Tetrahydrofuranylmethylamines: An Efficient and Simple One-Step Synthesis and Biological Activities

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Various tetrahydrofuran-2-ylmethylamines have been prepared in good yields by an efficient one-step synthesis utilizing the reaction of tetrahydrofurfurylchloride with different secondary cyclic amines without any catalyst. The compounds were tested for their *in vitro* affinity for the $(\alpha4)_2(\beta2)_3$ and $\alpha7$* nicotinic acetylcholine receptor (nAChR) subtypes. Pyrrolidine, piperidine and azepane containing analogs (**1a**, **1b**, **1c**) showed K_i values in the lower micromolar range for these neuronal nAChR subtypes in rat brain.

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Introduction.

Choline (2-hydroxyethyl-trimethylammonium hydroxide) is an essential physiological component of the cerebral spinal fluid (CSF), important for the structural integrity of cell membranes, acetylcholine synthesis, lipid and cholesterol transport, and metabolism [1]. Additionally, choline has been shown to be a selective activator of α7-type nicotinic acetylcholine receptors (nAChRs) exerting neuroprotective activity [2]. Over the recent years, there has been steadily increasing interest in nAChR ligands for the treatment and diagnosis of various neurological and mental disorders related to a dysfunction in the cholinergic system. Prototypical nAChR ligands such as the alkaloidal toxins nicotine [3], cytisine [4], anatoxin-a [5] and epibatidine [6] are accompanied by a variety of untoward effects. Quite recently, structural modifications of these alkaloids have been initiated to gain more insight into structure-activity relationships (SARs) and to develop receptor subtype selective compounds [7,8].

Using the endogenous ligand choline as a basic structure for potentially non-toxic nAChR ligands, we synthesized tetrahydrofuran-2-ylmethylamines as more rigid choline-like derivatives (**1**, Figure 1). Whereas no modification on the tetrahydrofuran-2-ylmethyl moiety in this series was achieved, the amine part was varied by the introduction of five-, six- and seven-membered nitrogen heterocycles.

Generally, saturated N-heterocycles can be prepared *via* an intramolecular nucleophilic substitution process (S_N2) [9] which is known from alkylamines reacting readily with alkyl halides. Alkyl dihalides whose halogen atoms are separated by four, five or six chain members are preferentially used for this kind of cyclization [10,11]. The rates of cyclization vary markedly with ring size [10,11]. To increase the yield of the desired amine derivatives in general, variations in alkylation reactions have been carried out using catalysts [9,12], high temperature, high pressure and catalysts [13,14,15], the presence of naphthalene lithium complex [16], the reaction with 1,3,5-trialkylhexahydro-1,3,5-triazines in the presence of water [17], or strong alkaline conditions at 110-140 °C [18-19].

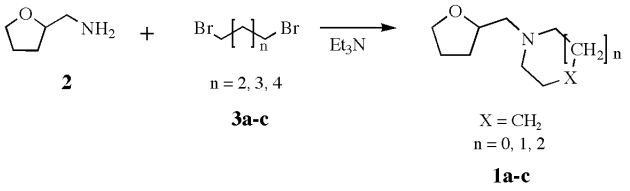
We describe here an improved procedure for the synthesis of known (**1a**, **1b**, **1d**, **1e, 1k**) [14,15,20-27] and novel (**1c**, **1f-j**) tetrahydrofuran-2-ylmethylamines under solvent-free conditions in a pressure tube. Three compounds of this series were additionally prepared using alkyl dibromides for the cyclization process to compare the yield of both synthetic routes. The affinities of these compounds were determined for $(\alpha4)_2(\beta2)_3$ and α7* nAChRs in rat forebrain membranes by competition with (±)-[^{3}H]epibatidine and [^{3}H]methyllycaconitine ([^{3}H]MLA), respectively.

Results and Discussion.

Synthesis of Tetrahydrofuran-2-ylmethylamines.

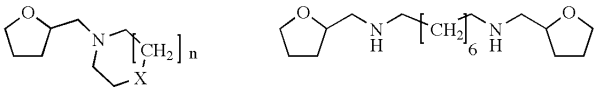
Compounds **1a-c** were prepared using the procedure by Whitesell *et al*. [20] whereas 1-(tetrahydrofuran-2-ylmethyl)pyrrolidine **1** was already synthesized by this group in lower yield. These tetrahydrofuran-2-ylmethylamines could be obtained by cyclization of alkyl dibromides **3a-c** with tetrahydrofuran-2-ylmethylamine **2** in the presence of triethylamine (Scheme 1).

