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The Use of Lithium Amides in the Palladium-Mediated Synthesis of [*Carbonyl*-^{11}C]Amides

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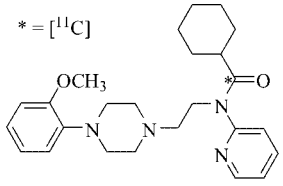
Weakly nucleophilic amines were converted into the corresponding lithium amides and used in either one- or two-pot palladium-mediated reactions with [^{11}C]carbon monoxide and aryl iodides. It was found that palladium acyl complexes may be prepared in a separate step and have sufficient lifetime to be used in a subsequent reaction with a nucleophile. This two-pot procedure was used for the labelling synthesis of eleven amides (nine of which are analogues of WAY-100635, a 5-HT$_{1A}$ radioligand) from weakly nucleophilic amines. The results were compared to a direct one-pot procedure using lithium amides. Both approaches extend the scope of palladium-mediated carbonylation using [^{11}C]carbon monoxide and aryl iodides allowing use of weakly nucleophilic amines.

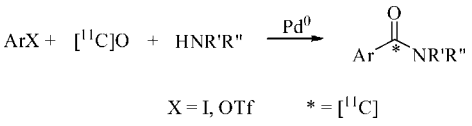
Introduction

Among the imaging techniques used for in vivo studies of neurotransmitter-receptor interactions on a molecular level, positron emission tomography (PET) has proved to be of great value.[1] The use of PET at different stages of drug development seems particularly promising.[2] The need for new radioactive tracers for PET has stimulated research in the synthetic chemistry of short-lived positron emitters. Carbon-11 is an important positron emitting radionuclide because the isotopic labelling does not change the biochemical properties of the labelled compound. However, employing typical preparative procedures is not easy in a labelling synthesis owing to the short half-life of the radionuclide (20.3 min) and practical difficulties in handling submicromolar amounts of labelled compounds.[3]



[*carbonyl*-^{11}C]WAY-100635

[*Carbonyl*-^{11}C]WAY-100635 has proved to be a valuable tracer for imaging 5-HT$_{1A}$-subtype serotonin receptors.[4] The tracer, however, undergoes rapid metabolism in humans,[4,5] and a more metabolically stable compound with good PET tracer properties would be of interest. Several structural analogues of WAY-100635 were studied, most of which retained the aryl–piperazine pharmacophore.[4–6] A compelling, but not yet explored, synthetic route to such analogues is palladium-mediated carbonylation of aryl halides or triflates using [^{11}C]carbon monoxide.[7]



We intended to use this approach to create a library of structurally related [*carbonyl*-^{11}C]amides using amine **1** (Figure 1) and various aryl iodides.[8] However, the previously described procedure[7] provided only 0–15% decay-corrected radiochemical yields of the amides. The bottleneck was, conceivably, the low reactivity of parent amine **1**. Indeed, difficulties in attaining high radiochemical yield when carrying out carbonylations with the use of low-reactive nucleophiles have already been noted.[9]

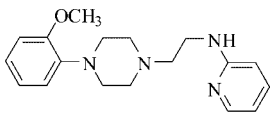


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Figure 1. Amine precursor for labelling analogues of WAY-100635.

This report describes stepwise and one-pot protocols used to perform carbonylation reactions with [^{11}C]carbon monoxide, employing lithium amides to promote the reactions.

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Results and Discussion

Eleven amides were selected as synthetic targets (Figure 2). Compounds **1a**–**i** were of interest for biological screening; compounds **2a** and **3a** were included to allow some generalization of the data. All reactions were performed in a 270-μL stainless steel batch-type reactor, using an automated remote-controlled system for the production and handling of [^{11}C]carbon monoxide.[10] [^{11}C]Carbon monoxide was used in amounts of ca. 20–30 nmol in a mixture with He as the carrier gas. The labelling syntheses were performed in a two- (method A) and one-step (method B) manner.

