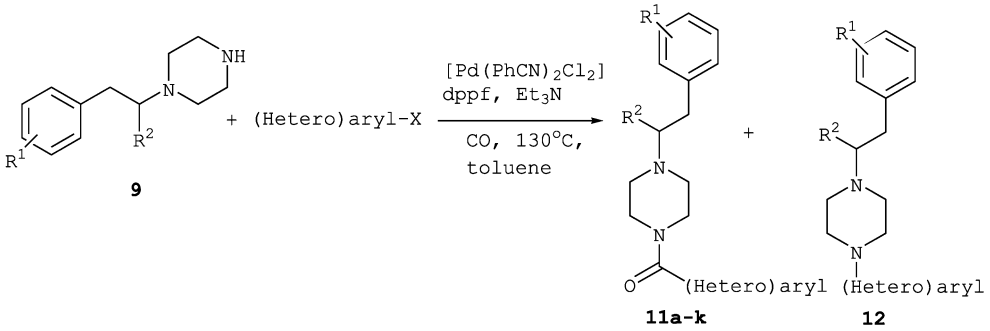
NMR spectra were recorded on a Bruker ARX 400 instrument. Chemical shifts (δ) are given in ppm and were referenced to residual solvent ($CDCl_3$) as internal standard in the case of ^{13}C NMR spectra and to tetramethylsilane as external standard in the case of ^1H NMR spectra. EI mass spectra were recorded on an AMD 402 spectrometer (70 eV, AMD Intectra GmbH) and high-resolution mass spectra were recorded on an AMD 402/3 spectrometer (70 eV, AMD Intectra GmbH). IR spectra were recorded on a Nicolet Magna 550. GC was performed on a Hewlett Packard HP 6890 chromatograph with a 30 m HP5 column.

Melting points are uncorrected, and no attempts were made to crystallize the molecules, which resist crystallization after purification.

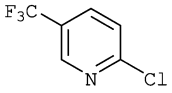
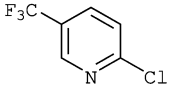
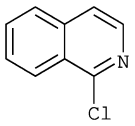
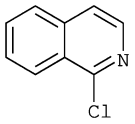
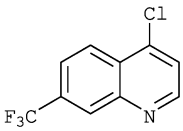
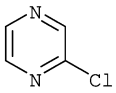
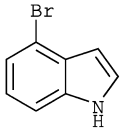
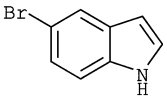
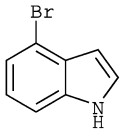
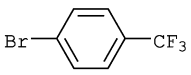
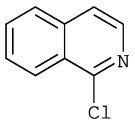
General procedure for NaH-catalyzed hydroamination of styrene with *N*-Boc-piperazine: *N*-Boc-piperazine (413 mg, 2.22 mmol) in THF (4 mL) was added slowly to a suspension of NaH (60% in mineral oil, 22.2 mg, 0.55 mmol) in THF (3 mL), in a dry threaded tube. This was followed by addition of styrene (0.5 mL, 4.44 mmol) and the mixture was stirred at 120°C. After 45 h the reaction mixture was allowed to come to rt. and quenched with methanol (1 mL). The solvent was removed under vacuum. The hydroamination product (**3**) was purified by column chromatography with AcOEt/hexane 4:1 as eluent.

***N*-Boc-*N'*-(2-phenethyl)piperazine (3)**: White amorphous solid; $R_f = 0.50$ (AcOEt/hexane 4:1); ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 7.36–7.28 (m, 2H; 9-H), 7.27–7.20 (m, 3H; 8-H, 10-H), 3.53 (t, ^3J(H,H) = 4.8 Hz, 4H; 2-H), 2.85 (m, 2H; 5-H), 2.52 (m, 2H; 6-H), 2.53 (t, ^3J(H,H) = 4.8 Hz, 4H; 3-H), 1.34 (s, 9H; *t*Bu) ppm; ^{13}C NMR

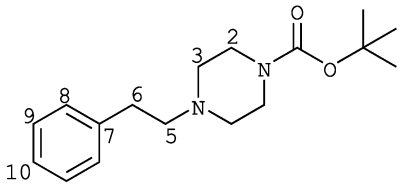
Table 5. Aminocarbonylation of heteroaromatic halides with (arylethyl)piperazines.[a]



9 **11a-k** **12**

Entry	R^1	R^2	(Hetero)aryl-X	Time [h]	pCO [bar]	Conv.[b] [%]	Product (yield[b] [%])
1	H	Me		24	25	92	**11a** (67)
							12a (<5)
2	4-F[c]	H		24	25	100	**11b** (97)
3	H	Me		20	25	100	**11c** (53)
							12c (<10)
4	4-F[c]	H		20	25	100	**11d** (66)
							12d (34)
5	4-F[c]	H		20	25	100	**11e** (68)
							12e (<10)
6	4-F[c]	H		20	25	100	**11f** (99)
7	4-F[c]	H		24	25	98	**11g** (83)
8	4-F[c]	H		24	25	98	**11h** (77)
9	4-OMe	H		24	25	85	**11i** (48)
10	4-OMe	H		20	10	100	**11j** (99)
11	4-Me	H		20	25	93	**11k** (79)
							12k (11)

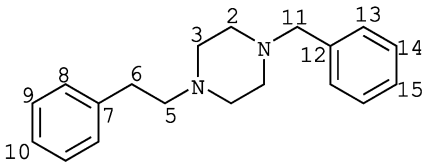
[a] Reaction conditions: *N*-(2-arylethyl)piperazine (1–3 mmol), (hetero)aryl-X (1.2 equiv), $[Pd(PhCN)_2Cl_2]$ (1 mol%), dppf (3 mol%), Et_3N (1.2 equiv), toluene (10 mL), 130 °C, autoclave (25 mL). [b] Determined by GC with hexadecane as internal standard. [c] Used as bis(hydrochloride salt), 3.5 equivalents of Et_3N were used.



(100 MHz, $CDCl_3$, 25 °C): δ = 154.7 (CO), 139.9 (C-7), 128.6, 128.2, 126.1 (C-10), 80.0 ($C(CH_3)_3$), 60.3 (C-5), 52.8 (C-2, C-3), 33.3 (C-6), 28.2 (CCH_3) ppm; IR (KBr): $\tilde{\nu}$ = 3026, 2977, 2927, 1687, 1415, 1172, 699 cm^{-1}; MS (70 eV, CI): *m/z* (%): 291 (57) $[M+1]^+$, 290 (2) $[M]^+$, 277 (13), 235 (53), 217 (7) $[M-OtBu]^+$, 199 (100) $[M-Bn]^+$, 143 (63); HRMS (70 eV, EI) calcd for $C_{17}H_{27}N_2O_2$: 291.20724; found 291.20752.

General procedure for *n*BuLi-catalyzed hydroamination of styrenes with *N*-benzylpiperazine: *n*BuLi (1.6 M in hexane, 10–20 mol%) was added slowly at room temperature to a THF (5 mL) solution of *N*-benzylpiperazine (391 mg, 2.22 mmol), and the mixture was stirred for 10 min. Styrene (1–2 equiv to amine) was then added, and the mixture was stirred at elevated temperature (120 °C, in a threaded tube; reflux conditions in ARES reactors). After 24 h the reaction mixture was allowed to come to rt. and quenched with methanol (1 mL), and the solvent was removed under vacuum. The hydroaminated products were purified by column chromatography with ethyl acetate/hexane 4:1 as eluent. A similar procedure was adopted for the BCH reaction at room temperature.

***N*-Benzyl-*N'*-(2-phenethyl)piperazine (4a)**: Colorless oil; R_f = 0.45 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.28–7.23 (m, 4H; Ar), 7.22–7.15 (m, 4H; Ar), 7.12 (d, ^3J(H,H) = 7.2 Hz, 2H; Ar), 3.45 (s, 2H; 11-H), 2.71 (m, 2H; 5-H), 2.52 (m, 2H;



6-H), 2.55–2.35 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.5, 138.3, 129.4, 128.9, 128.5, 128.4, 127.2, 126.2, 63.2 (C-11), 60.7 (C-5), 53.4 and 53.3 (C-3, C-2), 33.8 (C-6) ppm; IR (neat): $\tilde{\nu}$ = 3026, 2938, 2808, 1602, 1495, 1156, 1133, 1009, 742, 698 cm^{-1}; MS (70 eV, CI): *m/z* (%): 281 (35) $[M+1]^+$, 280 (7) $[M]^+$, 189 (100) $[M-Bn]^+$, 91 (17) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{19}H_{25}N_2$: 281.20178; found 281.20304.

***N*-Benzyl-*N'*-[2-(4-chlorophenyl)ethyl]piperazine (4b)**: Yellowish oil; R_f = 0.48 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.21 (m, 5H; Ar), 7.16 (d, ^3J(H,H) = 8.3 Hz, 2H; Ar), 7.04 (d, ^3J(H,H) = 8.3 Hz, 2H; Ar), 3.44 (s, 2H; 11-H), 2.68 (m, 2H; 5-H), 2.48 (m, 2H; 6-H), 2.36–2.55 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): 139.0, 138.0, 131.9, 130.2, 129.4, 128.6, 128.4, 127.2, 63.2 (C-11), 60.5 (C-5), 53.3 and 53.2 (C-2, C-3), 33.1 (C-6) ppm; IR (neat): $\tilde{\nu}$ = 3027, 2808, 2769, 1492, 1133, 1092, 1011, 739, 698 cm^{-1}; MS (70 eV, EI): *m/z* (%): 314 (0.5) $[M]^+$, 183 (100), 146 (12), 91 (43) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{19}H_{24}ClN_2$: 315.16280; found 315.17688.