Scheme 1
Method B



Based on a competition between hindrance of ring strain and the decreasing probability of the ends reaching each other, five- and six-membered rings close rapidly while formation of seven-membered rings for example is very much slower and in competition with polymerization [10,11]. Therefore, the synthesis must be performed in high dilution in order to avoid intermolecular reaction. The

cyclization proceeded very sluggishly, so that long reaction times were necessary (48 h) even for five- and six-membered rings. Yields were only moderate (31–37%) and were decreased by prolonged heating (> 48 h). In addition, this method is only suitable for the building of five-, six- and seven-membered rings. All attempts to prepare four- and nine-membered rings failed.

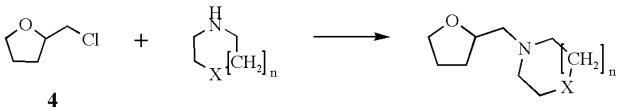


1 **6**

Figure 1

When 1,8-dibromooctane was used as starting material, the main product **6** (detected by GC-MS; GC: R_t = 13:30 min, MS (EI): *m/z* (%) = 313 (4) $[M+H]^{+\bullet}$, 241 (100) $[M-C_4H_7O]^+$) was formed by intermolecular reaction even if the dilution was increased (Figure 1). Furthermore, the reaction system is limited by the availability of multifarious alkyl dibromides. To get access to a greater variety of heterocyclic derivatives, cyclic amines **5a-j** were connected to tetrahydrofuran-2-ylmethylchloride **4**. It is known that the reactivity of chlorides is generally lower than of the corresponding bromides. To overcome this problem cyclic amines were activated by strong basic conditions using 1,8-diazabicyclo[5.4.0]unde-7-ene (DBU) [28], *n*-butyl lithium (n-BuLi) [29] or n-BuLi/N,N,N',N'-tetramethylenediamine (TMEDA) [30]. Our attempts failed yielding only small amounts of the desired product (*ca*. 10%).

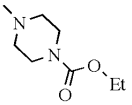
Scheme 2
Method A



4 **5a-j** **1a-j**

Therefore a method was transferred that has been used for the aminolysis of δ-chloro-γ-valerolactone [31]. For example, tetrahydrofuran-2-ylmethylchloride **4** was heated for 4 h at 150 °C in the presence of 3-5 equivalents of pyrrolidine **5a** in a pressure tube obtaining 1-(tetrahydrofuran-2-ylmethyl)-pyrrolidine **1a** as a colourless oil in 43% yield. The reaction was extended to a number of cyclic amines to give a series of tetrahydrofuran-2-ylmethylamines **1a-j** in 43–89% yields demonstrating an easy access to these choline derivatives (Scheme 2). The formation of quaternary ammonium salts was avoided by the strong basic work-up conditions (pH 9). After removal of the excess of amine *in vacuo*, the desired compounds were isolated by extraction with methylene chloride and purified by distillation or column chromatography. This efficient one-step method leads also to higher yields for the known tetrahydrofuran-2-ylmethylamines **1b**, **1d**, and **1e** being prepared *e.g. via* catalytic hydrogenation of the corresponding dihydrofuranyl or amide precursor [15,26,27] which requires an additional step in the synthetic route (Table 1). The only exception was compound **1k**, which was prepared *via* saponification of the carboxylic acid ethylester analog **1g**. All synthesized tetrahydrofuran-2-ylmethylamines exhibited the expected ^1H and ^{13}C NMR, IR, and mass spectral characteristics and gave satisfactory elemental analysis and/or high-resolution mass spectral data.

Table 1
Tetrahydrofuranylmethylamines

Compound No.	R	Yield % (Method A)	Yield % (Method B)
1a		43	37
1b		50	34
1c		89	31
1d		68	
1e		71	
1f		73	
1g		81	
1h		66	
1i		72	
1j		82	
1k		75 [a]	

[a] From tetrahydrofuran-2-ylmethylchloride.

In Vitro Receptor Binding.