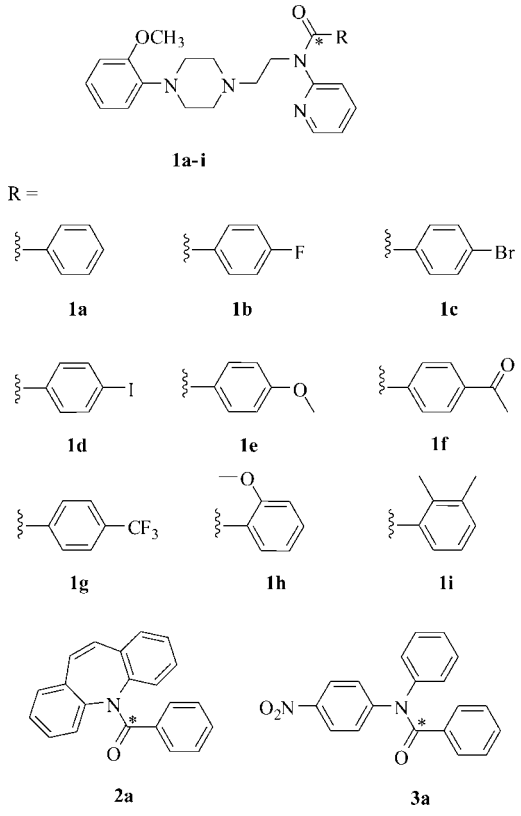


Figure 2. Amides labelled at carbonyl position with ^{11}C (marked by *).

The reactivity of the nucleophile in palladium-mediated carbonylation is an important factor influencing the radiochemical yield in reactions using [^{11}C]carbon monoxide.[7,9] It was shown that yields with unreactive amines, such as anilines, may be increased by converting them into the corresponding lithium amides before carbonylation with [^{11}C]-carbon monoxide.[9a] However, the yields were often low, presumably owing to side reactions. To avoid at least some of them we designed a stepwise procedure where [^{11}C]-carbon monoxide first reacts with a palladium/aryl iodide complex at high pressure, and then the formed reactive acyl complex is allowed to react with a lithium amide in a separate vessel at ambient pressure.

The two-step procedure, method A, proved to be feasible, as the results summarized in Table 1 show. The yield of **2a** was almost triple relative to that obtained previously by using the one-pot reaction.[9a] Generally, the conversion of [^{11}C]carbon monoxide was high, often nearly quantitative. The selectivity of the reactions was also good, except the reaction with 1-iodo-2-methoxybenzene, which gave a number of labelled byproducts, and thus low radiochemical yield (Table 1, Entries 9 and 10). Prefabricated tetrakis(triphenylphosphane)palladium(0) was normally used as a coupling catalyst or it was generated in situ from tris(dibenzylideneacetone)dipalladium(0) and triphenylphosphane (1:5). In a number of cases changing the catalyst ligand from triphenylphosphane to triphenylarsane led to improved radiochemical yields (Table 1, cf. Entries 7 and 8, 9 and 10, 11 and 12, 13 and 14). This improvement may be linked to the higher kinetic lability of $AsPh_3$ ligands.[11] In regard to the second step, the reaction of the palladium–acyl complex with lithium amides was complete within 1–2 min, and longer reactions time did not lead to any changes as monitored by HPLC.

Table 1. Decay corrected radiochemical yields of ^{11}C-labelled amides obtained by using method A.

Entry	Product	Catalyst	Conv. of [^{11}C]O [%][a]	LC yield [%][b]	Isolated yield [%][c]
1	**1a**	$Pd(PPh_3)_4$	99	79	43
2	**1b**	Pd_2dba_3/PPh_3	99	93	60
3	**1c**	Pd_2dba_3/PPh_3	81	64	44
4	**1d**	Pd_2dba_3/PPh_3	79	72	49
5	**1e**	Pd_2dba_3/PPh_3	99	94	64
6	**1f**	$Pd(PPh_3)_4$	54	30	
7	**1g**	$Pd(PPh_3)_4$	14	9	
8	**1g**	$Pd_2dba_3/AsPh_3$	69	27	
9	**1h**	$Pd(PPh_3)_4$	8	2	
10	**1h**	$Pd_2dba_3/AsPh_3$	58	22	
11	**1i**	$Pd(PPh_3)_4$	16	2	
12	**1i**	$Pd_2dba_3/AsPh_3$	96	9	
13	**2a**	Pd_2dba_3/PPh_3	95	95	71
14	**2a**	$Pd_2dba_3/AsPh_3$	99	91	72
15	**3a**	$Pd(PPh_3)_4$	97	17	