***N*-Benzyl-*N'*-[2-(4-methylphenyl)ethyl]piperazine (4c)**: Light yellow, amorphous solid; R_f = 0.50 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz $CDCl_3$, 25 °C, TMS): δ = 7.51–7.44 (m, 4H; Ar), 7.44–7.38 (m, 1H; Ar), 7.30 (br, 4H; Ar), 3.68 (s, 2H; 11-H), 2.92 (m, 2H; 5-H), 2.73 (m, 2H; 6-H), 2.78–2.59 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.2, 137.3, 135.4, 129.2, 129.1, 128.6, 128.2, 127.0, 63.1 (C-11), 60.8 (C-5), 53.2 and 53.1 (C-3, C-2), 33.2 (C-6), 21.0 (CH_3) ppm; IR (neat): $\tilde{\nu}$ = 2939, 2807, 1515, 1453, 1156, 1134, 1010, 808, 739, 698 cm^{-1}; MS (70 eV, CI): *m/z* (%): 295 (48) $[M+1]^+$, 189 (100), 91 (12) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{20}H_{27}N_2$: 295.21744; found 295.21701.

***N*-Benzyl-*N'*-[2-(4-methoxyphenyl)ethyl]piperazine (4d)**: Yellow oil; R_f = 0.48 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.20 (m, 4H; Ar), 7.19–7.12 (m, 1H; Ar), 7.04 (d, ^3J(H,H) = 8.5 Hz, 2H; Ar), 6.74 (d, ^3J(H,H) = 8.7 Hz, 2H; Ar), 3.68 (s, 3H; OMe), 3.44 (s, 2H; 11-H), 2.67 (m, 2H; 5-H), 2.48 (m, 2H; 6-H), 2.92–2.66 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.0 (C-10), 138.2, 135.8, 129.7, 129.3, 128.3, 127.1, 113.9, 63.2 (C-11), 60.9 (C-5), 55.3 (OMe), 53.3, 53.2 (C-2, C-3), 33.8 (C-6) ppm; IR (neat): $\tilde{\nu}$ = 2936, 2808, 1612, 1512, 1247, 1010, 699 cm^{-1}; MS (70 eV, EI): *m/z* (%): 310 (4.5) $[M]^+$, 190 (38), 189 (97) $[M-OMeBn]^+$, 121 (16), 91 (100) $[Bn]^+$, 70 (32 HRMS (70 eV, EI) calcd for $C_{20}H_{27}N_2O$: 311.21234; found 311.21062.

***N*-Benzyl-*N'*-[2-(4-fluorophenyl)ethyl]piperazine (4e)**: White, amorphous solid; R_f = 0.46 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.26–7.20 (m, 4H; Ar), 7.19–7.13 (m, 1H; Ar), 7.04 (dd, ^3J(H,H) = 8.7 Hz, ^4J(H,F) = 5.6 Hz, 2H; 8-H], 6.85 (t, ^3J(H,H) = ^3J(H,F) = 8.7 Hz, 2H; 9-H), 3.43 (s, 2H; 11-H), 2.67 (m, 2H; 5-H), 2.48 (m, 2H; 6-H), 2.57–2.28 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 161.5 (d, ^1J(C,F) = 241.1 Hz; C-10), 138.2 (C-12), 136.1 (d, ^4J(C,F) = 3.8 Hz; C-7), 130.2 (d, ^3J(C,F) = 7.6 Hz; C-8), 129.4 and 128.4 (C-13, C-14), 127.2 (C-15), 115.3 (d, ^2J(C,F) = 20.9 Hz; C-9), 63.2 (C-11), 60.7 (C-5), 53.3 and 53.2 (C-3, C-2), 32.9 (C-6) ppm; IR (KBr): $\tilde{\nu}$ = 2938, 2806, 2768, 1599, 1510, 1220, 1156, 1130, 823, 700, 548, 511 cm^{-1}; MS (70 eV, CI): *m/z* (%): 299 (58) $[M+1]^+$, 297 (17) $[M-1]^+$, 189 (100), 91 (18) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{19}H_{24}FN_2$: 299.19235; found 299.19147.

***N*-Benzyl-*N'*-[2-(3-chlorophenyl)ethyl]piperazine (4f)**: Colorless oil; R_f = 0.55 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz $CDCl_3$, 25 °C, TMS): δ = 7.26–7.20 (m, 4H; Ar), 7.20–7.12 (m, 1H; Ar), 7.12–7.04 (m, 3H; Ar), 6.98 (dd, ^3J(H,H) = 7 Hz, ^4J(H,H) = 1.8 Hz, 1H; Ar), 3.43 (s, 2H; 13-H), 2.65 (m, 2H; 5-H), 2.49 (m, 2H; 6-H), 2.55–2.35 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 142.6 (C-7), 138.2, 134.2, 129.8, 129.4, 129.0, 128.4, 127.2, 127.0, 126.4, 63.2 (C-13), 60.2 (C-5), 53.3 and 53.2 (C-2, C-3), 33.4 (C-6) ppm; IR (neat): $\tilde{\nu}$ = 2961, 2800, 1497, 1134, 1097, 1014, 738, 698 cm^{-1}; MS (70 eV, EI): *m/z* (%): 314 (1) $[M]^+$, 189 (100) $[M-ClBn]^+$, 146 (13), 91 (46) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{19}H_{24}ClN_2$: 315.16280; found 315.16688.

***N*-Benzyl-*N'*-[2-(3-methylphenyl)ethyl]piperazine (4g)**: Yellowish oil; R_f = 0.61 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.28–7.20 (m, 4H; Ar), 7.19–7.14 (m, 1H; Ar), 7.09 (dt, ^3J(H,H) = 8.1, ^4J(H,H) = 1.4 Hz, 1H; Ar), 6.91 (m, 3H; Ar), 3.62 (s, 2H; 13-H), 2.86 (m, 2H; 5-H), 2.69 (m, 2H; 6-H), 2.75–2.52 (br, 8H; 2-H, 3-H), 2.42 (s, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.3 (C-7), 138.2, 138.0, 129.6, 129.3, 128.4, 128.3, 127.1, 126.9, 125.8, 63.2 (C-13), 60.7 (C-5), 53.3 and 53.2 (C-2, C-3), 33.6 (C-6), 21.5 (CH_3) ppm; IR (neat): $\tilde{\nu}$ = 3026, 2938, 2807, 1609, 1156, 1133, 1010, 779, 739, 699 cm^{-1}; MS (70 eV, CI): *m/z* (%): 295 (67) $[M+1]^+$, 189 (100) $[M-MeBn]^+$, 91 (12) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{20}H_{27}N_2$: 295.21744; found 295.21645.

***N*-Benzyl-*N'*-[2-(3-bromophenyl)ethyl]piperazine (4h)**: Yellow oil; R_f = 0.53 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.19 (m, 6H; ArH), 7.19–7.15 (m, 1H; Ar), 7.10–7.03 (m, 2H; Ar), 3.44 (s, 2H; 13-H), 2.68 (m, 2H; 5-H), 2.49 (m, 2H; 6-H), 2.55–2.30 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 142.9 (C-7), 138.2 (C-14), 131.9, 130.1, 129.4, 129.3, 128.4, 127.5, 127.2, 122.5, 63.2 (C-13), 60.2 (C-5), 53.3 and 53.2 (C-2, C-3), 33.4 (C-6) ppm; IR (neat): $\tilde{\nu}$ = 2936, 2808, 2769, 1596, 1568, 1453, 1156, 1134, 1072, 1010, 740, 697 cm^{-1}; MS (70 eV, CI): *m/z* (%): 359 (28) $[M+1]^+$, 189 (100) $[M-BrBn]^+$; HRMS (70 eV, EI) calcd for $C_{19}H_{24}BrN_2$: 359.11227; found 359.10879.

***N*-Benzyl-*N'*-{2-[3-(trifluoromethyl)phenyl]ethyl}piperazine (4i)**: Light yellow oil; R_f = 0.50 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40–7.35 (m, 2H; Ar), 7.34–7.28 (m, 3H; Ar), 7.26–7.23 (m, 3H; Ar), 7.23–7.15 (m, 2H; Ar), 3.44 (s, 2H; 13-H), 2.76 (m, 2H; 5-H), 2.53 (m, 2H; 6-H), 2.65–2.30 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 141.5 (C-7), 138.3 (C-14), 132.3, 130.7 (q, ^2J(C,F) = 31.4 Hz; C-9), 129.4, 128.9, 128.4, 127.2, 125.6 (q, ^3J(C,F) = 3.8 Hz; C-8), 123.1 (q, ^3J(C,F) = 3.8 Hz; C-10), 63.3 (C-5), 60.2 (C-13), 53.4 and 53.3 (C-2, C-3), 33.6 (C-6) ppm; IR (neat): $\tilde{\nu}$ = 2936, 2809, 1332, 1164, 1126, 1073, 701 cm^{-1}; MS (70 eV, CI): *m/z* (%): 349 (61) $[M+1]^+$, 189 (100) $[M-CF_3Bn]^+$, 91 (13) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{20}H_{23}F_3N_2$: 348.18134; found 348.18070.

