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PAPER

Ring-opening reactions of 1,4-diazabicyclo[2.2.2]octane (DABCO) derived quaternary ammonium salts with phenols and related nucleophiles†‡

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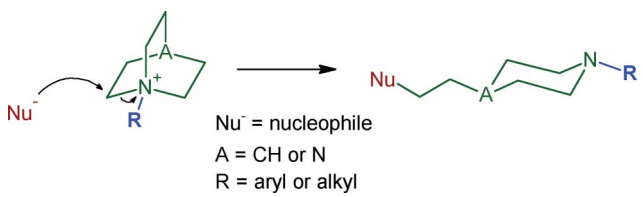
1,4-Diazabicyclo[2.2.2]octane (DABCO) has been evaluated as a starting material for the synthesis of 1-alkyl-4-(2-phenoxyethyl)piperazines and related derivatives. We found that 1-alkyl-1,4-diazabicyclo[2.2.2]octan-1-ium salts, resulting from the alkylation of DABCO, efficiently react with a variety of nucleophiles in polyethyleneglycol (PEG) or diglyme at high temperatures to give piperazine products resulting from the nucleophilic ring-opening reaction. The benzylation side reaction was found to be relevant with softer nucleophiles when using 1-benzyl-1,4-diazabicyclo[2.2.2]octan-1-ium salts, while other types of alkylations were not observed. One-pot methodologies allow for the synthesis of piperazines directly from primary alcohols, alkyl halides or sulfonates, using phenols, or other nucleophile sources, and DABCO.

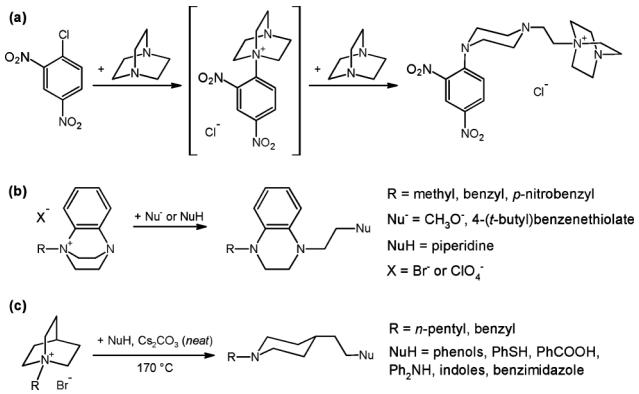
Introduction

Ring-opening reactions, resulting from a nucleophilic attack on 1-azoniabicyclo[2.2.2]octanes and analogous bicyclic quaternary amines, have already received some attention as a tool for the preparation of nitrogen-containing heterocycles, such as 1,4-disubstituted piperidines and piperazines (Scheme 1). The reaction seems to be efficient when starting from the relatively reactive 1-aryl-1-azoniabicyclo[2.2.2]octanes and related bicyclic quaternary ammonium ions. Generally, it requires very harsh conditions and is often limited by side reactions when starting from the 1-alkyl-substituted substrates.



Scheme 1 Nucleophilic ring-opening reactions on 1-azoniabicyclo-[2.2.2]octanes (A = CH) or 4-aza-1-azoniabicyclo[2.2.2]octanes (A = N).

Ross *et al.* reported that the reaction of 1-chloro-2,4-dinitrobenzene with DABCO gives a piperazine derivative as a result of the ring-opening reaction of the primarily formed quaternary ammonium intermediate by a second nucleophilic attack of the DABCO (Scheme 2, a).[1] Later studies reported a similar observation for the reaction of picryl chloride with DABCO and quinuclidine.[2] The literature on ring-opening reactions of quinuclidine derivatives has been reviewed up to the year 1984.[3] This type of reaction also found some use in polymer chemistry.[4] Luk'yanchuk *et al.* published their studies on the ring-opening reactions of benzoannulated DABCO derivatives using several nucleophiles (Scheme 2, b).[5] The reaction of an electron-poor aromatic compound like a cyclic chlorocarbaphosphazene with DABCO or quinuclidine was found to yield the corresponding 1-aryl-4-(2-chloroethyl)piperazines or 1-aryl-4-(2-chloroethyl)piperidines under the appropriate conditions.[6] Wang *et al.* and Gladstone *et al.* used this reaction to develop a new one-pot methodology for preparing 1-heteroarylpiperazines



Scheme 2 A few examples of published nucleophilic ring-opening reactions on 1-azoniabicyclo[2.2.2]octanes.