[a] Decay-corrected, the fraction of radioactivity left in the crude product after purging unreacted [^{11}C]O with nitrogen. [b] Decay-corrected radiochemical yield based on [^{11}C]O calculated by using analytical HPLC. [c] Isolated decay-corrected radiochemical yield.

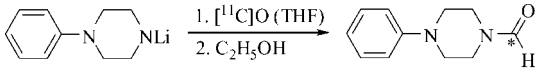
Table 2. Decay-corrected radiochemical yields of ^{11}C-labelled amides obtained by using method B.

Entry	Product	Catalyst	Conv. of [^{11}C]O [%][a]	LC yield [%][b]	Isolated yield [%][c]
1	**1a**	$Pd(PPh_3)_4$	97	90	50
2	**1d**	$Pd(PPh_3)_4$	97	64	28
3	**1f**	$Pd(PPh_3)_4$	98	38	27
4	**1g**	$Pd(PPh_3)_4$	99	78	67
5	**1h**	$Pd(PPh_3)_4$	97	87	67
6	**1i**	$Pd(PPh_3)_4$	96	29	18
7	**3a**	$Pd(PPh_3)_4$	97	16	

[a] Decay-corrected, the fraction of radioactivity left in the crude product after purging unreacted [^{11}C]O with nitrogen. [b] Decay-corrected radiochemical yield based on [^{11}C]O calculated by using analytical HPLC. [c] Isolated decay-corrected radiochemical yield.

The one-step procedure, method B, was used to synthesize amides **1a**, **1d**, **1f**–**i** and **3a** (Figure 2). To our surprise, the yields of some amides were improved. The improvement was most noticeable with *ortho*-substituted iodoarenes (cf. Table 1, Entries 10 and 12 with Table 2, Entries 5 and 6), which may be explained by a low stability of the acylating species formed from these substrates. The yield of amide **3a** was modest with either method (Table 1, Entry 15; Table 2, Entry 7). [^{11}C]Carbon monoxide was almost completely consumed in these reactions; however, we observed more labelled byproducts using method B than by using method A.

To better understand these results we considered the impact of side reactions. Most side reactions are tolerable to some extent provided that they do not consume the [^{11}C]-carbon monoxide because the nonradioactive reactant was used in excess over the amount of [^{11}C]carbon monoxide. Side reactions involving [^{11}C]O, which is the limiting reagent, are detrimental. A relevant process under the conditions of method B is the insertion of [^{11}C]carbon monoxide into the lithium–nitrogen bond with the formation of lithium carbamoyl compounds.[12] This reaction has found synthetic utility and was one of the first published examples of carbonylation using [^{11}C]carbon monoxide.[13] The products, lithium carbamoyls, are unstable species and react rapidly with electrophiles producing stable carbonyl compounds.[12,13] First, we repeated the reported carbonylation, but under modified conditions, which were closer to those used in method B. Lithium 1-phenylpiperazide (**4**) was reacted with [^{11}C]carbon monoxide (Scheme 1) under high pressure at 30 °C for 5 min, and the resulting mixture was transferred from the reactor to a vial containing ethanol at ambient conditions. In this way, formamide **5** was obtained in an excellent 75% isolated decay-corrected radiochemical yield; the conversion of [^{11}C]carbon monoxide was almost quantitative.



4 * = [^{11}C] **5**

Scheme 1. Carbonylation of a lithium amide.