***N*-Benzyl-*N*′-[2-(2-bromophenyl)ethyl]piperazine (4j)**: Yellow oil; R_f = 0.55 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz $CDCl_3$, 25 °C, TMS): δ = 7.43 (dd, ^3J(H,H) = 8.2, ^4J(H,H) = 1.0 Hz, 1H; Ar), 7.28–7.20 (m, 4H; Ar), 7.20–7.12 (m, 3H; Ar), 6.97 (ddd, ^3J(H,H) = 7.2, ^3J(H,H) = 7.1, ^4J(H,H) = 2.7 Hz, 1H; Ar), 3.45 (s, 2H; 13-H), 2.86 (m, 2H; 5-H), 2.52 (m, 2H; 6-H), 2.52–2.35 (br, 8H; 2-H, 3-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 139.8, 138.3, 132.9, 130.9, 129.3, 128.3, 127.9, 127.6, 127.2, 124.7, 63.2 (C-13), 60.5 (C-5), 53.2, 53.2 (C-2, C-3), 33.7 (C-6) ppm; IR (neat): $\tilde{\nu}$ = 2936, 2808, 2769, 1471, 1454, 1349, 1156, 1137, 1030, 1010, 747, 698 cm^{-1}; MS (70 eV, CI): *m*/*z* (%): 359 (49) $[M+1]^+$, 189 (100) $[M-\mathrm{BrBn}]^+$; HRMS (70 eV, EI) calcd for $C_{19}H_{24}BrN_2$: 359.11227; found 359.11051.

***N*-Benzyl-*N*′-(2-naphthalen-2-yl-ethyl)piperazine (4k)**: White solid, m.p. 60.9 °C, R_f = 0.43 (AcOEt/hexane 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.75–7.64 (m, 3H; Ar), 7.55 (s, 1H; Ar), 7.34 (d quintet, ^3J(H,H) = 7.1, ^4J(H,H) = 1.6 Hz, 2H; Ar), 7.28–7.20 (m, 5H; Ar), 7.19–7.13 (m, 1H; Ar), 3.44 (s, 2H), 2.87 (m, 2H), 2.60 (m, 2H), 2.62–2.25 (br, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.3, 138.0, 133.7, 132.2, 129.4, 128.3, 128.1, 127.8, 127.6, 127.5, 127.7, 126.9, 126.1, 125.4, 63.2, 60.6, 53.4, 53.2, 33.9; IR (KBr): $\tilde{\nu}$ = 2943, 2813, 1599, 1300, 1140, 1007, 835, 818, 744, 734 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 330 (1) $[M]^+$, 189 (100) $[M-\mathrm{naph.CH_2}]^+$, 91 (36) $[\mathrm{Bn}]^+$; HRMS (70 eV, EI) calcd for $C_{23}H_{27}N_2$: 331.21744; found 331.21808.

***N*-Benzyl-*N*′-(2-biphenyl-2-yl-ethyl)piperazine (4l)**: White solid, m.p. 75 °C; R_f = 0.50 (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.47 (d, ^3J(H,H) = 6.7 Hz, 2H; Ar), 7.41 (dd, ^3J(H,H) = 8.0, ^4J(H,H) = 1.5 Hz, 2H; Ar), 7.32 (t, ^3J(H,H) = 7.5 Hz, 2H; Ar), 7.25–7.12 (m, 8H; Ar), 3.44 (s, 2H), 2.75 (m, 2H), 2.55 (m, 2H), 2.58–2.35 (br, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 141.2, 139.7, 139.2, 138.2, 129.4, 129.3, 128.9, 128.4, 127.3, 127.2, 127.2, 127.2, 63.3, 60.7, 53.4, 53.3, 33.5 ppm; IR (KBr): $\tilde{\nu}$ = 3028, 2938, 2874, 2806, 1600, 1487, 1300, 1140, 1008, 906, 825, 761, 740, 695 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 356 (10) $[M]^+$, 190 (44), 189 (100), 167 (18), 165 (17), 91 (92) $[\mathrm{Bn}]^+$, 70 (36); HRMS (70 eV, EI) calcd for $C_{25}H_{28}N_2$: 356.22525; found 356.22470

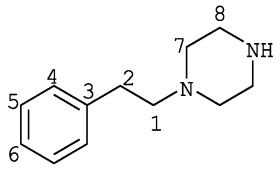
***N*-Benzyl-*N*′-(1,2,3,4-tetrahydronaphthalen-2-yl)piperazine (6)**: Colorless oil; R_f = 0.42 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.27–7.20 (m, 4H; Ar), 7.20–7.15 (m, 1H; Ar), 7.05–6.95 (m, 4H; Ar), 3.45 (s, 2H), 2.95–2.30 (m, 13H), 2.10–2.00 (m, 1H), 1.60–1.48 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.2, 136.5, 136.1, 129.6, 129.5, 128.7, 128.4, 127.2, 125.9, 125.8, 63.3, 60.6, 53.6, 49.2, 32.2, 29.6, 26.3 ppm; IR (neat): $\tilde{\nu}$ = 3025, 2928, 2809, 1494, 1453, 1153, 1138, 1012, 743, 698 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 306 (100) $[M]^+$, 215 (13) $[M-\mathrm{Bn}]^+$, 176 (46), 175 (27), 160 (49), 148 (29), 146 (49), 131 (58), 91 (67) $[\mathrm{Bn}]^+$; HRMS (70 eV, EI) calcd for $C_{21}H_{27}N_2$: 307.21744; found 307.21576.

General procedure for *n*-BuLi-catalyzed isomerization-hydroamination of allyl benzene with *N*-benzylpiperazine: *n*-BuLi (0.5 mmol) was added slowly at rt. to a THF solution (10 mL) of *N*-benzylpiperazine (441 mg, 2.5 mmol) in a dry threaded tube, and the mixture was stirred for 10 min. Allyl benzene (0.66 mL, 5.0 mmol) was then added, and the mixture was stirred at rt. After 24 h the reaction mixture was quenched with methanol (1 mL). The solvent was removed under vacuum. The products were purified by column chromatography with ethyl acetate as eluent.

***N*-Benzyl-*N*′-(1-methyl-2-phenylethyl)piperazine (8)**: Colorless oil; R_f = 0.43 (AcOEt/hexane 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.28–7.23 (m, 4H; Ar), 7.22–7.14 (m, 6H; Ar), 3.44 (s, 2H; 11-H), 2.94 (dd, ^2J(H,H) = 12.9, ^3J(H,H) = 4.0 Hz, 1H; 6-H), 2.72 (qdd, ^3J(H,H) = 10.1, ^3J(H,H) = 6.6, ^3J(H,H) = 4.0 Hz, 1H; 5-H), 2.57 (s, 4H; 3-H), 2.44 (s, 4H; 2-H), 2.31 (dd, ^2J(H,H) = 12.9, ^3J(H,H) = 10.1 Hz, 1H; 6-H), 0.86 (d, ^3J(H,H) = 6.6 Hz, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.9 and 138.3 (C-7, C-12), 129.4, 129.4, 128.4, 128.3, 127.2, 126.0, 63.3 (C-11), 61.5 (C-5), 53.7 (C-2), 48.5 (C-3), 39.5 (C-6), 14.6 (Me) ppm; IR (neat): $\tilde{\nu}$ = 3025, 2932, 2809, 1494, 1453, 1157, 1136, 1012, 739, 699; MS (70 eV, EI): *m*/*z* (%): 294 (0.3) $[M]^+$, 203 (100) $[M-\mathrm{Bn}]^+$, 146 (14), 91 (52) $[\mathrm{Bn}]^+$; HRMS (70 eV, EI) calcd for $C_{20}H_{27}N_2$: 295.21744; found 295.21709.

General procedure for debenzylation of *N*-benzyl-*N*′-(arylethyl)piperazines: 1-Benzyl-4-[2-(4-methoxyphenyl)ethyl]piperazine (**4d**, 2.87 g, 9.27 mmol) and Pearlman's catalyst (649 mg, 0.927 mmol) were placed in a 160 mL autoclave with a magnetic stirrer bar. After the autoclave had been flushed with argon, ethanol (60 mL) and triethylamine (130 μL, 0.93 mmol, 10 mol %) were added. The autoclave was clamped tightly and hydrogen was flushed three times. The reaction mixture was kept at 10 bars of H_2 pressure at 40 °C for 15 h with fast stirring. After cooling to rt. and evacuation of all the hydrogen gas from the autoclave the reaction mixture was filtered through a celite pad and washed with methanol (10 mL). The solvents were evaporated under vacuum to yield the *N*-[2-(4-methoxyphenyl)ethyl]piperazine (**9d**) as a yellow solid. For reactions performed up to 3–4 mmol scale levels, only 7 h of heating was required, with 30 mL of ethanolic solution.

***N*-(2-Phenylethyl)piperazine (9a)**: White solid; m.p. 156 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36–7.29 (m, 2H; 5-H), 7.27–7.20 (m, 3H; 4-H, 6-H), 4.93 (s, 1H; NH), 3.00 (dt, ^2J(H,H) = ^3J(H,H) = 5.0 Hz, 4H; 8-H), 2.83 (m, 2H; 2-H), 2.70–2.59 (m, 6H; 1-H, 7-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.1 (C-3), 128.7 and 128.4 (C-4, C-5), 126.1 (C-6), 60.7 (C-1), 53.1 (C-7), 45.3 (C-8), 33.4 (C-2) ppm; IR



(nujol): $\tilde{\nu}$ = 3421 (NH), 2957, 2850, 1589, 1460, 1377, 1141, 791, 725, 698 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 190 (3) $[M]^+$, 105 (20), 100 (18), 99 (100), 70 (38), 56 (70); HRMS (70 eV, EI) calcd for $C_{12}H_{18}N_2$: 190.1470; found 190.14744.

