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Straightforward three-component synthesis of diarylmethylpiperazines and 1,2-diarylethylpiperazines

Stéphane Sengmany, Erwan Le Gall,* Cédric Le Jean, Michel Troupel and Jean-Yves Nédélec

Laboratoire d'Electrochimie, Catalyse et Synthèse Organique, LECSO, CNRS-Université Paris 12 Val de Marne, UMR 7582, 2-8 rue Henri Dunant, 94320 Thiais, France

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Abstract—Several functionalized diarylmethylpiperazines and 1,2-diarylethylpiperazines have been synthesized in moderate to high yield according to a one-step three-component coupling between an aromatic or a benzylic organozinc reagent, a piperazine derivative, and an aromatic aldehyde. The procedure can be extended to the synthesis of benzylpiperazine derivatives or β-arylethylpiperazines toward the use of paraformaldehyde or aliphatic aldehydes.

1. Introduction

Diarylmethylpiperazines constitute an important class of compounds, which exhibit various biological activities ranging from antiemetic to anxiolytic, opioid agonists, or bradykinin antagonists. However, they are more commonly known for their activity as antihistamine agents and the synthesis of third-generation histamine H1 antagonists like levocetirizine has been particularly studied during the last years.[1–3] Nevertheless, there was alongside a particular emphasis on the synthesis of diarylmethylpiperazines for their activity as opioid agonists, and even if numerous structures have been thoroughly assessed,[4] only few procedures allowing the construction of the diarylmethylpiperazine core are available. For instance, Delorme et al. employed Corey's reductive chromium-mediated procedure[2] for the enantioselective synthesis of the opioid delta receptor ligand 4-((4-benzylpiperazin-1-yl)(phenyl)methyl)-*N*,*N*-diethylbenzamide[5] whereas Bishop and McNutt[6] or Rice et al.[7] described the diastereoselective syntheses of the opioid agonists BW373U86 or SNC-80 analogues toward nucleophilic displacement of α-benzotriazoylamines[8] using aromatic Grignard reagents. Numerous diarylmethylpiperazines were also synthesized using a multi-step reductive procedure starting from carbonyl compounds and involving the final displacement of benzhydryl halides by piperazines.[9]

Surprisingly, despite the fact that multi-component processes constitute a very attractive tool of organic synthesis, procedures related to the aromatic Mannich[10] or the Petasis[11] reaction have not been employed for the synthesis of functionalized diarylmethylpiperazines. We described recently a versatile three-component coupling among secondary amines, aromatic aldehydes, and aromatic organozinc reagents providing diarylmethylamines in high yields.[12] On the basis of an experiment featuring *N*-methylpiperazine as the amine,[12b] it was mentioned that this procedure should be relevant for the preparation of functionalized diarylmethylpiperazines. In the present paper, we describe the extension of this reaction to the synthesis of several diarylmethylpiperazines but we also explore other possibilities provided by this methodology like synthesis of 1,2-diarylethylpiperazines by using a benzylzinc reagent as the nucleophile. We also mention herein the possible use of paraformaldehyde for the synthesis of benzylpiperazines and β-arylethylpiperazines.

2. Results and discussion

In the first part of our study, we turned our attention to the synthesis of diarylmethylpiperazines starting either from 4-methylpiperazine or 4-phenylpiperazine, aromatic aldehydes, and functionalized arylzinc reagents, which were prepared in acetonitrile according to a previously described procedure.[12b,13] These piperazine derivatives were chosen as model compounds for their nitrogen substituent, which appeared sufficiently simple and representative. In addition, preliminary experiments showed that these substrates react in a same manner, providing coupling products in similar yields.

As described in previous papers,[12] two procedures were used for the coupling. The simplest protocol (coupling method A)

Keywords: Diarylmethylpiperazines; 1,2-Diarylethylpiperazines; Three-component reaction; Arylzinc reagents; Benzylzinc reagents.
* Corresponding author. Tel.: +33 (0) 149781135; fax: +33 (0) 149781148; e-mail: legall@glvt-cnrs.fr

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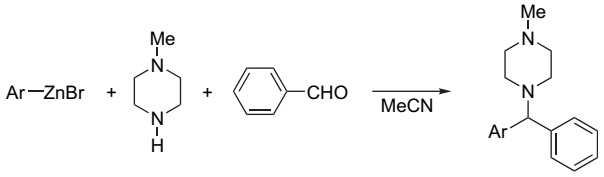
consisted of the addition of the aldehyde and the piperazine derivative to the solution of the organozinc reagent in acetonitrile. This procedure was particularly adapted to reactions involving stable electron-rich organozinc compounds. Surprisingly, contrary to what we reported in our previous study, cuprous iodide did not lead to significant improvements of yields and reaction times. Thus, in a simplification aim, we abandoned the addition of cuprous salts to the organozinc reagent before the introduction of both other substrates. For the coupling of unstable electron-deficient organozinc reagents, prone to dimerization during the course of time, the procedure was modified according to method B in which the organozinc-containing acetonitrile solution was added dropwise into a pre-heated mixture of aromatic aldehyde and piperazine derivative in acetonitrile. These conditions were chosen in order to favor the production of a presumed iminium ion equivalent, which might instantly been trapped by the organozinc reagent thus preventing possibilities of degradation.

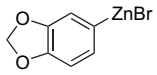
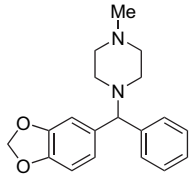
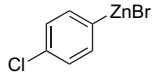
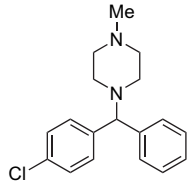
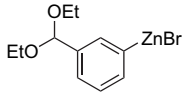
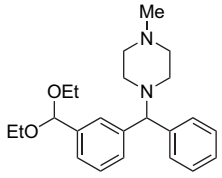
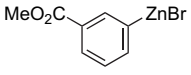
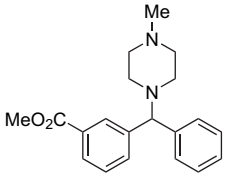
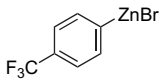
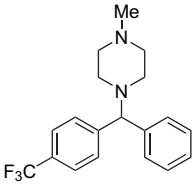
In the first series of experiments, we undertook to scan the arylzinc scope of the reaction. Functionalized aromatic organozinc reagents were then allowed to react with 4-methylpiperazine and benzaldehyde.

Results are presented in Table 1.