The lithium amide of **1**, on the other hand, gave a low yield of the corresponding formamide under the same reaction conditions. The conversion of [^{11}C]carbon monoxide was 2–6% at (37 ± 3) °C and 26% at 130 °C. Thus, whereas [^{11}C]carbon monoxide can be efficiently trapped by some lithium amides, this reaction probably played a minor role in the palladium-mediated carbonylation of amine **1** under the conditions of method B.

In general, we consider the two-pot method preferential because the reactions were cleaner in most cases. For some substrates the one-pot method may give better yields, but side reactions must be considered. These include the formation of lithium carbamoyls and reactions induced by lithium amide as a base or nucleophile such as elimination, substitution, etc.

Conclusions

Palladium-mediated carbonylation with the use of [^{11}C]-carbon monoxide can be performed in two steps: first, a palladium–acyl complex is prepared from [^{11}C]carbon monoxide under pressure, and in the next step it is reacted with a lithium amide at ambient pressure. This method could be a valuable tool for synthesizing labelled amides from unreactive amines. In some cases performing the reaction in one-pot manner may be a good option. More focused mechanistic studies of this reaction under the conditions used in labelling would be valuable.

Experimental Section

[^{11}C]Carbon dioxide was produced at Uppsala Imanet with a Scanditronix MC-17 cyclotron by using the ^{14}N(p,α)^{11}C nuclear reaction in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA, Oxygen 4.8), which was bombarded with 17 MeV protons. [^{11}C]Carbon monoxide was produced as described previously.[10] The radiolabelling syntheses were performed on an automated system for production and handling of [^{11}C]carbon monoxide.[10] HPLC analyses of radiolabelled compounds were performed with a Beckman Nouveau HPLC system equipped with a Beckman 166 variable-wavelength UV detector and a β^+-flow detector, using a gradient elution with an ammonium formate solution of pH 3.5 and 50:7 mixture of acetonitrile and water as mobile phase and C18 bonded stationary phase columns. Preparative LC purification was performed with a Beckman Gold HPLC system using the same mobile phase. The radioactivity was measured in an ion chamber, Veenstra Instrumenten bv, VDC-202. In the analysis of the ^{11}C-labelled compounds, isotopically unmodified reference substances were used for identification in all the LC runs. LC–MS analysis was performed with a Micromass VG Quattro mass spectrometer with electrospray ionization. THF was distilled under

an atmosphere of nitrogen from sodium/benzophenone. Chemicals were purchased from Sigma–Aldrich. The precursor for labelling, *N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}pyridine-2-amine (**1**) was prepared as described previously.[14]

Preparation of ^{11}C-Labelled Compounds 1a–i, 2a, 3a: Typical Procedures

Method A: A palladium reagent (2.5 μmol) was dissolved in THF (200 μL) in a capped 1-mL vial. The vial was flushed with nitrogen and shaken to dissolve the reagent. A 1-mL vial was charged with an aryl halide (7 μmol) and THF (150 μL) the same way, and the resulting solution was then added to the vial with the palladium reagent. The combined solution was injected into the reactor filled with [^{11}C]carbon monoxide in helium by using a pressure of 35 MPa. An amine (13 μmol) was placed in a 2-mL flat-bottom LC vial, dissolved in THF (200 μL), and then the solvent was evaporated with a flow of nitrogen. The residue was redissolved in THF (200 μL) and *n*BuLi (5 μL of 1.6 M in THF) was added to the solution. This vial was attached to the outlet of the reactor. The reactor was immersed in a heating bath (75 °C) for 5 min and then discharged into the vial containing the lithium amide, and the reaction mixture was heated at 70 °C for 5 min. After the measurement of the radioactivity the vial was purged with nitrogen to remove unreacted [^{11}C]O and the radioactivity was measured again. The solvent was then removed using a nitrogen flow. The crude product was redissolved in acetonitrile (0.4 mL) and water (0.8 mL) and injected into the preparative HPLC.