***N*-[2-(3-Methylphenyl)ethyl]piperazine (9b)**: Off-yellow solid; m.p. 136.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40 (dt, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.1 Hz, 1H; Ar), 7.25 (brs, 2H; Ar), 7.23 (d, ^4J(H,H) = 1.1 Hz, 1H; Ar), 3.15 (t, ^2J(H,H) = ^3J(H,H) = 4.8 Hz, 4H; 10-H), 3.00 (m, 2H; 1-H), 2.80 (m, 2H; 2-H), 2.78–2.62 (br, 4H; 9-H), 2.55 (s, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.3 (C-3), 137.9 (C-5), 129.6, 129.3, 126.8, 125.8, 61.3 (C-1), 54.6 (C-9), 46.2 (C-10), 33.4 (C-2), 21.4 (Me) ppm; IR (neat): $\tilde{\nu}$ = 3404 (NH), 2931, 2812, 1609, 1171, 1119, 1095, 999, 781, 700 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 204 (2) $[M]^+$, 99 (100), 70 (15), 56 (23); HRMS (70 eV, EI) calcd for $C_{13}H_{21}N_2$: 205.17047; found 205.16889.

***N*-[2-(4-Methylphenyl)ethyl)]piperazine (9c)**: Off-yellow solid; m.p. 128.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.10–7.03 (m, 4H; Ar), 6.10 (brs, 1H; NH), 3.08 (t, ^2J(H,H) = ^3J(H,H) = 5.1 Hz, 4H; 8-H), 2.72 (m, 2H; 1-H), 2.66 (t, ^2J(H,H) = ^3J(H,H) = 4.7 Hz, 4H; 7-H), 2.59 (m, 2H; 2-H), 2.29 (s, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 136.9, 135.8 (C-3, C-6), 129.3 and 128.7 (C-4, C-5), 60.6 (C-1), 51.8 (C-7), 44.7 (C-8), 33.1 (C-2), 21.2 (Me) ppm; IR (nujol): $\tilde{\nu}$ = 3415 (NH), 2925, 2853, 1514, 1459, 1377, 816 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 204 (1) $[M]^+$, 99 (100), 70 (14), 56 (26); HRMS (70 eV, EI) calcd for $C_{13}H_{21}N_2$: 205.17047; found 205.16920.

***N*-[2-(4-Methoxyphenyl)ethyl)]piperazine (9d)**: Off-yellow solid; m.p. 160 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.04 (d, ^3J(H,H) = 8.7 Hz, 2H; 5-H), 6.76 (d, ^3J(H,H) = 8.7 Hz, 2H; 4-H), 4.51 (brs, 1H; NH), 3.70 (s, 3H; OMe), 2.92 (t, ^2J(H,H) = ^3J(H,H) = 5 Hz, 4H; 8-H), 2.67 (m, 2H; 1-H), 2.54–2.46 (m, 6H; 2-H, 7-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.9 (C-6), 132.1 (C-3), 129.6 (C-4), 113.8 (C-5), 61.0 (C-1), 55.2 (OMe), 53.4 (C-7), 45.4 (C-8), 32.4 (C-2) ppm; IR (nujol): $\tilde{\nu}$ = 3462 (NH), 2953, 2844, 1610, 1512, 1455, 1246, 1177, 1028, 836, 820 cm^{-1}; MS (70 eV, CI): *m*/*z* (%): 221 (1) $[M+1]^+$, 99 (100) $[M-\mathrm{MeOBn}]^+$; HRMS (70 eV, EI) calcd for $C_{13}H_{21}N_2O$: 221.16539; found 221.16442.

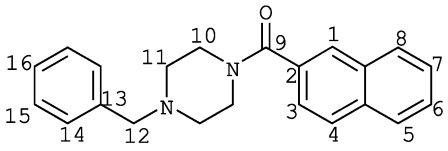
***N*-[2-(4-Fluorophenyl)ethyl]piperazine (9e)**: Colorless oil; ^{1}H NMR (400 MHz $CDCl_3$, 25 °C, TMS): δ = 7.06 (dd, ^3J(H,H) = 8.7 Hz, ^4J(H,F) = 5.5 Hz, 2H; 4-H), 6.87 (t, ^3J(H,H) = ^3J(H,F) = 8.7 Hz, 2H; 5-H), 2.83 (t, ^2J(H,H) = ^3J(H,H) = 5 Hz, 4H; 8-H), 2.68 (m, 2H; 1-H), 2.45 (m, 2H; 2-H), 2.40–2.30 (br, 4H; 7-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 161.4 (d, ^1J(C,F) = 242.7 Hz; C-6), 136.0 (d, ^4J(C,F) = 2.8 Hz; C-3), 130.0 (d, ^3J(C,F) = 7.6 Hz; C-4), 115.1 (d, ^2J(C,F) =

20.9 Hz; C-6), 61.6 (C-1), 54.5 (C-7), 46.1 (C-8), 32.6 (C-2) ppm; IR (neat): $\tilde{\nu}$= 3270 (NH), 2942, 2811, 1510, 1447, 1221, 826, 753 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 208 (3) $[M]^+$, 123 (21), 109 (21), 103 (15), 100 (21), 99 (71), 70 (57), 56 (100); HRMS (70 eV, EI) calcd for $C_{12}H_{17}FN_2$: 208.13757; found 208.13420.

***N*-(1-Methyl-2-phenylethyl)piperazine (9f)**: White solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.35–7.29 (m, 2H; 5-H), 7.26–7.19 (m, 3H; 4-H, 6-H), 3.06 (dd, ^2J(H,H) = 13.0, ^3J(H,H) = 4.2 Hz, 1H; 2-H), 3.10–2.92 (m, 4H; 8-H), 2.83 (qdd, ^3J(H,H) = 9.8, ^3J(H,H) = 6.4, ^3J(H,H) = 4.2 Hz, 1H; 1-H), 2.70–2.60 (m, 4H; 7-H), 2.44 (dd, ^2J(H,H) = 13, ^3J(H,H) = 9.8 Hz, 1H; 2-H), 1.00 (d, ^3J(H,H) = 6.4 Hz, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 140.8 (C-3), 129.4 and 128.3 (C-4, C-5), 125.9 (C-6), 62.0 (C-1), 49.7 (C-7), 46.5 (C-8), 39.3 (C-2), 14.4 (Me) ppm; IR (neat): $\tilde{\nu}$= 3470 (NH), 2969, 2935, 2811, 1602, 1493, 1453, 743, 701, 649 cm^{-1}; MS (70 eV, CI): *m*/*z* (%): 205 (33) $[M+1]^+$, 141 (7), 113 (100) $[M-Bn]^+$; HRMS (70 eV, EI) calcd for $C_{13}H_{20}N_2$: 204.16264; found 204.16078.

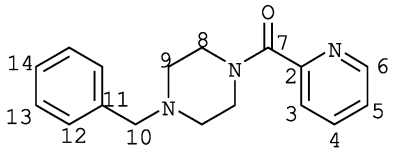
General procedure for Pd-catalyzed aminocarbonylation of aromatic/heteroaromatic halides with *N*-benzylpiperazine: An oven-dried Schlenk flask was evacuated and filled with argon (3 cycles), and then charged with $[Pd(PhCN)_2Cl_2]$ (7.6 mg, 0.02 mmol, 1.0 mol%), DPPF (33 mg, 0.06 mmol, 3.0 mol%), *N*-benzylpiperazine (353 mg, 2.0 mmol), *N*-heteroaryl halide (2.2 mmol), and toluene (10 mL) to give an orange solution. Et_3N (2.4 mmol) was added to the autoclave. After evacuation and filling of the autoclave with argon (3 cycles), the reaction mixture was transferred from the Schlenk flask into the autoclave through a PVC tube. The autoclave was closed, pressurized with CO, and heated to 130 °C under non-isobaric conditions. After 20 h the reaction mixture was cooled, the solvent was evaporated from the resultant blackish reaction mixture under vacuum and the products were purified by column chromatography with ethyl acetate/methanol in 9:1 ratio as eluent.

***N*-Benzyl-*N*′-(2-naphthylcarbonyl)piperazine (10a)**: White solid; R_f = 0.43 (AcOEt); m.p. 61 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.84 (s, 1H; Ar), 7.80–7.74 (m, 3H; Ar), 7.47–7.40 (m, 3H; Ar), 7.26–7.25



(m, 4H; Ar), 7.25—7.15 (m, 1H; Ar), 3.78 (brs, 2H; pip.), 3.46 (s, 2H; 12-H), 3.40 (brs, 2H; pip.), 2.48 (brs, 2H; pip.), 2.31 (brs, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.2 (C-9), 137.6, 133.6, 133.2, 132.7, 129.1, 128.4, 128.3 (C-15), 128.3, 127.8, 127.3, 127.2, 126.9, 126.7, 124.3, 62.9 (C-12), 53.3, 52.8, 47.8, 42.3 ppm; IR (KBr): $\tilde{\nu}$= 2923, 2446, 1633, 1624, 1422, 1288, 950 cm^{-1}; MS (70 eV, CI): *m*/*z* (%): 331 (100) $[M+1]^+$, 330 (27) $[M]^+$, 146 (15), 134 (16), 91 (20) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{22}H_{22}N_2O$: 330.17322; found 330.17276.