To address the issue of binding to $(\alpha4)_2(\beta2)_3$ and α7* nAChRs, affinities of the tetrahydrofuran-2-ylmethylamines **1a-k**, listed in Table 2, were measured in competition assays. The affinities for $(\alpha4)_2(\beta2)_3$ and α7* nAChR subtypes were determined utilizing previously described competition assays [32] with (±)-[^{3}H]epibatidine and [^{3}H]MLA, respectively, and the P2 membrane fraction of rat forebrain.

Table 2

Radioligand Binding Affinities of Tetrahydrofuran-2-ylmethylamines to $(\alpha4)_2(\beta2)_3$ and α7* nAChRs

Compound No.	$(\alpha4)_2(\beta2)_3$ [a] [^{3}H]epibatidine rat brain K_i (μM)	α7* [a] [^{3}H]MLA rat brain K_i (μM)
1a	2.7 ± 0.17	30 ± 0.20
1b	0.93 ± 0.20	8.5 ± 0.31
1c	2.9 ± 0.24	19 ± 0.31
1d	> 50	> 100
1e	> 10	> 100
1f	> 50	> 100
1g	12 ± 0.08	> 100
1h	15 ± 0.40	> 100
1i	51 ± 0.64	31 ± 0.30
1j	> 30	> 50
1k	> 100	> 100

Values represent mean ± SEM obtained from n independent experiments where n = 3-5. [a] Naturally expressed nAChRs.

Some of the tetrahydrofuran-2-ylmethylamines (Table 2) interact with neuronal subtypes of nAChRs. Pyrrolidine, piperidine and azepane containing analogs (**1a**, **1b**, **1c**) featured affinities with K_i = 0.9-3 μM for $(\alpha4)_2(\beta2)_3$ and K_i = 8.5-30 μM for a7* nAChRs. These heterocyclic compounds exhibited higher affinities in comparison with the parent compound choline whose K_i value for a7* nAChR is in the millimolar range [2]. Introduction of a bulky group like a benzyl moiety in the N-heterocyclic system of **1b** caused a loss of affinity in compound **1j**. Derivatives with an oxygen (X = O, **1d**) or another nitrogen atom (X = N-R, **1e-k**) in the tertiary amine moiety suffered also from a loss of affinity for $(\alpha4)_2(\beta2)_3$ and α7* nAChR subtypes.

Conclusion.

We have developed an efficient and simple synthetic method for the preparation of tetrahydro-2-ylmethylamines utilizing the reaction of tetrahydrofuran-2-ylmethylchloride **4** with different cyclic amines **5a-j** in a pressure tube. This reaction route afforded the desired tertiary amines in high yields and provided useful access to a greater variety of N-containing heterocyclic derivatives. Additionally, this method may open a general pathway for the alkylation of liquid secondary amines.

The most active tetrahydro-2-ylmethylamines, pyrrolidine, piperidine and azepane containing analogs (**1a**, **1b**, **1c**) showed K_i values in the lower micromolar range for neuronal nAChR subtypes. It might be of interest to achieve information about the activity of interaction of these compounds with muscarinic acetylcholine receptors (mAChR).

EXPERIMENTAL

General Remarks.

Each starting material was obtained from commercial suppliers and used without further purification. All reactions were carried out under dry argon atmosphere unless otherwise mentioned. Tetrahydrofurane (THF) was distilled from potassium/naphthaline; dichloromethane (DCM) was distilled from calcium hydride before use. Column chromatography was performed on Fluka silica gel 60 (0.063-0.2 mm). Melting and boiling points are uncorrected. GC-MS was obtained using a Finnigan MAT GCQ spectrometer (EI, 70 eV). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 at 298 K. Chemical shifts (δ) are reported in ppm and are referenced to the solvent (^{1}H NMR: δ/ppm = 7.26 for chloroform, ^{13}C NMR: δ/ppm = 77.0 for chloroform). IR spectra were obtained on a Perkin-Elmer 1310 IR spectrometer (in chloroform solutions or as KBr pellets). Elemental microanalyses were performed at the Pharmaceutical Institute, University of Bonn.

General Procedure for the Preparation of the Tetrahydrofuran-2-methylamines (**1a-j**).

Method A.