Yields are moderate but it appears that a good range of functionalities are tolerated by the reaction. It is also noticeable

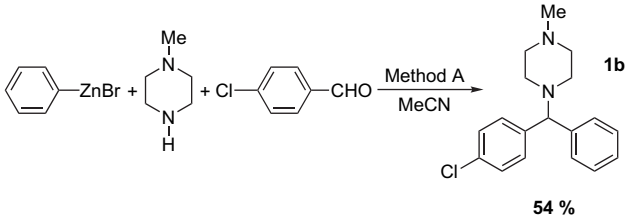
Table 1. Scope of arylzinc reagent



Entry	Organozinc reagent	Reaction time (h)	Product		Isolated yield[a] (%)
1		18[b]		**1a**	59
2		18,[b] 18[c]		**1b**	34, 28
3		16,[b] 18[c]		**1c**	21, 28
4		16[c]		**1d**	29
5		2[c]		**1e**	48

[a] Yields based on initial *N*-methylpiperazine and benzaldehyde amounts (10 mmol).
[b] Coupling method A: addition of *N*-methylpiperazine (10 mmol) and benzaldehyde (10 mmol) to the filtered organozinc solution (>20 mmol) at room temperature.
[c] Coupling method B: the organozinc-containing solution (>20 mmol) was added dropwise into the pre-heated mixture (70 °C) of *N*-methylpiperazine and benzaldehyde in acetonitrile (15 mL).

that organozinc reagents bearing protected aldehyde functions can be employed in the procedure (entry 3 of Table 1). In some cases, we postulated that yields might be enhanced by a simple exchange of functionalities between the organozinc reagent and the benzaldehyde derivative. This principle was applied to the synthesis of chlorcyclizine **1b** in which the reaction yield was enhanced from approximately 30% (entry 2 of Table 1) to 54% by simply reacting 4-methylpiperazine with phenylzinc bromide and 4-chlorobenzaldehyde instead of 4-chlorophenylzinc bromide and benzaldehyde (Scheme 1).



Scheme 1.

In a second series of experiments, we examined the behavior of various aldehydes in the coupling procedure. Aromatic or heteroaromatic aldehydes were reacted with 4-phenylpiperazine and 4-methoxyphenylzinc bromide, taken as model reagents.

Results are displayed in Table 2.

Results are satisfactory with a good range of functionalized aromatic or heteroaromatic aldehydes.

A supplementary experiment was realized with a non-aromatic aldehyde, paraformaldehyde, which was allowed to react with 4-methoxyphenylzinc bromide and *N*-phenylpiperazine for 16 h at 45 °C providing the coupling product in 69% yield (Scheme 2).

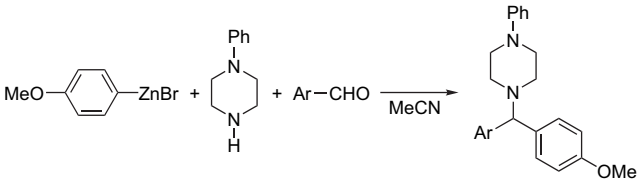
This feature gives rise to the possible formation of numerous substituted benzylamines by coupling amines with functionalized arylzinc reagents and paraformaldehyde. Further developments of this quite interesting result may be envisaged.

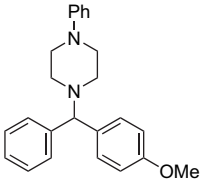
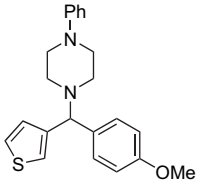
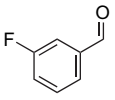
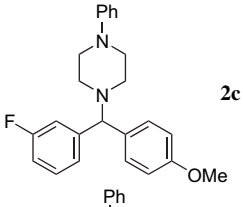
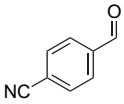
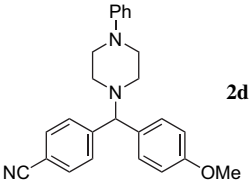
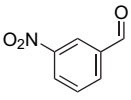
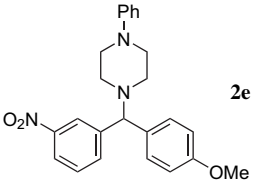
In the second part of the study, we investigated the impact of the nitrogen substituent of piperazine derivatives by means of experiments featuring benzaldehyde, 4-substituted piperazines, and benzylzinc bromide. This reagent was used instead of an arylzinc reagent because it gave the opportunity to obtain a new structural unit in the form of 1,2-diarylethylamine core.[14] For the synthesis of benzylzinc bromide, performed in acetonitrile as the solvent, we employed a very simple and efficient procedure derived from syntheses previously reported with tetrahydrofuran.[15]

Results are presented in Table 3.

The reaction proceeds fairly well with piperazine derivatives bearing either aromatic, heteroaromatic, or aliphatic substituents. The presence of an oxygenated side chain does not prevent the coupling (entry 2 of Table 3). This feature appears rather interesting. Indeed, multi-purpose bioactive compounds like hydroxyzine bear this substituent and might

Table 2. Scope of aldehyde

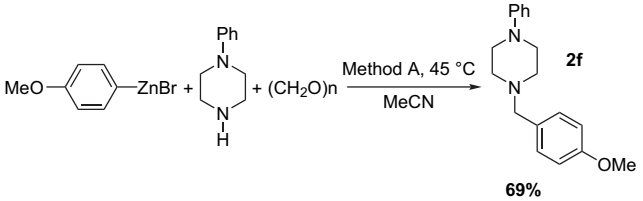


Entry	Aldehyde	Reaction time (h)	Product	Isolated yield[a] (%)
1		2[b]		**2a** 86
2		2[b]		**2b** 89
3		3[b]		**2c** 67
4		3[c]		**2d** 55
5		2[c]		**2e** 61

[a] Yields based on initial *N*-phenylpiperazine and aldehyde amounts (10 mmol).

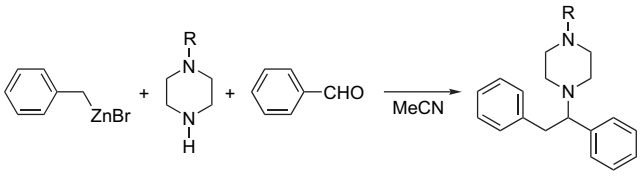
[b] Coupling method A: addition of *N*-phenylpiperazine (10 mmol) and aldehyde (10 mmol) to the filtered 4-methoxyphenylzinc bromide solution (>20 mmol) at room temperature.