***N*-Benzyl-*N*′-(2-pyridylcarbonyl)piperazine (10b)**: Brown solid; R_f = 0.64 (AcOEt/MeOH 9:1); m.p. 97 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.45 (br, 1H; 6-H), 7.64 (dt, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.5 Hz, 1H; 4-H), 7.51 (dd, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1 Hz, 1H; 3-



H), 7.24–7.10 (m, 6H; 5-, 12-, 13-, 14-H), 3.71 (br, 2H; pip.), 3.47 (br, 2H; pip.), 3.42 (s, 2H; 10-H), 2.45 (br, 2H; pip.), 2.33 (br, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.3 (C-7), 154.0 (C-2), 148.2 (C-6), 137.3, 136.9, 129.0, 128.2, 127.1, 124.3, 123.6, 62.6 (C-10), 53.1, 52.5, 47.0, 42.1 ppm; IR (KBr): $\tilde{\nu}$= 2918, 2810, 1634, 1444, 1424, 1300, 1172, 1025, 999, 807, 745, 701 cm^{-1}; MS (70 eV, CI): *m*/*z* (%): 282 (100) $[M+1]^+$, 281 (11) $[M]^+$, 146 (11), 132 (11), 91 (13) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{17}H_{20}N_3O$: 282.16064; found 282.16063.

***N*-Benzyl-*N*′-(5-chloropyrid-2-ylcarbonyl)piperazine (10c)**: Brown solid; R_f = 0.43 (AcOEt); m.p. 77 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.40 (d, ^4J(H,H) = 2 Hz, 1H; 6-H), 7.63 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 2 Hz, 1H; 4-H), 7.51 (d, ^3J(H,H) = 8.3 Hz, 1H; 3-H), 7.29–7.12 (m, 5H; 12-, 13-, 14-H), 3.70 (brt, ^2J(H,H) = ^3J(H,H) = 4.8 Hz, 2H; pip.), 3.49(brt, ^2J(H,H) = ^3J(H,H) = 4.8 Hz, 2H; pip.), 3.42(s, 2H; 10-H), 2.44 (brt, ^2J(H,H) = ^3J(H,H) = 4.8 Hz, 2H, pip.), 2.33 (brt, ^2J(H,H) = ^3J(H,H) = 4.5 Hz, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.2 (C-7), 152.0 (C-2), 147.0 (C-6), 137.5 (C-11), 136.7, 132.8, 129.0 and 128.2 (C-12, C-13), 127.2, 125.0, 62.8 (C-10), 53.2, 52.6, 47.2, 42.4 ppm; IR (KBr): $\tilde{\nu}$= 2916, 2809, 1634, 1439, 1299, 1169, 1109, 1000, 743, 700 cm^{-1}; MS (70 eV, CI): *m*/*z* (%): 316 (100) $[M+1]^+$, 315 (10) $[M]^+$, 146 (17), 91 (15) $[Bn]^+$; HRMS (70 eV, EI) calcd for $C_{17}H_{18}ClN_3O$: 315.1183; found 315.11373.

***N*-Benzyl-*N*′-(1-isoquinolylcarbonyl)piperazine (10d)**: White solid; R_f = 0.66 (AcOEt/MeOH 9:1); m.p. 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.39 (d, ^3J(H,H) = 5.7 Hz, 1H; Ar), 7.93 (d, ^3J(H,H) = 8.3 Hz, 1H; Ar), 7.74 (d, ^3J(H,H) = 8.1 Hz, 1H; Ar), 7.64–7.48 (m, 3H; Ar), 7.21–7.12 (m, 5H; Ar), 3.87 (t, ^3J(H,H) = ^2J(H,H) = 4.7 Hz, 2H; pip.), 3.43 (s, 2H; 12-H), 3.13 (t, ^3J(H,H) = ^2J(H,H) = 4.8 Hz, 2H; pip.), 2.53 (t, ^3J(H,H) = ^2J(H,H) = 5.0 Hz, 2H; pip.), 2.25 (t, ^2J(H,H) = ^3J(H,H) = 5.0 Hz, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.8 (C-9), 155.4 (C-1), 141.8 (C-3), 137.5, 136.4, 130.9, 129.2 (C-14), 128.4 (C-15), 128.2, 127.3, 127.1, 125.9, 125.5 (C-8a), 121.4, 62.8 (C-12), 53.8, 52.3, 46.8, 41.8 ppm; IR (KBr): $\tilde{\nu}$= 2921, 2807, 1640, 1440, 1280, 999, 828, 744, 699 cm^{-1}; MS (70 eV, CI): *m*/*z* (%): 332 (100) $[M+1]^+$, 331 (23) $[M]^+$, 205 (19), 146 (20), 107 (37); HRMS (70 eV, EI) calcd for $C_{21}H_{21}N_3O$: 331.16846; found 331.17073.

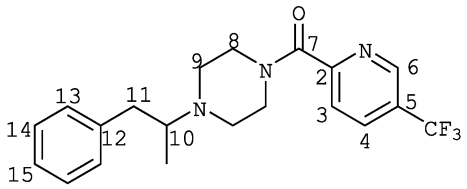
***N*-Benzyl-*N*′-[7-(trifluoromethyl)quinol-4-ylcarbonyl]piperazine (10e)**: Yellow oil; R_f = 0.66 (AcOEt/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.96 (d, ^{3}J(H,H) = 4.4 Hz, 1H; 2-H), 8.37 (s, 1H; 8-H), 7.89 (d, ^3J(H,H) = 8.5 Hz, 1H; 5-H), 7.69 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 1.6 Hz, 1H; 6-H), 7.34 (d, ^3J(H,H) = 4.4 Hz, 1H; 3-H), 7.32–7.14 (m, 5H; Ar), 3.93 (br, 1H; pip.), 3.80 (br, 1H; pip.), 3.46 (s, 2H; 12-H), 3.20–3.08 (m, 2H; pip.), 2.76–2.48 (m, 2H; pip.), 2.26 (br, 1H; pip.), 2.19 (br, 1H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.1 (C-9), 151.6 (C-2), 147.6, 142.5, 137.5, 135.9, 132.1 (q, ^2J(C,F) = 33.2 Hz; C-7), 129.2, 128.5 (C-14, C-15), 128.1 (q, ^3J(C,F) = 3.8 Hz; C-8), 127.6, 126.4, 123.5 (q, ^3J(C,F) = 3.8 Hz; C-6), 119.8 (C-3), 60.2 (C-12), 53.7, 53.0, 47.3, 42.1, 32.8 (C-13) ppm; IR (KBr): $\tilde{\nu}$= 2934, 2811, 1642, 1588, 1459, 1329, 1296, 1195, 1128, 1063, 836, 740, 700 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 400 (100) $[M+1]^+$, 373 (23), 372 (90), 371 (27); HRMS (70 eV, EI) calcd for $C_{22}H_{20}F_3N_3O$: 399.15585; found 399.15428.

***N*-Benzyl-*N*′-(5-indolylcarbonyl)piperazine (10f)**: Brownish solid; R_f = 0.63 (AcOEt/MeOH 9:1); m.p. 87.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.28 (s, 1H; NH), 7.60 (br, 1H; Ar), 7.25–7.14 (m, 5H; Ar), 7.12 (d, ^3J(H,H) = 8.3 Hz, 1H; Ar), 7.08 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 1.4 Hz; Ar), 7.03 (t, ^3J(H,H) = 2.8 Hz, ^3J(H,H) = 2.6 Hz, 1H; 2-H), 6.40 (t, ^3J(H,H) = ^4J(H,H) = 2.2 Hz, 1H; 3-H), 3.75–3.44 (br, 4H; pip.), 3.44 (s, 2H; 11-H), 2.55–2.27 (br, 4H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.3 (C-8), 137.7, 136.7, 129.3 (C-13), 128.5 (C-14), 127.4 (quat. and C-15), 126.8, 125.9, 121.2, 120.2, 111.4 (C-7), 102.7 (C-3), 63.0 (C-11), 53.3 (br, C-9, C-10) ppm; IR (KBr): $\tilde{\nu}$= 3414 (NH), 2918, 2808, 1603, 1519, 1454, 1435, 1299, 999, 896, 748, 699 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 319 (33) $[M]^+$, 159 (23), 146 (43), 144 (59), 134 (23), 132 (23), 116 (37), 91 (100); HRMS (70 eV, EI) calcd for $C_{20}H_{22}N_3O$: 320.17630; found 320.17460.

General procedure for Pd-catalyzed aminocarbonylation of aromatic/heteroaromatic halides with (arylethyl)piperazines: An oven-dried Schlenk flask was evacuated and filled with argon (3 cycles), and was then charged with $[Pd(PhCN)_2Cl_2]$ (7.6 mg, 0.02 mmol, 1.0 mol%), DPPF (33 mg, 0.06 mmol, 3.0 mol%), (arylethyl)piperazine (2.0 mmol), *N*-heteroaryl halide (2.4 mmol), and toluene (10–15 mL) to give an orange-red solution/suspension. Et_3N (7 mmol) was then added to the autoclave. After evacuation and filling of the autoclave with argon (3 cycles), the reaction

mixture was transferred from the Schlenk flask into the autoclave through a PVC tube. The autoclave was closed, pressurized with CO, and heated to 130 °C under non-isobaric conditions. After 20 h the reaction mixture was cooled and the solvent was evaporated from the resultant blackish reaction mixture under vacuum. The products were purified by column chromatography with ethyl acetate/methanol in 9:1 ratio as eluent.