Tetrahydrofuran-2-ylmethylchloride **4** and 3 to 5 equivalents of amine **5a-j** were placed in a pressure tube under argon atmosphere. The reaction mixture was stirred for 4 h at 150 °C, and then allowed to cool to 20 °C while stirring. The excess amine was evaporated *in vacuo* and the residue was diluted with water. The product was extracted with dichloromethane (DCM) at pH 9 and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting product was purified by distillation or column chromatography.

Method B.

Tetrahydrofuran-2-methylamine **2** was added dropwise to a refluxing solution of alkyl dibromide **3a-c** and triethylamine in 100 mL anhydrous tetrahydrofuran. After 48 h at reflux, the mixture was cooled to 20 °C and then extracted three times with NaOH solution (6 *N*). The aqueous layer was extracted with ether. The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The product was purified by distillation.

1-(Tetrahydrofuran-2-ylmethyl)pyrrolidine (**1a**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and pyrrolidine **5a** (3.556 g, 50 mmol). Distillation afforded **1a** (0.667 g, 43%) as a colourless oil, bp 95 °C (22 mbar), n_D^{20} = 1.4691. GC: R_t =

2:24 min, ms (EI): *m/z* (%) = 155 (30) $[M+H]^+$, 112 (8), 84 (100), 70 (4), 56 (7); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.48 (m, 1 H), 1.75 (m, 4 H), 1.84 (m, 2 H), 1.97 (m, 1 H), 2.48 (dd, *J* = 4.1 and 12.3 Hz, 1 H), 2.56 (m, 5 H), 3.69 (m, 1 H), 3.84 (m, 1 H), 3.98 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 23.4, 25.5, 30.3, 54.6, 61.0, 67.9, 77.8; ir ($CHCl_3$): = 2920, 2845, 2770, 1440, 1130, 1070, 1045, 865 cm^{-1}. HRMS calcd. for $C_9H_{17}NO$, 155.1310. Found: 155.1311.

1-(Tetrahydrofuran-2-ylmethyl)pyrrolidine (**1a**).

The synthesis was done according to method B with 1,4-dibromobutane **3a** (2.591 g, 12 mmol), triethylamine (2.529 g, 25 mmol) and tetrahydrofuran-2-methylamine **2** (1.112 g, 11 mmol). Distillation afforded **1a** (0.634 g, 37%) as a colourless oil. Analytical data correspond with **1a**, method A.

1-(Tetrahydrofuran-2-ylmethyl)piperidine (**1b**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and piperidine **5b** (4.258 g, 50 mmol). Distillation afforded **1b** (0.842 g, 50%) as a colourless oil, bp 110 °C (22 mbar), n_D^{20} = 1.4749. GC: R_t = 2:48 min, ms (EI): *m/z* (%) = 170 (18) $[M+H]^+$, 98 (100), 70 (27), 55 (4), 42 (13); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.41 (m, 3 H), 1.55 (m, 4 H), 1.81 (m, 2 H), 1.94 (m, 1 H), 2.33 (dd, *J* = 3.8 and 12.9 Hz, 1 H), 2.41 (m, 5 H), 3.69 (m, 1 H), 3.83 (m, 1 H), 3.99 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 24.3, 25.4, 25.9, 30.5, 55.1, 64.2, 68.0, 77.3; ir ($CHCl_3$): = 2920, 2850, 2780, 1435, 1295, 1150, 1070, 1050, 980, 855 cm^{-1}. HRMS calcd. for $C_{10}H_{19}NO$, 169.1467. Found: 169.1464.

1-(Tetrahydrofuran-2-ylmethyl)piperidine (**1b**).

The synthesis was done according to method B with 1,5-dibromopentane **3b** (5.518 g, 24 mmol), triethylamine (5.060 g, 50 mmol) and tetrahydrofuran-2-methylamine **2** (2.225 g, 22 mmol). Distillation afforded **1b** (1.283 g, 34%) as a colourless oil. Analytical data correspond with **1b**, method A.