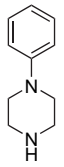
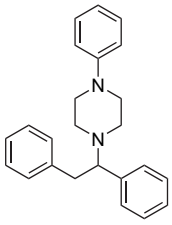
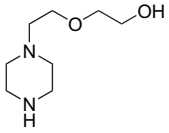
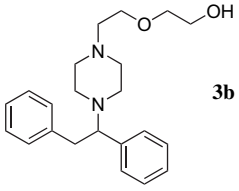
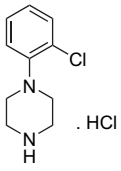
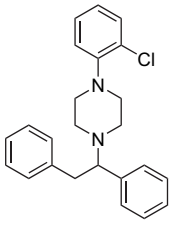
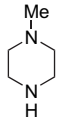
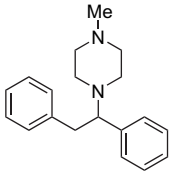
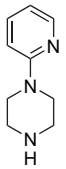
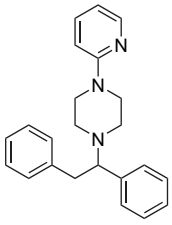
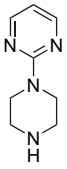
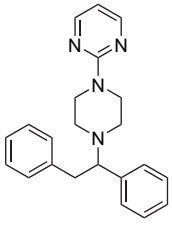
[c] Coupling method B: the 4-methoxyphenylzinc bromide-containing solution (>20 mmol) was added dropwise into the pre-heated mixture (70 °C) of *N*-phenylpiperazine and aldehyde in acetonitrile (15 mL).



Scheme 2.

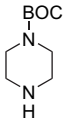
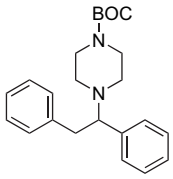
Table 3. Scope of piperazine derivative



Entry	Piperazine	Reaction time (h)	Product	Isolated yield[a] (%)
1		3[b]		**3a** 79
2		4[c]		**3b** 80
3		3[c]		**3c** 55
4		4[b]		**3d** 76
5		4[b]		**3e** 78
6		4[b]		**3f** 84

(*continued*)

Table 3. (*continued*)

Entry	Piperazine	Reaction time (h)	Product	Isolated yield[a] (%)
7		4[b]		**3g** 78

[a] Yields based on initial piperazine derivative and benzaldehyde amounts (10 mmol).
[b] Coupling method A: addition of piperazine derivative (10 mmol) and benzaldehyde (10 mmol) to the filtered benzylzinc bromide solution (>20 mmol) at room temperature.
[c] Coupling method A was followed, but amounts of piperazine derivative and benzaldehyde are 7.5 mmol.

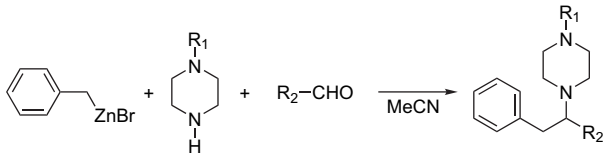
be easily synthesized starting from 4-chlorobenzaldehyde, phenylzinc bromide, and commercial 2-(2-(piperazine-1-yl)-ethoxy)ethanol.

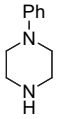
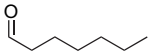
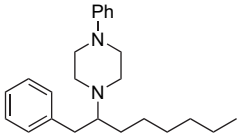
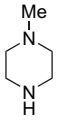
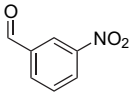
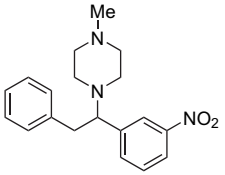
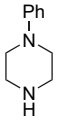
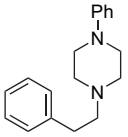
The result presented in entry 7 of Table 3 shows that the *N*-Boc protected piperazine also undergoes the reaction whereas preliminary experiments had revealed that, as a possible consequence of its very low solubility in acetonitrile, piperazine itself does not provide coupling products, even under thermal activation.

It is worth noting that for the coupling of piperazine derivatives bearing one acidic hydrogen (entries 2 and 3 of Table 3), at least 3 equiv of the organozinc reagent was required for the coupling reaction to proceed. This result is consistent with the fact that in the absence of additional acidic hydrogens on substrates, 2 equiv of the organozinc reagent is necessary, as mentioned in our previous study.[12]

In a general manner, it can be noted that benzylzinc bromide, prepared by stirring benzyl bromide and zinc dust in acetonitrile for several minutes at room temperature, reacts as well as aromatic organozinc reagents.[16] In addition to what we had mentioned in a previous paper,[12b] this observation constitutes a further indication that cobalt salts, which are still present in the reaction medium when arylzinc compounds are employed in the three-component coupling,[17] are not required for the reaction to proceed. In our preceding study,[12b] we mentioned that commercial tetrahydrofuran solutions of aromatic organozinc reagents[18] are inefficient in the three-component coupling. In order to verify that arylzinc reagents are particularly ineffective when used as tetrahydrofuran solutions, we prepared 4-methoxyphenylzinc bromide in tetrahydrofuran, starting from 4-bromoanisole, by a metal–halogen exchange using butyllithium and a transmetalation by means of zinc chloride.[19] This organozinc reagent did not lead to satisfactory results, only traces of its coupling product with benzaldehyde and piperidine being detected in the reaction mixture, even after several hours stirring at room temperature. Thus, in order to verify the hypothesis that the choice of the solvent is of crucial importance for the reaction, and particularly that tetrahydrofuran is able to minimize the coupling, we prepared benzylzinc bromide in tetrahydrofuran instead of acetonitrile. Surprisingly, this reagent gave rise to the coupling

Table 4. Coupling of benzylzinc bromide with some aldehydes and piperazine derivatives



Entry	Piperazine	Aldehyde	Reaction time (h)	Product		Isolated yield (%)[a]
1			3[b]		**4a**	94
2			3[c]		**4b**	60
3		$(CH_2O)_n$	3[d]		**4c**	89

[a] Yields based on initial piperazine derivative and aldehyde amounts (10 mmol).
[b] Coupling method A: addition of piperazine derivative (10 mmol) and aldehyde (10 mmol) to the filtered benzylzinc bromide solution (>20 mmol) at room temperature.
[c] Coupling method B: the benzylzinc bromide-containing solution (>20 mmol) was added dropwise into the pre-heated mixture (70 °C) of piperazine derivative and aldehyde in acetonitrile (15 mL).
[d] Coupling method A was followed, but heating at 45 °C.

product in a similar GC yield to that observed in acetonitrile. These quite singular results are not explained to date.

In a further will to demonstrate that aldehydes other than benzaldehyde, especially enolisable aldehydes, undergo the coupling when allowed to react with benzylzinc bromide and piperazine derivatives, we realized another series of experiments.

Results are shown in Table 4.