***N*-[5-(Trifluoromethyl)pyrid-2-ylcarbonyl]-*N*′-(1-methyl-2-phenylethyl)piperazine (11a)**: Brownish solid; R_f = 0.59 (AcOEt/MeOH 9:1); m.p. 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.79 (d, ^4J(H,F) =



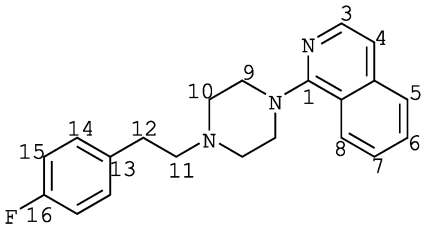
0.6 Hz, 1H; Ar), 7.97 (dd, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 2.2 Hz, 1H; Ar), 7.70 (d, ^3J(H,H) = 8.1 Hz, 1H; Ar), 7.24–7.18 (m, 2H; Ar), 7.17–7.06 (m, 3H; Ar), 3.76 (t, ^2J(H,H) = ^3J(H,H) = 4.9 Hz, 2H; pip.), 3.49 (t, ^2J(H,H) = ^3J(H,H) = 4.9 Hz, 2H; pip.), 2.90 (dd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 4.6 Hz, 1H; 11-H), 2.84–2.79 (m, 1H; 10-H), 2.70–2.62 (m, 2H; pip.), 2.60–2.52 (m, 2H; pip.), 2.36 (dd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 9.1 Hz, 1H; 11-H), 0.89 (d, ^3J(H,H) = 6.5 Hz, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.2 (C-7), 157.6 (C-2), 145.5 (q, ^3J(C,F) = 3.8 Hz; C-6), 140.3 (C-12), 134.5 (q, ^3J(C,F) = 3.8 Hz; C-4), 129.4 (C-14), 128.5 (C-13), 127.4 (q, ^2J(C,F) = 30.3 Hz; C-5), 126.2 and 124.0 (C-3, C-15), 61.7 (C-10), 49.1, 48.2, 47.8, 43.0, 39.6 (C-11), 14.5 (*C*H$_3$) ppm; IR (KBr): $\tilde{\nu}$ = 2972, 2956, 1644, 1605, 1495, 1443, 1329, 1165, 1128, 1076, 1017, 738, 701 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 377 (0.1) $[M]^+$, 287 (15), 286 (100) $[M-\mathrm{Bn}]^+$, 243 (10), 146 (18); HRMS (70 eV, EI) calcd for $C_{20}H_{23}F_3N_3O$: 378.17932; found 378.17652.

***N*-[5-(Trifluoromethyl)pyrid-2-ylcarbonyl]-*N*′-[2-(4-fluorophenyl)ethyl]piperazine (11b)**: Off-white solid; R_f = 0.57 (AcOEt/MeOH 9:1); m.p. 78 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.75 (s, 1H; 6-H), 7.94 (d, ^3J(H,H) = 7.9 Hz, 1H; 4-H), 7.69 (d, ^3J(H,H) = 7.9 Hz; 3-H), 7.05 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,F) = 5.7 Hz, 2H; 13-H), 6.85 (t, ^3J(H,H) = ^3J(H,F) = 8.5 Hz, 2H; 14-H), 3.75 (br, 2H; pip.), 3.49 (br, 2H; pip.), 2.71–2.65 (m, 2H; 10-H), 2.55–2.49 (m, 4H; pip., 11-H), 2.42 (br, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.0 (C-7), 161.4 (d, ^1J(C,F) = 242.6 Hz; C-15), 157.3 (C-2), 145.3 (q, ^3J(C,F) = 3.8 Hz; C-6), 135.6 (d, ^4J(C,F) = 2.8 Hz; C-12), 134.4 (q, ^3J(C,F) = 3.8 Hz; C-4), 130.0 (d, ^3J(C,F) = 6.6 Hz; C-13), 127.1 (q, ^2J(C,F) = 33.2 Hz; C-5), 123.8 (C-3), 115.1 (d, ^2J(C,F) = 20.8 Hz; C-14), 60.1 (C-10), 53.4, 52.6, 47.1, 42.4, 32.6 (C-11) ppm; IR (KBr): $\tilde{\nu}$ = 2946, 2825, 1634, 1605, 1506, 1465, 1435, 1329, 1300, 1278, 1151, 1128, 1075, 1000, 834 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 382 (100) $[M+1]^+$, 273 (10), 272 (66); HRMS (70 eV, EI) calcd for $C_{19}H_{20}F_4N_3O$: 382.15424; found 382.15206.

***N*-[1-Isoquinolylcarbonyl]-*N*′-(1-methyl-2-phenylethyl)piperazine (11c)**: Brown solid; R_f = 0.50 (AcOEt/MeOH 9:1); m.p. 123 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.43 (d, ^3J(H,H) = 5.76 Hz, 1H; 3-H), 7.96 (dd, ^3J(H,H) = 8.5 Hz, ^5J(H,H) = 0.8 Hz, 1H; 8-H), 7.77 (d, ^3J(H,H) = 8.3 Hz, 1H; 5-H), 7.63 (ddd, ^3J(H,H) = 8.5 Hz, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.2 Hz, 1H; 7-H), 7.60 (dd, ^3J(H,H) = 5.8 Hz, ^5J(H,H) = 0.8 Hz, 1H; 4-H), 7.54 (ddd, ^3J(H,H) = 8.3 Hz, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.2 Hz, 6-H), 7.18 (dt, ^3J(H,H) = 6.5 Hz, ^4J(H,H) = 1.4 Hz, 2H; 16-H), 7.13–7.03 (m, 3H; 15-H, 17-H), 3.88 (t, ^2J(H,H) = ^3J(H,H) = 5.1 Hz, 2H; pip.), 3.15 (t, ^3J(H,H) = ^3J(H,H) = 5.1 Hz, 2H; pip.), 2.87 (dd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 4.8 Hz, 1H; 13-H), 2.82–2.76 (m, 1H; 12-H), 2.74–2.65 (m, 2H; pip.), 2.47–2.37 (m, 2H; pip.), 2.33 (dd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 9.1 Hz, 1H; 13-H), 0.87 (d, ^3J(H,H) = 6.6 Hz, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.8 (C-9), 155.5 (C-1), 141.9 (C-3), 140.3, 136.6, 131.0 (C-4), 129.3 and 128.4 (C-15, C-16), 128.2, 127.2, 126.1, 126.0, 125.6 (C-8a), 121.4 (C-17), 61.6 (C-12), 49.1, 48.4, 47.4, 42.3, 39.6 (C-13), 14.5 (*C*H$_3$) ppm; IR (KBr): $\tilde{\nu}$ = 2930, 2813, 1641, 1587, 1472, 1443, 1281, 1251, 999, 829, 737, 702 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 359 (2) $[M]^+$, 269 (25), 268 (100), 199 (25), 128 (62), 91 (18) $[\mathrm{Bn}]^+$; HRMS (70 eV, EI) calcd for $C_{23}H_{25}N_3O$: 359.19977; found 359.19580.

***N*-[1-Isoquinolylcarbonyl]-*N*′-[2-(4-luorophenyl)ethyl]piperazine (11d)**: White solid; R_f = 0.41 (AcOEt/MeOH 9:1); m.p. 85 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.42 (d, ^3J(H,H) = 5.7 Hz, 1H; 3-H), 7.95 (d, ^3J(H,H) = 8.3 Hz, 1H; 8-H), 7.76 (d, ^3J(H,H) = 8.1 Hz, 1H; 5-H), 7.65–7.50 (m, 3H; 4-H, 6-H, 7-H), 7.04 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,F) = 5.8 Hz, 2H; 15-H), 6.85 (t, ^3J(H,H) = ^3J(H,F) = 8.7 Hz, 2H; 16-H), 3.89 (t, ^2J(H,H) = ^3J(H,H) = 4.8 Hz, 2H; pip.), 3.17 (t, ^2J(H,H) = ^3J(H,H) = 5.0 Hz, 2H; pip.), 2.69–2.63 (m, 2H; 12-H), 2.60 (t, ^2J(H,H) = ^3J(H,H) = 5.0 Hz, 2H; pip.), 2.53–2.46 (m, 2H; 13-H), 2.32 (t, ^2J(H,H) = ^3J(H,H) = 4.9 Hz, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.7 (C-9), 161.4 (d, ^1J(C,F) = 242.6 Hz; C-17), 155.3 (C-1), 141.8 (C-3), 136.5 (C-4a), 135.7 (d, ^4J(C,F) = 2.8 Hz; C-14), 130.9, 130.1 (d, ^3J(C,F) = 7.6 Hz; C-15), 128.2, 127.1, 125.9, 125.6 (C-8a), 121.4, 115.2 (d, ^2J(C,F) = 20.8 Hz; C-16), 60.2 (C-12), 53.6, 52.9, 46.8, 41.8, 32.7 (C-13) ppm; IR (KBr): $\tilde{\nu}$ = 2990, 2966, 2809, 2769, 1639, 1507, 1465, 1439, 1250, 1218, 1134, 997, 829 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 364 (100) $[M+1]^+$, 336 (23) $[M+1-\mathrm{CO}]^+$, 254 (30), 191 (10); HRMS (70 eV, EI) calcd for $C_{22}H_{22}FN_3O$: 363.17468; found 363.17201.