1-(Tetrahydrofuran-2-ylmethyl)azepane (**1c**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and azepane **5c** (4.959 g, 50 mmol). Distillation afforded **1c** (1.631 g, 89%) as a colourless oil, bp 109 °C (15 mbar), n_D^{20} = 1.4797. GC: R_t = 3:38 min, ms (EI): *m/z* (%) = 184 (6) $[M+H]^+$, 112 (100), 84 (4), 58 (86), 44 (8); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.49 (m, 1H), 1.54-1.61 (m, 8 H), 1.82 (m, 2 H), 1.95 (m, 1 H), 2.51 (dd, *J* = 4.6 and 13.1 Hz, 1 H), 2.61 (dd, *J* = 6.9 and 13.1 Hz, 1 H), 2.70 (m, 4 H), 3.70 (m, 1 H), 3.84 (m, 1 H), 3.96 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 25.4, 27.1, 27.8, 30.3, 56.0, 62.1, 68.0, 77.7; ir ($CHCl_3$): = 2910, 2850, 1445, 1355, 1335, 1132, 1065, 1020, 955, 910 cm^{-1}. HRMS calcd. for $C_{11}H_{21}NO$, 183.1230. Found: 183.1230.

Anal. Calcd. for $C_{11}H_{21}NO$ (183.3): C, 72.08; H, 11.55; N, 7.64. Found: C, 71.69; H, 11.31; N, 7.51.

1-(Tetrahydrofuran-2-ylmethyl)azepane (**1c**).

The synthesis was done according to method B with 1,6-dibromohexane **3c** (5.367 g, 22 mmol), triethylamine (5.060 g, 50 mmol) and tetrahydrofuran-2-methylamine **2** (2.023 g, 20 mmol). Distillation afforded **1c** (1.129 g, 31%) as a colourless oil. Analytical data correspond with **1c**, method A.

4-(Tetrahydrofuran-2-ylmethyl)morpholine (**1d**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and morpholine **5d** (4.356 g, 50 mmol). Distillation afforded **1d** (1.174 g, 68%) as a colourless oil, bp 115 °C (20 mbar), n_D^{20} = 1.4704. GC: R_t = 3:01 min, ms (EI): *m/z* (%) = 172 (14) $[M+H]^+$, 100 (100), 73 (13), 70 (23), 56 (11); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.46 (m, 1 H), 1.82 (m, 2 H), 1.95 (m, 1 H), 2.36 (dd, *J* = 3.5 and 12.9 Hz, 1 H), 2.46 (m, 5 H), 3.70 (m, 5 H), 3.84 (m, 1 H), 4.00 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 25.4, 30.3, 54.3, 63.8, 66.9, 68.1, 76.4; ir ($CHCl_3$): = 2940, 2860, 2820, 1452, 1298, 1270, 1115, 1065, 1017, 915, 865 cm^{-1}. HRMS calcd. for $C_9H_{17}NO_2$, 171.1259. Found: 171.1257.

1-Ethyl-4-(tetrahydrofuran-2-ylmethyl)piperazine (**1e**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and 1-ethylpiperazine **5e** (5.709 g, 50 mmol). Distillation and column chromatography afforded **1e** (1.412 g, 71%) as a colourless oil, bp 128-129 °C (14 mbar), n_D^{20} = 1.4683. GC: R_t = 4:09 min, ms (EI): *m/z* (%) = 198 (4) $[M]^{+\bullet}$, 127 (71), 112 (12), 98 (30), 84 (100), 70 (88), 56 (33), 42 (65); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.05 (t, *J* = 7.3 Hz, 3 H), 1.46 (m, 1 H), 1.82 (m, 2 H), 1.95 (m, 1 H), 2.35-2.74 (m, 12 H), 3.68 (m, 1 H), 3.82 (m, 1 H), 4.00 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 11.9, 25.4, 30.4, 52.3, 52.7, 53.8, 63.4, 68.1, 76.7; ir ($CHCl_3$): = 2940, 2860, 2820, 1450, 1380, 1305, 1160, 1015, 930 cm^{-1}. HRMS calcd. for $C_{11}H_{22}N_2O$, 198.1733. Found: 198.1741.

Anal. Calcd. for $C_{11}H_{22}N_2O$ (198.3): C, 66.62; H, 11.18; N, 14.13. Found: C, 66.35; H, 11.11; N, 14.02.