As attested by entry 1 of Table 4, an enolisable aldehyde like heptanal can be very efficient in the process. This result is rather interesting when the introduction of a saturated side chain at the α position to the nitrogen is expected. Numerous α-alkyl-β-arylethylamines might thus be prepared starting from aliphatic aldehydes, amines, and functionalized benzylzinc reagents.

The association of a benzylzinc reagent and paraformaldehyde allows the formation of the β-arylethylpiperazine subunit (entry 3 of Table 4). It should be noted that a two-step one-pot procedure relying on the addition of benzylzinc bromides to iminium salts preformed by the reaction of amine salts with paraformaldehyde had already been employed by Ku et al. for the efficient synthesis of several β-arylethylamines.[20] In comparison, our procedure appears more attractive by the fact that the reaction occurs more quickly and does not require to preform iminium ions since they are presumably evolved in situ without further handling. One can imagine that numerous functionalized β-arylethylamines could be easily accessible by reacting functionalized benzylzinc reagents and amines in the presence of paraformaldehyde.

3. Conclusion

In conclusion, results reported in this study show that organozinc reagents are very convenient nucleophiles in the three-component Mannich-type synthesis of piperazine derivatives. Arylzinc and benzylzinc reagents are efficient in the process. Their reaction with aromatic aldehydes as well as enolisable aldehydes or paraformaldehyde allows the formation of several subunits like the diarylmethylamine, the 1,2-diarylethylamine, the β-arylethylamine, and the benzylamine core. Considering that last-generation piperazine-based drugs are generally available as a single enantiomer, many efforts are now directed toward enantioselective syntheses of diarylmethylamines, which may likely be realized by means of chiral mediators.

4. Experimental

4.1. General

Solvents (acetonitrile and tetrahydrofuran in analytical grades) and starting materials were purchased from commercial suppliers and used without further purification. All reactions were monitored by gas chromatography (GC) using

a Varian *3400* chromatograph equipped with a 5 m SGE *BP1* column. Melting points (mp) were determined on a Kofler apparatus and were not corrected. Infrared spectra were recorded in $CHCl_3$ on a Perkin–Elmer *Spectrum BX* FTIR. NMR spectra were recorded in $CDCl_3$ at 400 MHz (^1H), 100 MHz (^{13}C), and 376 MHz (^{19}F) on a Bruker *Avance II 400* spectrometer. Data are presented as follows: chemical shift (multiplicity, coupling constants, integration). Mass spectra were recorded on a Finnigan GC/MS *GCQ* spectrometer. Elemental analyses were realized at the 'Service central d'analyses', Vernaison, France. Compounds labeled by asterisk (*) are, to the best of our knowledge, new compounds.

4.2. Typical experimental procedure for the synthesis of organozinc reagents

A dried 100 mL flask was flushed with argon and charged with acetonitrile (40 mL). Dodecane (0.2 mL, used as internal standard), cobalt bromide (0.66 g, 3 mmol), zinc bromide (0.68 g, 3 mmol), phenyl bromide (0.32 mL, 3 mmol), and zinc dust (6 g, 92 mmol) were added to the solution. Trifluoromethanesulfonic acid (0.2 mL) was added to the mixture under vigorous stirring. After ca. 15 min, the aryl bromide (30 mmol) was added to the solution and as soon as the exothermic reaction had begun (ca. 5 min), a water bath at room temperature was used to moderate the temperature of the medium. The reaction time, which was monitored using gas chromatography, did not exceed 30 min in most cases. Yields of organozinc compounds thus obtained were estimated as follows: a sample of the reaction medium was exposed to iodine crystals and then to sodium thiosulfate, and extracted with diethyl ether. The amount of iodinated product was compared to the amount of the starting aryl bromide via the internal standard using gas chromatography (GC). After completion of the reaction, the acetonitrile solution was taken up using a syringe fitted with a 25 mm glass fiber filter.

4.3. Synthesis of benzylzinc bromide

A dried 100 mL flask was flushed with argon and charged with acetonitrile or tetrahydrofuran (40 mL). Dodecane (0.2 mL, used as internal standard) and zinc dust (6 g, 92 mmol) were added to the solution. Trifluoromethanesulfonic acid (0.2 mL) was added to the mixture under vigorous stirring. After ca. 5 min, benzyl bromide (3.6 mL, 30 mmol) was added carefully (ca. 30 s) to the solution, maintained at room temperature using a water bath, and kept for additional 10 min at room temperature. The solution was taken up using a syringe fitted with a 25 mm glass fiber filter.

4.4. Typical coupling method A

To the solution of the organozinc reagent were added the aldehyde (10 mmol) and the piperazine derivative (10 mmol). Stirring was continued for additional 4 h at room temperature.

4.5. Typical coupling method B

The solution of the organozinc reagent was added dropwise (2 h) under stirring to a pre-heated mixture (ca. 70 °C) of the aldehyde (10 mmol) and the piperazine derivative (10 mmol) in acetonitrile (15 mL). Stirring was continued for additional 2 h at 70 °C.

4.6. Typical acid–base work-up[†]

The reaction mixture was poured into a 150 mL of a 5% sodium hydroxide aqueous solution and extracted with dichloromethane (2×100 mL). The combined organic fractions were dried over sodium sulfate and concentrated to dryness. Diethyl ether (150 mL) was added to the residue and after complete dissolution, concentrated sulfuric acid (~1 mL) was added carefully to the vigorously stirred solution and allowed to react for 5 min. The resulting ammonium salt was filtered and washed with diethyl ether (2×50 mL). The solid was then poured, under stirring, into a mixture of a 5% sodium hydroxide aqueous solution (100 mL) and dichloromethane (100 mL). After complete dissolution, the aqueous phase was extracted with additional 100 mL of dichloromethane. The combined organic fractions were dried over sodium sulfate and concentrated to dryness. In the case of liquid crude products, an additional chromatographic purification was performed over silica gel (SDS 70–200 μm) using a solvent gradient from pentane/diethyl ether: 90/10 to diethyl ether/methanol: 90/10 whereas solids were recrystallized using pentane/diethyl ether mixtures.

4.7. Synthesis of *N*-Boc piperazine

In a 500 mL flask were added 250 mL dichloromethane and 8.6 g (100 mmol) piperazine. To the resulting solution, maintained at 0 °C using an ice bath, was added dropwise (20 min) a di-*tert*-butyldicarbonate solution (10.91 g, 50 mmol in 100 mL dichloromethane). The mixture was stirred for additional 1 h, filtered, and the filtrate concentrated to dryness. Water (150 mL) was added to the resulting oil and the mixture filtered. The filtrate was saturated with potassium carbonate and extracted with diethyl ether (3×75 mL). The solvent was dried over sodium sulfate and concentrated to dryness yielding 7.67 g *tert*-butyl piperazine-1-carboxylate (82%), which was sufficiently pure (>98% GC) for our purpose.