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† Dedicated to Professor Ferenc Fülöp, University of Szeged, Hungary, on the occasion of his 60th birthday.

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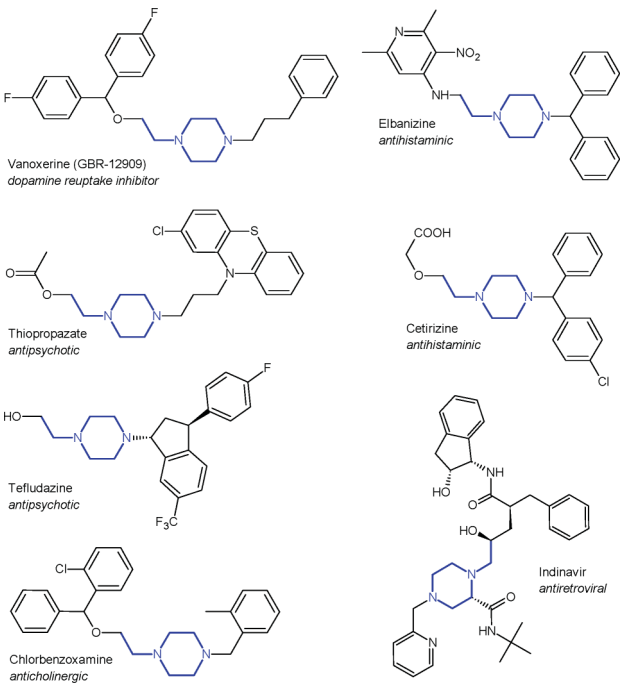
from DABCO, electron-poor (hetero)aryl chlorides and various nucleophiles.[7] The related 1-aryl-1-azabicyclo[2.2.1]heptan-1-ium salts also give ring-opening products upon nucleophilic attack.[8] All these reports focused on the quaternary ammonium compounds in which the ammonium nitrogen is directly connected to an aromatic nucleus. Such compounds are considerably more reactive toward nucleophiles; an example of their synthetic utility is the methylation of phenols by trimethylphenylammonium salts (*e.g.*, $PhMe_3NCl$).[9] On the other hand, Axelsson and Peters described the ring-opening reaction of 1-alkylquinuclidinium salts as a new route to 1,4-dialkylpiperidines (Scheme 2, c).[10] Forcing conditions (170 °C) with Cs_2CO_3 as a base had to be used to give low-to-moderate yields of the ring-opening products.

The development of such simple syntheses of unsymmetrically 1,4-disubstituted piperazines or piperidines starting from DABCO, quinuclidine or their derivatives are of importance for the never ending search for new, biologically active compounds, because this type of heterocyclic moieties can be considered particularly promising for medicinal chemistry. The ethylene bridging element from these bicyclo[2.2.2]octanes becomes incorporated into the product. Many drugs of different biological activities incorporate exactly this structural moiety (Scheme 3). While several examples and methodologies for such syntheses of 1-aryl-4-alkylpiperazines already exist, similar approaches toward 1,4-dialkylpiperazines remain elusive, due to the reactivity or side-reaction issues.



Scheme 3 Examples of pharmacologically active 1,4-dialkylpiperazines containing the ethylenepiperazinyl structural element.

On the basis of our studies on the synthetic application of phenolic compounds,[11] particularly their reactions with quaternary ammonium salts, we decided to study the ring-opening reaction of 1-alkyl-1-azoniabicyclo[2.2.2]octanes, applying phenolates as nucleophiles.