Method B: A palladium reagent (2.5 μmol) was dissolved in THF (200 μL) in a capped 1 mL LC vial. Another 1 mL vial was charged with an aryl halide (5.0 μmol) and THF (200 μL) and the resulting solution was then added to the vial with the palladium reagent. An amine (10.0 μmol) was dissolved in THF (200 μL) in a 2 mL LC vial and the THF was evaporated with a flow of nitrogen. The residue was redissolved in THF (200 μL) and a solution of *n*BuLi (4 μL of 1.6 M in THF) added to it. The resulting solution of the lithium amide was transferred with a syringe to the vial containing the aryl halide-palladium complex. The combined solution was injected into the reactor filled with [^{11}C]carbon monoxide in helium using a pressure of 35 MPa. The reactor was immersed in a heating bath (130 °C) for 5 min and then discharged into an empty vial. After the radioactivity measurement, the vial was purged with nitrogen to remove unreacted [^{11}C]O, and the radioactivity was measured again. The solvent was removed with a nitrogen flow. The crude product was redissolved in acetonitrile (0.4 mL) and water (0.8 mL), and then injected into the preparative HPLC.

Synthesis of 4-Phenylpiperazine-1-[*carbonyl*-^{11}C]carbaldehyde (5): 1-Phenylpiperazine (10 μL) was dissolved in THF (500 μL) in a capped 1-mL LC vial. After flushing the vial with nitrogen, *t*BuLi (36 μL of 1.7 M in THF) was added. The resulting mixture was transferred to the reactor filled with [^{11}C]carbon monoxide in helium using the pressure of 35 MPa. The reactor was kept at 30 °C for 5 min and then discharged into a 2-mL LC vial containing ethanol (200 μL). After the measurement of the radioactivity, the vial was purged with nitrogen and the radioactivity was measured again. The crude product was diluted with acetonitrile (0.6 mL) and water (0.8 mL) and injected into the preparative HPLC.

Preparation of Reference Compounds: Melting points were determined with a Bibby Sterlin, Stuart Scientific Melting point apparatus SMP3. NMR spectra of isotopically unmodified reference compounds were recorded with a Varian Unity spectrometer at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, at 25 °C in $CDCl_3$ (solvent peak used as reference). LC–MS analyses were performed with a Gilson HPLC and Finnigan AQA mass spectrometer, in ESI-mode. Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 aluminium plates. Silica gel 60, Merck was used for column chromatography. 1-mm precoated plates silica gel 60, F_{254}, Merck were used for preparative TLC.

Isotopically Unmodified Compounds 1a–e, 1g–i: The compounds prepared from the corresponding acyl chlorides and amine **1**. Amine **1** and triethylamine were dissolved in dry dichloromethane (10 mL). After cooling to 0 °C, a solution of the respective substituted acyl chloride was added dropwise. The reaction mixture was stirred at room temp. under an atmosphere of nitrogen overnight and thereafter extracted with a 10% water solution of $NaCO_3$ and dichloromethane. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column or preparative thin-layer chromatography.

***N*-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide[6c] (1a):** A colourless oil was obtained after purification by preparative TLC (dichloromethane/methanol, 10:1), yield: 0.108 g (65%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.41 (ddd, J = 0.8, 2.0, 4.8 Hz, 1 H), 7.36–7.32 (m, 2 H), 7.30–7.25 (m, 2 H), 7.23–7.17 (m, 2 H), 7.02–6.95 (m, 2 H), 6.91–6.87 (m, 2 H), 6.86–6.82 (m, 1 H), 6.76 (dm, J = 8.0 Hz, 1 H), 4.33 (t, J = 6.8 Hz, 2 H), 3.84 (s, 3 H), 2.97 (m, 4 H), 2.80 (t, J = 6.8 Hz, 2 H), 2.69 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.5, 156.3, 152.1, 148.4, 141.2, 136.9, 136.0, 130.0, 129.6, 128.6, 127.8, 122.7, 120.8, 120.7, 118.0, 111.1, 56.1, 55.2, 53.1, 50.4, 45.2 ppm. ESI-MS: m/z = 417 $[M + H]^+$.