4.8. Analytical data

4.8.1. 1-(Benzo[1,3]dioxol-5-yl(phenyl)methyl)-4-methylpiperazine (1a)*. Pale yellow solid, mp: 89 °C; ^1H NMR, δ (ppm): 2.30 (s, 3H), 2.46 (br s, 8H), 4.15 (s, 1H), 5.89 (d, J=10.0 Hz, 2H), 6.71 (d, J=8.0 Hz, 1H), 6.87 (d, J=8.0 Hz, 1H), 6.98 (s, 1H), 7.19 (t, J=7.4 Hz, 1H), 7.29 (t, J=7.5 Hz, 2H), 7.42 (d, J=7.6 Hz, 2H); ^{13}C NMR, δ (ppm): 46.00, 51.93, 55.46, 75.86, 100.85, 107.91, 108.04, 121.11, 126.90, 127.73, 128.50, 137.01, 142.99, 146.43, 147.81; MS, *m*/*z* (relative intensity): 311 (8), 310 (33), 253 (9), 252 (44), 251 (100), 250 (21), 239 (13), 238 (38), 224 (7), 212 (9), 211 (45), 194 (10), 181 (28), 153 (29), 152 (20), 135 (5), 99 (9), 70 (6), 56 (7). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 75.52; H, 7.14; N, 9.03. Found: C, 75.59; H, 7.13; N, 8.90.

[†] Note: due to a predictable sensitivity, a careful neutral aqueous work-up followed by silica gel chromatography was applied for compounds **1a** and **1c**.

4.8.2. 1-((4-Chlorophenyl)(phenyl)methyl)-4-methylpiperazine (1b). Yellow oil; ^{1}H NMR, δ (ppm): 2.19 (s, 3H), 2.34 (br s, 8H), 4.11 (s, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.11–7.20 (m, 4H), 7.26–7.29 (m, 4H); ^{13}C NMR, δ (ppm): 45.98, 51.88, 55.38, 75.51, 127.14, 127.84, 128.59, 128.66, 129.19, 132.53, 141.48, 142.27; MS, *m/z* (relative intensity): 302 (10), 301 (7), 300 (35), 245 (12), 244 (32), 243 (41), 242 (100), 241 (67), 240 (33), 231 (8), 230 (21), 229 (29), 228 (80), 206 (18), 201 (22), 179 (6), 167 (6), 166 (42), 165 (53), 164 (7), 163 (5), 99 (17), 72 (7), 70 (9), 58 (8), 56 (10). Anal. Calcd for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04; N, 9.31. Found: C, 71.85; H, 7.11; N, 9.07.

4.8.3. 1-((3-(Diethoxymethyl)phenyl)(phenyl)methyl)-4-methylpiperazine (1c)*. Yellow oil; ^{1}H NMR, δ (ppm): 1.22–1.25 (m, 6H), 1.29 (s, 3H), 2.45 (br s, 8H), 3.48–3.64 (m, 4H), 4.26 (s, 1H), 5.48 (s, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.25–7.33 (m, 4H), 7.39 (d, J=7.3 Hz, 1H), 7.43 (d, J=7.7 Hz, 2H), 7.53 (s, 1H); ^{13}C NMR, δ (ppm): 15.19, 45.98, 51.91, 55.42, 60.99, 76.14, 101.54, 125.29, 125.52, 126.28, 126.86, 127.96, 128.14, 128.32, 128.81, 139.25, 142.76; MS, *m/z* (relative intensity): 369 (8), 368 (21), 324 (6), 323 (8), 322 (13), 312 (6), 311 (17), 310 (50), 297 (14), 296 (52), 294 (8), 293 (15), 266 (17), 265 (100), 263 (8), 250 (9), 237 (5), 236 (25), 234 (11), 226 (11), 225 (62), 223 (8), 222 (13), 195 (13), 194 (24), 179 (9), 167 (22), 166 (8), 165 (15), 152 (7), 105 (5), 103 (9), 99 (13), 91 (5), 70 (5), 56 (5). Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 74.51; H, 8.79; N, 7.35.

4.8.4. Methyl 3-((4-methylpiperazin-1-yl)(phenyl)methyl)benzoate (1d)*. Yellow oil; IR, ν (cm^{-1}): 1719; ^{1}H NMR, δ (ppm): 2.28 (s, 3H), 2.45 (br s, 8H), 3.89 (s, 3H), 4.30 (s, 1H), 7.18 (t, J=7.3 Hz, 1H), 7.27 (t, J=7.7 Hz, 2H), 7.35 (t, J=7.3 Hz, 1H), 7.43 (d, J=7.7 Hz, 2H), 7.66 (d, J=7.7 Hz, 1H), 7.86 (d, J=7.7 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR, δ (ppm): 45.94, 51.90, 52.05, 55.33, 75.94, 127.15, 127.90, 128.24, 128.61, 128.63, 129.07, 130.41, 132.39, 142.22, 143.45, 167.04; MS, *m/z* (relative intensity): 325 (6), 324 (23), 293 (10), 267 (33), 266 (67), 265 (48), 264 (22), 225 (6), 206 (14), 195 (6), 194 (6), 193 (14), 167 (6), 166 (13), 165 (36), 99 (8), 72 (8), 70 (8), 56 (7). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.03; H, 7.40; N, 8.45.

4.8.5. 1-Methyl-4-((phenyl(4-trifluoromethyl)phenyl)methyl)piperazine (1e). Yellow oil; ^{1}H NMR, δ (ppm): 2.31 (s, 3H), 2.46 (br s, 8H), 4.31 (s, 1H), 7.22 (t, J=7.4 Hz, 1H), 7.30 (t, J=7.4 Hz, 2H), 7.41 (d, J=7.6 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H); ^{13}C NMR, δ (ppm): 45.94, 51.87, 55.33, 75.84, 125.54 (q, J= 272.0 Hz), 125.48 (q, J=3.8 Hz), 127.34, 127.92, 128.10, 128.67, 129.14 (q, J=32.3 Hz), 141.76, 147.05; ^{19}F NMR, δ (ppm): −62.41; MS, *m/z* (relative intensity): 335 (9), 334 (37), 315 (8), 290 (7), 277 (35), 276 (100), 275 (64), 274 (23), 264 (8), 263 (50), 262 (91), 235 (20), 233 (6), 216 (7), 215 (15), 214 (7), 206 (7), 179 (5), 166 (21), 165 (34), 99 (9), 70 (10), 58 (16), 56 (11). Anal. Calcd for $C_{19}H_{21}F_3N_2$: C, 68.25; H, 6.33; N, 8.38. Found: C, 68.32; H, 6.58; N, 8.22.