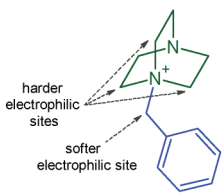
Results and discussion

We found that the starting ammonium compounds can be easily prepared *in situ* from DABCO and the appropriate alkyl halides or tosylates and further used in the ring-opening reaction. However, to study the one-pot methodology we first decided to investigate the ring-opening reaction itself, and for this reason we prepared some 1-alkyl-4-aza-1-azoniabicyclo[2.2.2]octanes (**1**). Compounds **1a–c**, containing a carbon atom attached to the ammonium nitrogen, potentially having an increased reactivity for S_N2 substitutions, were chosen to evaluate the relevance of the competing reaction of the 1-alkyl group transfer (the transfer of methyl, benzyl and allyl groups, respectively). This side reaction was already observed by Axelsson and Peters in the case of 1-benzylquinuclidinium salts[10] and it is of importance for realizing the limitations of the synthetic method and some mechanistic aspects of the reaction.

We observed that when using the minimum amount of polyethyleneglycol (PEG) as a solvent, the reaction of ammonium salts **1** with phenols in the presence of K_2CO_3 as a base generally proceeded satisfactorily after heating for 4 h at 140 °C. Preliminary experiments of **1b** with unsubstituted phenol as the model nucleophile showed that increasing the reaction temperature did not increase the yields or alter the ratio of the products **3** and **4**. The reaction could not be observed at temperatures lower than 120 °C. This is still an improvement over the harsh conditions used in some related previous studies. Nevertheless, *N*-methyl-DABCO tosylate (**1a**) was found to be an exception and required heating to 150 °C (the yield of **3a** at 140 °C was only 12%). Diglyme was also found to be an efficient solvent, though the ammonium salts **1** were considerably less soluble in it. Due to its properties it is nevertheless the solvent of choice for nucleophiles incompatible with the protic solvent PEG ($NaOCH_3$ and $NaBH_4$ are given as such examples).

Interestingly, products of the type **4** could only be observed in the reactions of the *N*-benzyl-DABCO chloride (**1b**). This is in contrast to our earlier observation that during the related alkylations of phenols with benzyltrimethylammonium chloride ($BnMe_3NCl$), the methyl group is also transferred to some degree (*e.g.*, the ratio of benzylated *vs.* methylated product was 88 : 12 for the alkylation of 2-naphthol).[11c] An earlier study of the benzenethiolate alkylation in HMPTA as a solvent reported the ratio of methylation *vs.* ring opening to be 0.46 for *N*,*N*-dimethylpyrrolidinium tosylate, whereas only methylation and no ring opening was observed by alkylation with the less strained *N*,*N*-dimethylpiperidinium tosylate.[12] Thus, we expected at least some anisole formation in the reaction of the phenol with the *N*-methyl-DABCO tosylate (**1a**), but it could be detected neither chromatographically nor using NMR spectroscopy. The explanation could be that the 1-azoniabicyclo[2.2.2]octane systems are considerably more strained than the pyrrolidinium systems, thus leading to even more selective ring opening. Similarly, though the benzyl and allyl moieties exhibit some resemblance, allylation of the phenol did not occur in the reactions with *N*-allyl-DABCO bromide (**1c**). Furthermore, in the reactions of **1b**, the amount of benzylation products **4** was comparable, regardless of the electronic properties of the *para* substituent on the phenol applied, or with the related naphthol and 2,6-dimethylphenol. The benzylation: ring-opening ratio varied from 0.41 to 0.54,

thus in favor of the piperazine products **3**, but it is dependent more on the nature of the nucleophile used. For example, nucleophiles such as 2-mercaptobenzothiazol, benzenethiol, $NaBH_4$, potassium phthalimidate, or $NaOCH_3$ gave **4** : **3** ratios, ranging from 1.00 (with thiols) to zero (with $NaOCH_3$, giving **3k** only). Apparently, this ratio mostly relates to the hard-soft properties of the nucleophile, according to the hard and soft acids and bases theory (HSAB theory[13]). The experimental results interpreted with these theoretical principles indicate that the exocyclic benzylic position of **1b** is a softer electrophilic site when compared to the reactive endocyclic positions, a difference that can be explained by the "softening" influence of the neighboring π-system of the phenyl group. Hard nucleophiles, such as the methanolate ion, therefore preferentially attack only the bridgehead positions, while any softer or borderline nucleophile attacks both the bridgehead and the benzylic position, giving a mixture of **3** and **4** (Fig. 1).