4-Fluoro-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide (1b):[15] A colourless oil was obtained after purification by preparative TLC (dichloromethane/methanol, 10:1), yield: 0.069 g (42%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.42 (ddd, J = 0.8, 1.9, 4.9 Hz, 1 H), 7.43–7.38 (m, 1 H), 7.36–7.30 (m, 2 H), 7.04–7.00 (m, 1 H), 6.99–6.94 (m, 1 H), 6.91–6.81 (m, 5 H), 6.75 (dm, J = 8.0 Hz, 1 H), 4.28 (t, J = 6.7 Hz, 2 H), 3.83 (s, 3 H), 2.92 (m, 4 H), 2.76 (t, J = 6.7 Hz, 2 H), 2.64 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.5, 164.7, 162.2, 156.4, 152.1, 148.6, 141.2, 137.1, 132.2, 132.1, 131.0, 130.9, 122.8, 122.7, 120.9, 120.8, 118.0, 115.1, 114.9, 111.2, 56.3, 55.3, 53.3, 50.5, 45.5 ppm. ESI-MS: m/z = 435 $[M + H]^+$.

4-Bromo-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide (1c): A colourless oil was obtained after purification by preparative TLC (dichloromethane/methanol, 10:1), yield: 0.120 g (71%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.40 (ddd, J = 0.8, 2.0, 4.8 Hz, 1 H), 7.44–7.39 (m, 1 H), 7.34–7.30 (m, 2 H), 7.21–7.17 (m, 2 H), 7.05–7.00 (m, 1 H), 6.99–6.94 (m, 1 H), 6.91–6.80 (m, 3 H), 6.76 (dm, J = 8.0 Hz, 1 H), 4.26 (t, J = 6.8 Hz, 2 H), 3.82 (s, 3 H), 2.92 (m, 4 H), 2.74 (t, J = 6.8 Hz, 2 H), 2.64 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.4, 156.2, 152.1, 148.6, 141.2, 137.1, 135.0, 131.1, 130.2, 124.5, 122.7, 122.6, 121.0, 120.8, 117.9, 111.1, 56.2, 55.3, 53.2, 50.5, 45.5 ppm. ESI-MS: m/z (%) = 495 (50.5), 497 (49.5) $[M + H]^+$.

4-Iodo-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide (1d):[16] A colourless oil was obtained after purification by preparative TLC (dichloromethane/methanol, 10:1), yield: 0.160 g (51%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.41 (ddd, J = 0.9, 1.9, 4.9 Hz, 1 H), 7.55–7.52 (m, 2 H), 7.44–7.39 (m, 1 H), 7.07–7.01 (m, 3 H), 6.99–6.94 (m, 1 H), 6.91–6.81 (m, 3 H), 6.77 (dm, J = 8.1 Hz, 1 H), 4.27 (t, J = 6.8 Hz, 2 H), 3.83 (s, 3 H), 2.93 (m, 4 H), 2.74 (t, J = 6.8 Hz, 2 H), 2.64 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.5, 156.1, 152.1, 148.6, 141.2, 137.1, 137.0, 135.5, 130.2, 122.6, 122.6, 120.9, 120.8, 117.9, 111.1, 96.7, 56.2, 55.2, 53.2, 50.5, 45.5 ppm. ESI–MS: m/z = 543 $[M + H]^+$.

4-Methoxy-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide (1e): A colourless oil was obtained after purification by preparative TLC (dichloromethane/methanol, 10:1), yield: 0.154 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.41 (ddd, J = 0.8, 2.0, 4.9 Hz, 1 H), 7.38–7.34 (m, 1 H), 7.30–7.26 (m, 2 H), 7.00–6.92 (m, 2 H), 6.90–6.80 (m, 3 H), 6.73–6.67 (m, 3 H), 4.28 (t, J = 6.8 Hz, 2 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 2.92 (m, 4 H), 2.75 (t, J = 6.8 Hz, 2 H), 2.63 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.0, 160.8, 156.8, 152.0, 148.3, 141.2, 136.7, 130.6, 128.1, 122.7, 122.5, 120.7, 120.3, 117.9, 113.0, 111.0, 56.3, 55.1, 55.0, 53.1, 50.4, 45.4 ppm. ESI–MS: m/z = 447 $[M + H]^+$.