4.8.6. 1-((4-Methoxyphenyl)(phenyl)methyl)-4-phenylpiperazine (2a)*. White solid, mp: 164 °C; ^{1}H NMR, δ (ppm): 2.70 (t, J=4.7 Hz, 4H), 3.33 (t, J=4.7 Hz, 4H), 3.86 (s, 3H), 4.39 (s, 1H), 6.97–7.01 (m, 3H), 7.05 (d, J=8.0 Hz, 2H), 7.31–7.46 (m, 5H), 7.51 (d, J=8.6 Hz, 2H), 7.61 (d, J=7.4 Hz, 2H); ^{13}C NMR, δ (ppm): 49.34, 52.08, 55.30, 75.65, 114.10, 115.92, 119.58, 127.06, 127.96, 128.70, 129.12, 129.24, 134.91, 143.22, 151.50, 158.77; MS, *m/z* (relative intensity): 359 (14), 358 (71), 331 (9), 330 (49), 239 (12), 238 (71), 226 (15), 225 (66), 224 (72), 199 (6), 198 (23), 197 (100), 182 (23), 167 (12), 166 (16), 165 (23), 162 (13), 161 (34), 159 (5), 154 (11), 153 (20), 152 (11), 134 (29), 133 (36), 132 (20), 121 (21), 120 (38), 119 (5), 106 (8), 105 (8), 104 (10), 91 (8), 77 (9), 56 (23). Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.44; H, 7.36; N, 7.71.

4.8.7. 1-((4-Methoxyphenyl)(thiophen-3-yl)methyl)-4-phenylpiperazine (2b)*. White solid, mp: 136 °C; ^{1}H NMR, δ (ppm): 2.46 (br s, 4H), 3.10 (t, J=4.3 Hz, 4H), 3.70 (s, 3H), 4.34 (s, 1H), 6.72–6.78 (m, 3H), 6.81 (d, J=7.9 Hz, 2H), 7.02 (d, J=4.7 Hz, 1H), 7.08 (br s, 1H), 7.12–7.19 (m, 3H), 7.26 (d, J=8.4 Hz, 2H); ^{13}C NMR, δ (ppm): 49.30, 51.61, 55.26, 70.62, 113.86, 115.86, 119.49, 121.67, 125.75, 127.25, 129.09, 129.17, 133.90, 143.95, 151.38, 158.70; MS, *m/z* (relative intensity): 365 (27), 364 (84), 336 (28), 244 (35), 231 (60), 230 (32), 204 (19), 203 (100), 161 (34), 134 (23), 133 (26), 132 (13), 121 (15), 120 (16), 77 (10), 56 (18). Anal. Calcd for $C_{22}H_{24}N_2OS$: C, 72.49; H, 6.64; N, 7.69. Found: C, 72.31; H, 6.64; N, 7.61.

4.8.8. 1-((3-Fluorophenyl)(4-methoxyphenyl)methyl)-4-phenylpiperazine (2c)*. White solid, mp: 116 °C; ^{1}H NMR, δ (ppm): 2.62 (t, J=4.5 Hz, 4H), 3.27 (t, J=4.6 Hz, 4H), 3.83 (s, 3H), 4.3 (s, 1H), 6.86–7.00 (m, 6H), 7.25–7.35 (m, 5H), 7.40 (d, J=8.5 Hz, 2H); ^{13}C NMR, δ (ppm): 49.26, 51.91, 55.26, 75.02, 113.85 (d, J=21.0 Hz), 114.10, 114.47 (d, J=22.0 Hz), 115.89, 119.59, 123.47 (d, J=2.0 Hz), 129.07, 129.15, 130.05 (d, J=8.0 Hz), 134.03, 145.99 (d, J=6.0 Hz), 151.34, 158.88, 163.13 (d, J=245.0 Hz); ^{19}F NMR, δ (ppm): −112.85; MS, *m/z* (relative intensity): 377 (22), 376 (80), 349 (12), 348 (33), 270 (6), 257 (5), 256 (26), 244 (8), 243 (86), 242 (100), 216 (14), 215 (67), 200 (14), 184 (10), 183 (20), 172 (12), 171 (17), 165 (8), 162 (6), 161 (27), 135 (5), 134 (35), 133 (30), 132 (13), 122 (5), 121 (43), 120 (7), 106 (12), 104 (8), 77 (6), 56 (25). Anal. Calcd for $C_{24}H_{25}FN_2O$: C, 76.57; H, 6.69; N, 7.44. Found: C, 76.30; H, 6.75; N, 7.47.

4.8.9. 4-((4-Methoxyphenyl)(4-phenylpiperazin-1-yl)methyl)benzonitrile (2d)*. Orange oil; IR, ν (cm^{-1}): 2230; ^{1}H NMR, δ (ppm): 2.55–2.67 (m, 4H), 3.26 (t, J=4.8 Hz, 4H), 3.81 (s, 3H), 4.35 (s, 1H), 6.88–6.98 (m, 5H), 7.26–7.38 (m, 4H), 7.57–7.77 (m, 4H); ^{13}C NMR, δ (ppm): 49.21, 51.86, 55.31, 75.12, 110.71, 114.32, 115.95, 118.96, 119.75, 128.47, 129.14, 129.20, 132.53, 133.10, 148.86, 151.22, 159.12; MS, *m/z* (relative intensity): 384 (21), 383 (66), 356 (10), 355 (24), 277 (6), 263 (10), 251 (23), 250 (100), 249 (86), 223 (12), 222 (58), 207 (14), 191 (6), 190 (23), 178 (11), 162 (5), 161 (20), 134 (19), 133 (13), 132 (18), 121 (40), 120 (8), 106 (19), 105 (6), 104 (7), 91 (7), 77 (7), 56 (18). Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.27; H, 6.60; N, 10.90.

4.8.10. 1-((4-Methoxyphenyl)(3-nitrophenyl)methyl)-4-phenylpiperazine (2e)*. Yellow solid, mp: 146 °C; IR, ν (cm^{-1}): 1530, 1352; ^1H NMR, δ (ppm): 2.54–2.62 (m, 4H), 3.25–3.23 (m, 4H), 3.80 (s, 3H), 4.40 (s, 1H), 6.86–6.90 (m, 3H), 6.93 (d, J=8.8 Hz, 2H), 7.28 (t, J=8.0 Hz, 2H), 7.35 (d, J=8.6 Hz, 2H), 7.49 (t, J=8.0 Hz, 1H), 7.83 (d, J=7.7 Hz, 1H), 8.07 (d, J=8.2 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR, δ (ppm): 49.21, 51.84, 55.27, 74.71, 114.29, 115.92, 119.70, 122.04, 122.62, 129.06, 129.12, 129.55, 133.04, 133.86, 145.61, 148.58, 151.19, 159.08; MS, *m/z* (relative intensity): 404 (13), 403 (48), 386 (11), 375 (11), 297 (6), 270 (100), 269 (50), 253 (13), 242 (27), 226 (6), 225 (12), 195 (7), 196 (13), 161 (17), 153 (13), 152 (7), 134 (11), 132 (8), 191 (22), 120 (6), 56 (11). Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.32; H, 6.30; N, 10.28.