1-Methyl-4-(tetrahydrofuran-2-ylmethyl)piperazine (**1f**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and 1-methylpiperazine **5f** (5.709 g, 50 mmol). Distillation and column chromatography afforded **1f** (1.345 g, 73%) as a colourless oil, bp 120-121 °C (20 mbar), n_D^{20} = 1.4793; GC: R_t = 3:27 min, ms (EI): *m/z* (%) = 184 (8) $[M]^{+\bullet}$, 113(48), 98 (15), 70 (100), 42 (45); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.46 (m, 1 H), 1.82 (m, 2 H), 1.95 (m, 1 H), 2.25 (s, 3 H), 2.31-2.75 (m, 9 H), 3.71 (m, 1 H), 3.84 (m, 1 H), 3.99 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 25.4, 30.4, 46.0, 53.8, 55.0, 63.3, 68.1, 76.7; ir ($CHCl_3$): = 2920, 2800, 2780, 1455, 1282, 1160, 1010, 920 cm^{-1}. HRMS calcd. for $C_{10}H_{20}N_2O$, 184.1576. Found: 184.1579.

4-(Tetrahydrofuran-2-ylmethyl)piperazine-1-carboxylic Acid Ethylester (**1g**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and ethyl 1-piperazinecarboxylate **5g** (7.997 g, 33 mmol). Distillation and column chromatography afforded **1g** (1.965 g, 81%) as a light yellow oil, bp 132-135 °C (12 mbar), n_D^{20} = 1.4858; GC: R_t = 7:38 min, ms (EI): *m/z* (%) = 242 (4) $[M]^{+\bullet}$, 171 (100), 143 (40), 97 (53), 70 (12), 56 (14), 42 (12); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, *J* = 7.1 Hz, 3 H), 1.46 (m, 1 H), 1.83 (m, 2 H), 1.95 (m, 1 H), 2.36-2.48 (m, 6 H), 3.46 (m, 4 H), 3.71 (m, 1 H), 3.85 (m, 1 H), 4.00 (m, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 14.7, 25.4, 30.3, 43.6, 53.5, 61.2, 63.4, 68.2, 76.6, 155.5; ir ($CHCl_3$): = 2975, 2900, 2850, 1700, 1472, 1445, 1300, 1258, 1150, 1115, 840 cm^{-1}. HRMS calcd. for $C_{12}H_{22}N_2O_3$, 242.1630. Found, 242.1635.

Anal. Calcd. for $C_{12}H_{22}N_2O_3$ (242.3): C, 59.48; H, 9.15; N, 11.56. Found: C, 59.46; H, 9.18; N, 11.39.

1-Phenyl-4-(tetrahydrofuran-2-ylmethyl)piperazine (**1h**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and 1-phenylpiperazine **5h** (4.867 g, 30 mmol). Distillation and column chromatography afforded **1h** (1.645 g, 66%) as a light yellow solid, mp 48-49 °C. GC: R_t = 10:15 min, ms (EI): *m/z* (%) = 246 (34) $[M]^{+\bullet}$, 175 (100), 160 (17), 132 (46), 104 (20), 70 (69), 42 (17); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.50 (m, 1 H), 1.85 (m, 2 H), 1.98 (m, 1 H), 2.49 (m, 2 H), 2.62-2.72 (m, 4 H), 3.15-3.25 (m, 4 H), 3.73 (m, 1 H), 3.87 (m, 1 H), 4.05 (m, 1 H), 6.81 (m, 1 H), 6.90 (m, 2 H), 7.23 (m, 2 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 25.4, 30.4, 49.0, 53.8, 63.4, 68.2, 76.8, 116.0, 119.5, 129.0, 151.4; ir (KBr): = 3080, 3040, 2960, 2900, 2855, 2820, 1585, 1490, 1440, 1230, 1140, 1065, 1015, 920, 740, 675 cm^{-1}. HRMS calcd. for $C_{15}H_{22}N_2O$, 246.1732. Found: 246.1734.

Anal. Calcd. for $C_{15}H_{22}N_2O$ (246.4): C, 73.13; H, 9.00; N, 11.37. Found: C, 72.75; H, 8.91; N, 11.26.