1-{4-[2-(4-Fluorophenyl)ethyl]piperazin-1-yl}isoquinoline (12d): White solid; R_f = 0.59 (AcOEt/MeOH 9:1); m.p. 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.05 (d, ^3J(H,H) = 5.7 Hz, 1H; 3-H), 7.99 (d, ^3J(H,H) = 8.3 Hz, 1H; 8-H), 7.64 (d, ^3J(H,H) = 8.1 Hz, 1H; 5-H), 7.49



(ddd, ^3J(H,H) = 8.1 Hz, ^3J(H,H) = 6.9 Hz, ^4J(H,H) = 1.2 Hz, 1H; 6-H), 7.40 (ddd, ^3J(H,H) = 8.3 Hz, ^3J(H,H) = 6.9 Hz, ^4J(H,H) = 1.2 Hz, 1H; 7-H), 7.14 (d, ^3J(H,H) = 5.7 Hz, 1H; 4-H), 7.10 (dd, ^3J(H,H) = 8.7 Hz, ^4J(H,F) = 5.3 Hz, 2H; 14-H), 6.88 (t, ^3J(H,H) = ^3J(H,F) = 8.7 Hz, 2H; 15-H), 3.39 (br, 4H; pip.), 2.75 (m, 2H; 11-H), 2.71 (br, 4H; pip.), 2.61 (m, 2H; 12-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 161.5 (d, ^1J(C,F) = 241.7 Hz; C-16), 161.4 (C-1), 140.8 (C-3), 138.2 (C-4a), 136.0 (d, ^4J(C,F) = 3.8 Hz; C-13), 130.2 (d, ^3J(C,F) = 7.6 Hz; C-14), 129.8, 127.3, 125.7, 121.8 (C-8a), 116.0, 115.4 (d, ^2J(C,F) = 21.8 Hz; C-15), 60.7 (C-11), 53.6 (C-9), 51.3 (C-10), 32.9 (C-12) ppm; IR (KBr): $\tilde{\nu}$ = 2947, 2931, 2819, 1557, 1509, 1403, 1215, 818, 684 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 335 (8) $[M]^+$, 226 (14) $[M-\mathrm{FBn}]^+$, 191 (46), 171 (38), 169 (17), 157 (100), 145 (23), 128 (23), 82 (30), 70 (19), 69 (19); HRMS (70 eV, EI) calcd for $C_{21}H_{22}N_3F$: 335.17978; found 335.17883.

***N*-[7-(Trifluoromethyl)quinol-4-ylcarbonyl]-*N*′-[2-(4-fluoro- phenyl)-ethyl]piperazine (11e)**: Yellow, amorphous solid; R_f = 0.46 (AcOEt/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.98 (d, ^3J(H,H) = 4.2 Hz, 1H; 2-H), 8.39 (brs, 1H; 8-H), 7.90 (d, ^3J(H,H) = 8.7 Hz, 1H; 5-H), 7.70 (dd, ^3J(H,H) = 8.7 Hz, ^4J(H,H) = 1.7 Hz, 1H; 6-H), 7.36 (d, ^3J(H,H) = 4.2 Hz, 1H; 3-H), 7.06 (dd, ^3J(H,H) = 8.7 Hz, ^4J(H,F) = 5.6 Hz, 2H; 15-H), 6.88 (t, ^3J(H,H) = ^3J(H,F) = 8.7 Hz, 2H; 16-H), 3.96 (br, 1H; pip.), 3.82 (br, 1H; pip.), 3.20–3.08 (m, 2H, pip.), 2.80–2.50 (m, 6H, 13-H, 12-H, pip.), 2.34 (br, 1H, pip.), 2.24 (br, 1H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.1 (C-9), 161.6 (d, ^1J(C,F) = 242.6 Hz; C-17), 151.6 (C-2), 147.7 (C-8a), 142.5 (C-4), 135.9 (C-4a), 135.6 (d, ^4J(C,F) = 2.8 Hz; C-14), 132.1 (q, ^2J(C,F) = 33.2 Hz; C-7), 130.2 (d, ^3J(C,F) = 7.6 Hz; C-15), 128.1 (d, ^3J(C,F) = 3.8 Hz; C-8 or C-6), 126.4 (C-5), 123.5 (d, ^3J(C,F) = 3.8 Hz; C-6 or C-8), 119.8 (C-3), 115.4 (d, ^2J(C,F) = 20.8 Hz; C-16), 60.2 (C-12), 53.7, 53.0, 47.3, 42.1, 32.8 (C-13) ppm; IR (KBr): $\tilde{\nu}$ = 2935, 2814, 1640, 1589, 1510, 1460, 1444, 1329, 1157, 1130, 836, 739 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 432 (100)

$[M+1]^+$, 404 (53) $[M+1-CO]^+$, 322 (50), 294 (33), 232 (57); HRMS (70 eV, EI) calcd for $C_{23}H_{22}F_4N_3O$: 432.16989; found 432.16513.

***N*-(2-Pyrazylcarbonyl)-*N'*-[2-(4-fluorophenyl)ethyl]piperazine (11f)**: White crystals; R_f = 0.38 (AcOEt/MeOH 9:1); m.p. 96°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 8.84 (s, 1H; 3-H), 8.52 (s, 1H; Ar), 8.44 (s, 1H; Ar), 7.04 (dd, ^3J(H,H) = 8.7 Hz, ^4J(H,F) = 5.5 Hz, 2H; 13-H), 6.85 (t, ^3J(H,H) = ^3J(H,F) = 8.7 Hz, 2H; 14-H), 3.75 (t, ^2J(H,H) = ^2J(H,H) = 4.9 Hz, 2H; pip.), 3.54 (t, ^2J(H,H) = ^3J(H,H) = 5 Hz, 2H; pip.), 2.68 (m, 2H; 10-H), 2.53–2.48 (m, 4H; 11-H, pip.), 2.43 (t, ^2J(H,H) = ^3J(H,H) = 5.0 Hz, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 164.9 (C-7), 161.2 (d, ^1J(C,F) = 241.7 Hz; C-15), 149.2 (C-2), 145.4, 145.2, 142.5, 135.5 (d, ^4J(C,F) = 3.8 Hz; C-12), 129.9 (d, ^3J(C,F) = 7.6 Hz; C-13), 115.0 (d, ^2J(C,F) = 20.8 Hz; C-14), 60.0 (C-10), 53.3, 52.5, 47.0, 42.3, 32.5 (C-11) ppm; IR (KBr): $\tilde{\nu}$ = 2936, 2811, 1637, 1509, 1443, 1018, 733 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 314 (5) $[M]^+$, 206 (49), 205 (72) $[M-BnF]^+$, 177 (21), 150 (40), 123 (18), 107 (27), 98 (100), 79 (59), 56 (24); HRMS (70 eV, EI) calcd for $C_{17}H_{19}FN_4O$: 314.15430; found 314.15607.

***N*-(4-Indolylcarbonyl)-*N'*-[2-(4-fluorophenyl)ethyl]piperazine (11g)**: Yellow solid; R_f = 0.62 (AcOEt/MeOH 9:1); m.p. 80°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 8.98 (s, 1H; NH), 7.24 (dd, ^3J(H,H) = 7.2, ^4J(H,H) = 1.8 Hz, 1H; Ar), 7.10–7.00 (m, 5H; Ar), 6.87 (t, ^3J(H,H) = ^3J(H,F) = 8.7 Hz, 2H; 15-H), 6.41 (t, ^3J(H,H) = ^4J(H,H) = 2.9 Hz, 3H; Ar), 3.82 (br, 2H; pip.), 3.32 (br, 2H; pip.), 2.68 (m, 2H; 11-H), 2.55 (br, 2H; pip.), 2.51 (m, 2H; 12-H), 2.31 (br, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 170.6 (C-8), 161.6 (d, ^1J(C,F) = 242.6 Hz; C-16), 136.2 (C-7a), 135.8 (d, ^4J(C,F) = 3.8 Hz; C-13), 130.2 (d, ^3J(C,F) = 7.6 Hz; C-14), 127.7, 125.7, 125.3, 121.6, 118.5, 115.3 (d, ^2J(C,F) = 20.8 Hz; C-15), 112.8 (C-7), 101.3 (C-3), 60.4 (C-11), 54.0, 53.2, 47.6, 42.2, 32.8 (C-12) ppm; IR (nujol): $\tilde{\nu}$ = 3400 (NH), 2956, 2816, 1625, 1599, 1508, 1463, 999, 825, 758 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 352 (100) $[M+1]^+$, 242 (40), 144 (23); HRMS (70 eV, EI) calcd for $C_{21}H_{23}FN_3O$: 352.18253; found 352.17824.