4.8.11. 1-(4-Methoxybenzyl)-4-phenylpiperazine (2f). White solid, mp: 107 °C; ^1H NMR, δ (ppm): 2.64 (t, J=4.9 Hz, 4H), 3.23 (t, J=4.9 Hz, 4H), 3.55 (s, 2H), 3.84 (s, 3H), 6.86–6.96 (m, 5H), 7.29–7.31 (m, 4H); ^{13}C NMR, δ (ppm): 49.11, 53.00, 55.28, 62.44, 113.68, 116.06, 119.60, 129.09, 129.35, 130.44, 151.40, 158.86; MS, *m/z* (relative intensity): 283 (25), 282 (99), 281 (7), 254 (17), 176 (18), 175 (10), 164 (6), 162 (10), 161 (26), 150 (14), 149 (100), 148 (78), 135 (6), 134 (24), 133 (9), 132 (16), 122 (6), 121 (64), 120 (8), 118 (10), 119 (6), 106 (11), 105 (7), 104 (8), 91 (9), 77 (11), 56 (13). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.47; H, 7.88; N, 9.71.

4.8.12. 1-(1,2-Diphenylethyl)-4-phenylpiperazine (3a). White solid, mp: 108 °C; ^1H NMR, δ (ppm): 2.53–2.65 (m, 4H), 2.89 (dd, J=13.1, 9.4 Hz, 1H), 3.10 (t, J=4.8 Hz, 4H), 3.30 (dd, J=13.2, 5.1 Hz, 1H), 3.52 (dd, J=9.0, 5.4 Hz, 1H), 6.75 (t, J=7.3 Hz, 1H), 6.81 (d, J=7.9 Hz, 2H), 6.87–6.92 (m, 2H), 6.98–7.09 (m, 5H), 7.11–7.19 (m, 5H); ^{13}C NMR, δ (ppm): 39.47, 49.42, 50.57, 72.03, 116.00, 119.63, 125.85, 127.18, 127.96, 128.83, 129.09, 129.45, 139.41, 151.40; MS, *m/z* (relative intensity): 342 (3), 252 (20), 251 (100), 160 (16), 159 (8), 146 (15), 132 (25), 117 (5), 105 (8), 104 (10), 91 (34), 77 (5). Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.01; H, 7.65; N, 8.18.

4.8.13. 2-(2-(4-(1,2-Diphenylethyl)piperazin-1-yl)ethoxy)ethanol (3b)*. Yellow oil; IR, ν (cm^{-1}): 3250 (br); ^1H NMR, δ (ppm): 2.59 (t, J=5.4 Hz, 2H), 2.61 (br s, 8H), 2.90 (dd, J=13.2, 9.6 Hz, 1H), 3.35 (dd, J=9.5, 4.9 Hz, 1H), 3.52 (dd, J=9.5, 5.0 Hz, 1H), 3.57–3.60 (m, 2H), 3.64 (t, J=5.4 Hz, 2H), 3.66–3.69 (m, 2H), 6.90–6.95 (m, 2H), 7.05–7.25 (m, 10H); ^{13}C NMR, δ (ppm): 39.58, 50.33, 53.60, 57.90, 61.92, 67.52, 72.13, 72.46, 125.74, 127.04, 127.87, 128.33, 128.71, 129.39, 139.30, 140.07; MS, *m/z* (relative intensity): 264 (16), 263 (100), 181 (12), 177 (10), 173 (9), 172 (76), 166 (8), 165 (5), 97 (23), 91 (13). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 73.74; H, 8.69; N, 7.79.

4.8.14. 1-(2-Chlorophenyl)-4-(1,2-diphenylethyl)piperazine (3c)*. White solid, mp: 122 °C; ^1H NMR, δ (ppm): 2.71–2.88 (m, 4H), 3.04 (dd, J=13.2, 9.3 Hz, 1H), 3.11–3.19 (m, 4H), 3.46 (dd, J=5.2, 13.2 Hz, 1H), 3.69 (dd, J=5.2, 9.3 Hz, 1H), 7.00 (td, J=7.6, 1.4 Hz, 1H), 7.04–7.06 (m, 2H), 7.10 (dd, J=8.1, 1.4 Hz, 1H), 7.14–7.33 (m, 9H), 7.40 (dd, J=7.9, 1.4 Hz, 1H); ^{13}C NMR, δ (ppm): 39.50, 50.79, 51.56, 72.18, 120.35, 123.59, 125.84, 127.16, 127.60, 127.98, 128.01, 128.19, 128.76, 128.86, 129.47, 130.68, 139.52, 149.39; MS, *m/z* (relative intensity): 288 (5), 287 (32), 286 (15), 285 (100), 195 (5), 194 (16), 193 (7), 168 (9), 166 (28), 165 (5), 146 (10), 138 (8), 105 (6), 91 (58). Anal. Calcd for $C_{24}H_{25}ClN_2$: C, 76.48; H, 6.69; N, 7.43. Found: C, 76.18; H, 6.69; N, 7.37.

4.8.15. 1-(1,2-Diphenylethyl)-4-methylpiperazine (3d). Yellow-orange oil; ^1H NMR, δ (ppm): 2.15 (s, 3H), 2.33 (br s, 4H), 2.43 (br s, 4H), 2.82 (dd, J=13.2, 9.4 Hz, 1H), 3.22 (dd, J=13.2, 5.2 Hz, 1H), 3.43 (dd, J=9.4, 5.2 Hz, 1H), 6.83–6.86 (m, 2H), 6.93–7.12 (m, 8H); ^{13}C NMR, δ (ppm): 39.45, 46.01, 50.42, 55.48, 72.02, 125.77, 127.65, 128.12, 128.56, 129.18, 129.69, 139.49, 139.80; MS, *m/z* (relative intensity): 190 (14), 189 (100), 165 (6.37), 146 (18), 98 (7), 91 (23), 70 (24). Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.31; H, 8.63; N, 9.84.