4-Acetyl-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide (1f): Thionyl chloride (0.22 mL, 3.02 mmol) was added dropwise to the solution of 4-acetylbenzoic acid (0.164 g, 1.00 mmol) in ethyl acetate (3 mL). The reaction mixture was stirred at 77 °C under an atmosphere of nitrogen for 4 h, and the solvent was then removed under reduced pressure to yield 4-acetylbenzoyl chloride, which was used directly in the next step, following the above procedure. A yellow oil was obtained after purification by column chromatography (dichloromethane/methanol, 10:1), yield: 0.037 g (50%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.40 (ddd, J = 0.9, 2.0, 4.9 Hz, 1 H), 7.79–7.76 (m, 2 H), 7.44–7.34 (m, 3 H), 7.05–7.01 (m, 1 H), 6.99–6.94 (m, 1 H), 6.92–6.77 (m, 4 H), 4.28 (t, J = 6.6 Hz, 2 H), 3.83 (s, 3 H), 2.93 (m, 4 H), 2.75 (t, J = 6.6 Hz, 2 H), 2.64 (m, 4 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.3, 169.5, 155.9, 152.1, 148.7, 141.3, 140.5, 137.7, 137.2, 128.7, 127.9, 122.8, 122.6, 121.2, 120.9, 118.0, 111.2, 56.2, 55.3, 53.3, 50.6, 45.5, 26.6 ppm. ESI–MS: m/z = 459 $[M + H]^+$.

***N*-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]-ethyl}-*N*-pyridin-2-yl-4-(trifluoromethyl)benzamide (1g):** A colourless oil was obtained after purification by preparative TLC (dichloromethane/methanol, 10:1), yield: 0.100 g (61%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.40 (ddd, J = 0.8, 2.0, 4.9 Hz, 1 H), 7.47–7.40 (m, 5 H), 7.03 (ddd, J = 1.0, 4.9, 7.4 Hz, 1 H), 6.99–6.94 (m, 1 H), 6.91–6.78 (m, 4 H), 4.29 (t, J = 7.2 Hz, 2 H), 3.82 (s, 3 H), 2.94 (m, 4 H), 7.76 (t, J = 7.2 Hz, 2 H), 2.66 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.1, 155.9, 152.1, 148.7, 141.2, 139.7, 139.7, 137.3, 131.6 (q, $^2J_{C,F}$ = 32.6 Hz), 128.8, 124.9 (q, $^3J_{C,F}$ = 3.8 Hz), 122.7, 122.6, 121.3, 120.8, 118.0, 111.1, 56.2, 55.3, 53.3, 50.5, 45.5 ppm. ESI–MS: m/z = 485 $[M + H]^+$.

2-Methoxy-*N*-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-*N*-pyridin-2-ylbenzamide (1h): A colourless oil was obtained after purification by preparative TLC (dichloromethane/methanol, 10:1), yield: 0.069 g (42%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.40 (ddd, J = 0.8, 1.9, 4.8 Hz, 1 H), 7.41–7.34 (m, 1 H), 7.28–7.24 (m, 2 H), 7.01–6.94 (m, 3 H), 6.92–6.84 (m, 4 H), 6.73 (dm, J = 8.4 Hz, 1 H), 4.29 (m, 2 H), 3.85 (s, 3 H), 3.64 (s, 3 H), 2.97 (m, 4 H), 2.75 (m, 2 H), 2.65 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.7, 155.5, 152.1, 147.9, 141.2, 136.4, 130.7, 129.0, 126.3, 122.7, 121.3, 121.0, 120.8, 120.6, 120.4, 118.0, 111.1, 110.7, 56.3, 55.3, 55.2, 53.2, 50.5, 44.5 ppm. ESI–MS: m/z = 447 $[M + H]^+$.