***N*-(5-Indolylcarbonyl)-*N'*-[2-(4-fluorophenyl)ethyl]piperazine (11h)**: Yellow solid; R_f = 0.60 (AcOEt/MeOH 9:1); m.p. 97°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 9.73 (s, 1H; NH), 7.60 (s, 1H; Ar), 7.17–6.95 (m, 5H; Ar), 6.84 (t, ^3J(H,H) = ^3J(H,F) = 8.5 Hz, 2H; 15-H), 6.37 (br, 1H; 3-H), 3.76–3.32 (br, 4H; pip.), 2.63 (m, 2H; 11-H), 2.48 (m, 2H; 12-H), 2.50–2.30 (br, 4H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 172.3 (C-8), 161.4 (d, ^1J(C,F) = 241.7 Hz; C-16), 136.7 (C-7a), 135.6 (d, ^4J(C,F) = 2.8 Hz; C-13), 130.0 (d, ^3J(C,F) = 7.6 Hz; C-14), 127.3, 126.3, 126.1, 120.9, 120.0, 115.2 (d, ^2J(C,F) = 20.9 Hz; C-15), 111.5 (C-7), 102.4 (C-3), 60.4 (C-11), 53.2, 47.9, 42.4, 32.5 (C-12) ppm; IR (KBr): $\tilde{\nu}$ = 3417 (NH), 2923, 2854, 1625, 1603, 1509, 1436, 1024, 823, 750 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 351 (0.4) $[M]^+$, 242 (47), 144 (100), 116 (17); HRMS (70 eV, EI) calcd for $C_{21}H_{23}FN_3O$: 352.18253; found 352.18034.

***N*-(4-Indolylcarbonyl)-*N'*-[2-(4-methoxyphenyl)ethyl]piperazine (11i)**: Yellow solid; R_f = 0.58 (AcOEt/MeOH 9:1); m.p. 143°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 9.57 (s, 1H; NH), 7.15 (dd, ^3J(H,H) = 6 Hz, ^4J(H,H) = 3.2 Hz, 1H, Ar), 7.03–6.97 (m, 4H; Ar), 6.91 (t, ^3J(H,H) = ^4J(H,H) = 2.6 Hz, 1H; Ar), 6.71 (d, ^3J(H,H) = 8.7 Hz, 2H; 14-H), 6.35 (br, 1H; 3-H), 3.92–3.74 (br, 2H; pip.), 3.65 (s, 3H; OMe), 3.38–3.22 (br, 2H; pip.), 2.63 (m, 2H; 11-H), 2.60–2.45 (br, 2H; pip.), 2.49 (m, 2H; 12-H), 2.40–2.22 (br, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 170.7 (C-8), 158.0 (C-16), 136.1 and 132.0 (C-7a, C-13), 129.6 (C-14), 127.3 and 125.9 (C-2, C-4), 125.1 (C-3a), 121.2 and 118.2 (C-5, C-6), 113.9 (C-15), 112.9 (C-7), 100.7 (C-3), 60.5 (C-11), 55.2 (O*C*H$_3$), 53.8, 53.0, 47.5, 42.1, 32.5 (C-12) ppm; IR (KBr): $\tilde{\nu}$ = 3247 (NH), 2934, 1653, 1608, 1512, 762, 735 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 364 (100) $[M+1]^+$, 243 (12), 242 (76), 144 (31); HRMS (70 eV, EI) calcd for $C_{22}H_{25}N_3O_2$: 363.19467; found 363.19280.

***N*-[4-(Trifluoromethyl)phenylcarbonyl]-*N'*-[2-(4-methoxyphenyl)-ethyl]-piperazine (11j)**: Colorless crystals; R_f = 0.62 (AcOEt/MeOH 9:1); m.p. 100°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 7.66 (d, ^3J(H,H) = 8.1 Hz, 2H; 2-H), 7.50 (d, ^3J(H,H) = 8.1 Hz, 2H; 3-H), 7.09 (d, ^3J(H,H) = 8.5 Hz, 2H; 12-H), 6.81 (d, ^3J(H,H) = 8.5 Hz, 2H; 11-H), 3.81 (br, 2H; pip.), 3.76 (s, 3H; OMe), 3.39 (br, 2H; pip.), 2.72 (m, 2H; 8-H), 2.59 (m, 4H; pip., 9-H), 2.43 (br, 2H; pip.) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 168.9 (C-5), 158.2 (C-13), 139.6, 132.0 (C-1, C-10), 131.8 (q, ^2J(C,F) = 32.2 Hz; C-4), 129.7 (C-11), 127.6 (C-2), 128.1 (q, ^3J(C,F) = 3.8 Hz; C-3), 114.0 (C-12), 60.6 (C-8), 55.4 (OMe), 53.6, 52.9, 47.8, 42.3, 32.7 (C-9) ppm; IR (KBr): $\tilde{\nu}$ = 2959, 2930, 2823, 1640, 1512, 1439, 1327, 1250, 1165, 1119, 1065, 847, 603 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 392 (0.3) $[M]^+$, 272 (20), 271 (100) $[M-BnOMe]^+$, 216 (18), 173 (56), 145 (20); HRMS (70 eV, EI) calcd for $C_{21}H_{23}F_3N_2O_2$: 392.17117; found 392.17041.

***N*-(1-Isoquinolylcarbonyl)-*N'*-[2-(4-tolyl)ethyl]piperazine (11k)**: Light yellow solid; R_f = 0.62 (AcOEt/MeOH 9:1); m.p. 110°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 8.43 (d, ^3J(H,H) = 5.8 Hz, 1H; 3-H), 7.96 (dd, ^3J(H,H) = 8.4 Hz, ^5J(H,H) = 0.9 Hz, 1H; 8-H), 7.77 (d, ^3J(H,H) = 8.3 Hz, 1H; 5-H), 7.64 (ddd, ^3J(H,H) = 8.4 Hz, ^3J(H,H) = 7 Hz, ^4J(H,H) = 1 Hz, 1H; 7-H), 7.60 (d, ^3J(H,H) = 5.8 Hz, 1H; 4-H), 7.54 (ddd, ^3J(H,H) = 8.3 Hz, ^3J(H,H) = 6.9 Hz, ^4J(H,H) = 1.2 Hz, 1H; 6-H), 7.05–6.97 (m, 4H; 15-H, 16-H), 3.92 (t, ^3J(H,H) = ^2J(H,H) = 5.1 Hz, 2H; pip.), 3.20 (t, ^3J(H,H) = ^2J(H,H) = 5.2 Hz, 2H; pip.), 2.73–2.61 (m, 4H; 12-H, pip.), 2.55 (m, 2H; 13-H), 2.37 (t, ^2J(H,H) = ^3J(H,H) = 5.1 Hz, 2H; pip.), 2.22 (s, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 166.8 (C-9), 155.4 (C-1), 141.9 (C-3), 136.8, 136.6, 135.8, 131.0, 129.3 (C-16), 128.7 (C-15), 128.3, 127.2, 126.0, 125.7 and 121.5 (C-8a, C-5), 60.4 (C-12), 53.5, 52.9, 46.8, 41.8, 33.0 (C-13), 21.1 (*C*H$_3$) ppm; IR (neat): $\tilde{\nu}$ = 2924, 2809, 1644, 1585, 1471, 1443, 1250, 998, 828, 811, 751, 734, 704 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 359 (5) $[M]^+$, 255 (18), 254 (100) $[M-MeBn]^+$, 199 (15), 128 (42); HRMS (70 eV, EI) calcd for $C_{23}H_{26}N_3O$: 360.20759; found 360.20617.

1-{[2-(4-Tolyl)ethyl]piperazin-1-yl}isoquinoline (12k): Yellow solid; R_f = 0.50 (AcOEt/MeOH 9:1); m.p. 119°C, ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 8.07 (d, ^3J(H,H) = 5.8 Hz, 1H; 3-H), 8.01 (d, ^3J(H,H) = 8.3 Hz, 1H; 8-H), 7.66 (d, ^3J(H,H) = 7.9 Hz, 1H; 5-H), 7.51 (ddd, ^3J(H,H) = 8.3 Hz, ^3J(H,H) = 7.0 Hz, ^4J(H,H) = 1.2 Hz, 1H; 7-H), 7.41 (ddd, ^3J(H,H) = 7.9 Hz, ^3J(H,H) = 6.9 Hz, ^3J(H,H) = 1.2 Hz, 1H; 6-H), 7.16 (d, ^3J(H,H) = 5.8 Hz, 1H; 4-H), 7.09–6.99 (m, 4H; 15-H, 16-H), 3.41 (t, ^2J(H,H) = ^3J(H,H) = 4.6 Hz, 4H; pip.), 2.80–2.71 (m, 6H; 11-H, pip.), 2.66–2.60 (m, 2H; 12-H), 2.61 (s, 3H; Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 161.5 (C-1), 140.9 (C-3), 138.3, 137.4, 135.8, 129.8 (C-6), 129.3 (C-15), 128.8 (C-14), 127.3, 126.2, 125.8, 121.9 (C-8a), 116.0, 61.0 (C-11), 53.6 (C-9), 51.4 (C-10), 32.3 (C-12), 21.2 (Me) ppm; IR (KBr): $\tilde{\nu}$ = 2925, 2841, 2811, 1621, 1557, 1499, 1448, 1404, 1367, 1007, 814, 750 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 331 (12) $[M]^+$, 226 (35) $[M-MeBn]^+$, 187 (57), 171 (52), 169 (22), 157 (100), 145 (23), 128 (26), 118 (17), 82 (16); HRMS (70 eV, EI) calcd for $C_{22}H_{26}N_3$: 332.21267; found 332.21060.

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