4.8.16. 1-(1,2-Diphenylethyl)-4-(pyridin-2-yl)piperazine (3e)*. White solid, mp: 94 °C; ^1H NMR, δ (ppm): 2.61–2.73 (m, 4H), 3.02 (dd, J=13.2, 9.2 Hz, 1H), 3.43 (dd, J=13.3, 5.4 Hz, 1H), 3.58 (t, J=5.0 Hz, 4H), 3.66 (dd, J=9.1, 5.4 Hz, 1H), 6.61–6.67 (m, 2H), 7.03 (d, J=6.9 Hz, 2H), 7.12–7.22 (m, 5H), 7.23–7.32 (m, 3H), 7.45–7.49 (m, 1H), 8.22 (dd, J=5.1, 1.5 Hz, 1H); ^{13}C NMR, δ (ppm): 39.44, 45.50, 50.34, 72.01, 106.99, 113.17, 125.85, 127.17, 127.96, 128.81, 129.44, 137.37, 139.42, 147.98, 159.58; MS, *m/z* (relative intensity): 253 (18), 252 (100), 149 (6), 149 (6), 148 (56), 147 (53), 121 (28), 119 (5), 107 (6), 78 (7). Anal. Calcd for $C_{23}H_{25}N_3$: C, 80.45; H, 7.34; N, 12.23. Found: C, 80.20; H, 7.32; N, 12.29.

4.8.17. 2-(4-(1,2-Diphenylethyl)piperazin-1-yl)pyrimidine (3f)*. White solid, mp: 154 °C; ^1H NMR, δ (ppm): 2.60 (br s, 4H); 3.03 (dd, J=13.0, 9.3 Hz, 1H), 3.40 (dd, J=13.1, 5.0 Hz, 1H), 3.66 (dd, J=8.6, 5.6 Hz, 1H), 3.85 (br s, 4H), 6.46 (t, J=4.7 Hz, 1H), 7.02–7.04 (m, 2H), 7.11–7.21 (m, 5H), 7.22–7.29 (m, 3H), 8.29 (d, J=4.7 Hz, 2H); ^{13}C NMR, δ (ppm): 39.29, 43.93, 50.31, 71.96, 109.67, 125.84, 127.16, 127.96, 128.81, 129.39, 139.45, 157.67, 161.60; MS, *m/z* (relative intensity): 254 (16), 253 (100), 162 (7), 150 (6), 149 (73), 148 (26), 122 (13). Anal. Calcd for $C_{22}H_{24}N_4$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.92; H, 6.91; N, 16.00.

4.8.18. *tert*-Butyl 4-(1,2-diphenylethyl)piperazine-1-carboxylate (3g)*. Yellow oil; IR, ν (cm^{-1}): 1683; ^1H NMR, δ (ppm): 1.50 (s, 9H), 2.49 (br s, 4H), 3.00 (dd, J=13.5, 9.1 Hz, 1H), 3.36 (dd, J=13.4, 5.5 Hz, 1H), 3.41–3.50 (m, 4H), 3.63 (dd, J=9.0, 5.6 Hz, 4H), 7.00–7.04 (m, 2H), 7.11–7.21 (m, 4H), 7.23–7.32 (m, 3H), 7.36–7.43 (m, 1H); ^{13}C NMR, δ (ppm): 28.48, 39.24, 50.24, 64.98, 71.87, 79.51, 125.89, 127.22, 127.99, 128.46, 129.03, 129.38, 139.38, 154.72; MS, *m/z* (relative intensity): 276 (14), 275 (64), 220 (16), 219 (100), 181 (5), 176 (8), 175 (52), 91 (17). Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.49; H, 8.34; N, 7.71.

4.8.19. 1-Phenyl-4-(1-phenyloctan-2-yl)piperazine (4a)*. White solid, mp: 50 °C; ^{1}H NMR, δ (ppm): 1.94 (t, J=6.9 Hz, 3H), 1.25–1.65 (m, 10H), 2.46 (dd, J=13.3, 8.3 Hz, 1H), 2.75–2.95 (m, 5H), 3.67 (dd, J=13.3, 5.1 Hz, 1H), 3.2–3.4 (m, 4H), 6.95 (t, J=7.3 Hz, 1H), 7.02 (d, J=8.5 Hz, 2H), 7.24–7.27 (m, 3H), 7.31–7.37 (m, 4H); ^{13}C NMR, δ (ppm): 14.20, 22.73, 26.93, 29.41, 30.41, 31.93, 35.98, 48.42, 49.85, 66.25, 116.14, 119.59, 125.74, 128.27, 129.13, 129.32, 141.30, 151.75; MS, *m/z* (relative intensity): 260 (19), 259 (100), 160 (13), 154 (5), 132 (28), 104 (7), 70 (14). Anal. Calcd for $C_{24}H_{34}N_2$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.18; H, 9.89; N, 7.48.

4.8.20. 1-Methyl-4-(1-(3-nitrophenyl)-2-phenylethyl)-piperazine (4b)*. Brown oil; IR, ν (cm^{-1}): 1531, 1350; ^{1}H NMR, δ (ppm): 2.28 (s, 3H), 2.35–2.65 (m, 8H), 2.88 (dd, J=13.2, 9.9 Hz, 1H), 3.41 (dd, J=13.2, 5.1 Hz, 1H), 3.68 (dd, J=9.9, 5.1 Hz, 1H), 6.92 (d, J=8.0 Hz, 2H), 7.10–7.16 (m, 3H), 7.33–7.41 (m, 3H), 8.02–8.05 (m, 1H); ^{13}C NMR, δ (ppm): 39.29, 45.90, 50.42, 55.27, 71.27, 122.09, 123.25, 126.19, 128.18, 128.67, 129.30, 134.84, 138.22, 142.74, 148.06; MS, *m/z* (relative intensity): 235 (14), 234 (100), 191 (43), 178 (8), 98 (9), 70 (22). Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.88; H, 7.18; N, 12.16.

4.8.21. 1-Phenethyl-4-phenylpiperazine (4c). White solid, mp: 75 °C; ^{1}H NMR, δ (ppm): 2.71–2.77 (m, 6H), 2.90–2.94 (m, 2H), 3.29–3.32 (m, 4H), 6.93 (t, J=7.3 Hz, 1H), 7.01 (d, J=8.5 Hz, 2H), 7.28–7.39 (m, 7H); ^{13}C NMR, δ (ppm): 33.73, 49.23, 53.32, 60.57, 116.11, 119.74, 126.15, 128.48, 128.78, 129.17, 140.33, 151.40; MS, *m/z* (relative intensity): 266 (9), 176 (14), 175 (100), 132 (33), 104 (12), 70 (31). Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.04; H, 8.24; N, 10.41.

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