1-Benzyl-4-(tetrahydrofuran-2-ylmethyl)piperazine (**1i**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and 1-benzylpiperazine **5i** (5.287 g, 30 mmol). Distillation and column chromatography afforded **1i** (1.8642 g, 72%) as a brown oil, n_D^{20} = 1.5318; GC: R_t = 9:48 min, ms (EI): *m/z* (%) = 260 (8) $[M]^{+\bullet}$, 189 (100), 146 (28), 91 (75), 70 (39), 42 (21); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.41 (m, 1 H), 1.78 (m, 2 H), 1.90 (m, 1 H), 2.31-2.57 (m, 10 H), 3.46 (m, 4 H), 3.44 (d, *J* = 1.9 Hz, 2 H), 3.66 (m, 1 H), 3.80 (m, 1 H), 3.95 (m, 1 H), 7.15–7.25 (m, 5 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 25.4, 30.4, 52.9, 53.8, 63.1, 63.4, 68.1, 76.7, 126.9, 128.1, 138.2; ir ($CHCl_3$): = 2970, 2910, 2850, 1465, 1310, 1170, 1152, 1085, 1025, 840 cm^{-1}. HRMS calcd. for $C_{16}H_{24}N_2O$, 260.1889. Found: 260.1887.

Anal. Calcd. for $C_{16}H_{24}N_2O$ (260.4): C, 73.81; H, 9.29; N, 10.76. Found: C, 73.80; H, 9.21; N, 10.85.

1-Benzyl-4-(tetrahydrofuran-2-ylmethyl)piperidine (**1j**).

The synthesis was done according to method A with tetrahydrofuran-2-methylchloride **4** (1.206 g, 10 mmol) and 4-benzyl-piperidine **5j** (5.258 g, 30 mmol). Distillation and column chromatography afforded **1j** (2.1433 g, 82%) as a yellow oil, n_D^{20} = 1.5292; GC: R_t = 9:59 min, ms (EI): *m/z* (%) = 259 (4) $[M]^{+\bullet}$, 188 (100), 129 (3), 97 (17), 91 (11), 70 (17), 44 (11); ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.31-1.56 (m, 4 H), 1.60 (m, 2 H), 1.78-2.00 (m, 5 H), 2.37 (dd, *J* = 3.8 and 12.9 Hz, 1 H), 2.46 (m, 1 H), 2.52 (m, 2 H), 3.72 (m, 1 H), 3.86 (m, 1 H), 4.01 (m, 1 H), 7.12-7.19 (m, 3 H), 7.26 (m, 2 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 25.4, 30.5, 32.0, 32.1, 37.8, 43.2, 54.3, 54.7, 63.7, 68.1, 76.8, 125.7, 128.1,129.1, 140,8; ir ($CHCl_3$): =2940, 2880, 2830, 2800, 1450, 1303, 1145, 1072, 979 cm^{-1}. HRMS calcd. for $C_{17}H_{25}NO$, 259.1936. Found: 259.1941.

Anal. Calcd. for $C_{17}H_{25}NO$ (259.4): C, 78.72; H, 9.71; N, 5.40. Found: C, 78.63; H, 9.63; N, 5.78.

1-(Tetrahydrofuran-2-ylmethyl)piperazine (**1k**).

To a solution of 0.530 g (2.2 mmol) 4-(tetrahydrofuran-2-ylmethyl)piperazine-1-carboxylic acid ethylester **1g** dissolved in 5 ml EtOH, a solution of 2.240 g (40.0 mmol) KOH in 8 ml EtOH/H_2O (6:2) was added. The mixture was heated at reflux for 20 h. After cooling to room temperature, the mixture was extracted with ether. The combined organic phases were dried over sodium sulfate and the solvent was evaporated. Column chromatography (DCM/MeOH 2:1) of the crude product afforded **1k** (0.347 g, 93%) as a colourless solid, mp 115-117 °C; ^{1}H nmr (500 MHz, $CDCl_3$, 25 °C): δ = 1.44 (m, 1 H), 1.76 (m, 2 H), 1.90 (m, 1 H), 2.36 (dd, *J* = 7.1 and 13.1 Hz, 1 H), 2.43 (dd, *J* = 4.3 and 13.1 Hz, 1 H), 2.54-2.69 (m, 4 H), 2.95 (m, 4 H), 3.58 (m, 1 H), 3.71 (m, 1 H), 3.90 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$, 25 °C): δ = 25.0, 29.8, 43.2, 50.4, 62.0, 67.3, 71.9. HRMS calcd. for $C_9H_{18}N_2O$, 170.1419. Found: 170.1417.

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