***N*-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-2,3-dimethyl-*N*-pyridin-2-ylbenzamide (1i):** A colourless oil was obtained after purification by column chromatography (dichloromethane/methanol, 10:1), yield: 0.069 g (42%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.38 (ddd, J = 0.8, 2.0, 4.8 Hz, 1 H), 7.42–7.33 (m, 1 H), 7.04–6.81 (m, 9 H), 4.26 (m, 2 H), 3.82 (s, 3 H), 2.95 (m, 4 H), 2.68 (m, 2 H), 2.60 (m, 4 H), 2.26 (s, 3 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.3, 152.1, 148.2, 141.3, 137.2, 136.9, 136.7, 134.7, 130.2, 128.6, 125.3, 125.1, 124.8, 122.7, 122.4, 120.8, 118.0, 111.1, 56.3, 55.3, 53.2, 50.5, 44.3, 20.0, 16.5 ppm. ESI–MS: m/z = 445 $[M + H]^+$.

5-Benzoyl-5H-dibenzo[*b*,*f*]azepine (2a):[17] A solution of benzoyl chloride in dichloromethane was added dropwise to an ice-bath cooled solution of amine **2** and triethylamine in dichloromethane. The reaction mixture was warmed up to room temp. and stirred for 1 h. After the addition of water, the mixture was extracted with dichloromethane three times. The combined organic solvent was removed under reduced pressure and the product was purified on silica by column chromatography (100% ethyl acetate) to yield 0.150 g (74%) of yellow crystals. M.p. 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.39–7.32 (m, 3 H), 7.28–7.20 (m, 6 H), 7.17–7.12 (m, 4 H), 7.08–7.06 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.9, 135.3, 133.3, 130.0, 129.5, 129.0, 128.9, 128.4, 128.3, 128.1, 127.6, 127.2 ppm. ESI–MS: m/z = 298 $[M + H]^+$.

***N*-(4-Nitrophenyl)-*N*-phenylbenzamide (3a):**[18] A solution of sodium hydride (0.006 g, 0.25 mmol) in dry DMF was added to a solution of amine **3** (0.050 g, 0.23 mmol) in dry DMF. The reaction mixture was stirred 15 min at room temp. under an atmosphere of nitrogen and thereafter benzoyl chloride (0.04 mL, 0.35 mmol) was added dropwise. The mixture was stirred at room temp. under an atmosphere of nitrogen overnight. Workup and purification was performed as described previously. A colourless oil was obtained after purification by preparative TLC (100% dichloromethane), yield: 0.024 g (33%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.19–8.15 (m, 2 H), 7.48–7.45 (m, 2 H), 7.37–7.23 (m, 8 H), 7.13–7.09 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.7, 149.5, 144.8, 142.8, 135.1, 130.9, 129.7, 129.2, 128.1, 128.1, 127.4, 126.6, 124.4 ppm. ESI–MS: m/z = 319 $[M + H]^+$.

4-Phenylpiperazine-1-carbaldehyde[19] **(5):** A mixture of 1-phenylpiperazine (0.662 g, 4.1 mmol) and formamide (5 mL, 126 mmol) was stirred at 80 °C under reduced pressure overnight. Then the mixture was poured into water (200 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic fractions were dried with $MgSO_4$, and the product was concentrated under reduced pressure. Chromatographic purification (dichloromethane/methanol, 10:1) yielded **5** as white crystals (0.686 g, 88%). M.p. 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.10 (s, 1 H), 7.32–7.27 (m, 2 H), 6.96–6.91 (m, 3 H), 3.71 (t, J = 5.3 Hz, 2 H), 3.52 (t, J = 5.3 Hz, 2 H), 3.20–3.12 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.6, 150.8, 129.1, 120.7, 116.9, 50.4, 49.2, 45.4, 39.8 ppm. ESI–MS: m/z = 191 $[M + H]^+$.

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