Nucleophile	Benzylation / Ring-opening ratio
Methanolate	0.00
Phthalimidate	0.22
Phenolate	0.41
p-Methoxyphenolate	0.47
p-Propionylphenolate	0.52
6-Bromo-2-naphtholate	0.52
2,6-Dimethylphenolate	0.54
Tetrahydroborate	0.61
Benzenethiolate	0.75
Benzothiazole-2-thiolate	1.00

Fig. 1 Sites of the *N*-benzyl-DABCO ion reactive toward nucleophiles and the selectivity of various nucleophiles.

Furthermore, the reaction with the *S*-nucleophiles, which are known to be considerably more nucleophilic than phenolates, proceeded well even at 100 °C. Thus, lower temperatures can be used with more reactive nucleophiles. It is interesting to note that the nucleophilic substitution applying $NaBH_4$ proceeded well in diglyme at the reflux temperature and *N*-ethylpiperazine **3j** was obtained as a result. The nucleophilic reductive dealkylation of tetraalkylammonium salts with $NaBH_4$ was otherwise reported previously to occur in solvents like HMPA, DMSO or sulfolane.[14] The reactions of the phenylpropyl DABCO salt **1d** proceeded, as expected, to give piperazines **3m** and **3n** from the corresponding phenols. Similarly, the pentamethylene linked bisammonium salt **1e** gave the symmetrical bispiperazine **3o** with an isolated yield of 62%.

From the results thus obtained (Table 1), it is also evident that only the benzyl derivative **1b** gives the benzylated phenol and related compounds, whereas the other starting compounds **1** did not result in any alkylated by-products. These reactions could be dependent on several factors (from the *N*-alkyl-DABCO substituent, the reaction conditions, the anionic part of the substrate, *etc.*). However, some previous results,[10a] where the same phenomenon was observed with *N*-benzylquinuclidinium bromide and various nucleophiles, yielding a related mixture of products to that in our case, might be evidence that the counter ion has no significant effect in these reactions. On this basis one might conclude that the nature of the alkyl group on the DABCO is the main factor in the distribution of products under our conditions.

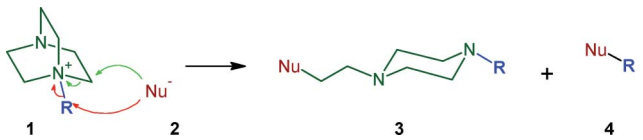
Finally, the ring-opening reaction was evaluated as a one-pot modification to prepare 1-alkyl-4-(2-phenoxyethyl)piperazines directly from the DABCO using a variety of alkylating reagents and phenols. The *N*-alkylation of the DABCO was first performed in PEG with the reaction time and temperature depending on the alkyl halide or sulfonate reactivity. The conditions for this *N*-alkylation step are listed in Table 2. The required temperature was therefore chosen arbitrarily; when monitoring the reaction by HPLC indicated the consumption of the alkyl halide, the phenol and K_2CO_3 were added and the reaction mixture was heated at 140 °C for 4 h. The reaction work up was simplified as much as possible when it was observed that a pure product could be obtained by a simple extraction procedure, yielding the products as crystalline hydrochloride salts rather than the free-base amines that are commonly less manageable viscous liquids or resinous materials. Such isolation makes the use of chromatographic separation unnecessary and is thus perfectly suited for larger-scale preparations.

When using primary alkyl halides the isolated yields of piperazines were moderate to good (31–79%), but the two secondary halides employed (**5i** and **5j**) only gave low yields. Additionally, the alkyl halides, prone to any type of elimination reactions, gave either complex mixtures of products or very low yields in the reaction applying phenols (not shown in Table 2). For example, 2-phenylethyl bromide gave only very low yields of 1-phenethyl-4-(2-phenoxyethyl)piperazine dihydrochloride additionally contaminated with impurities. Similarly, nopol tosylate,[15] a terpenoid homoallylic tosylate, gave no expected product on account of its elimination products. It is thus quite obvious and to be expected that such a susceptibility to elimination is the major limitation on the scope of these reactions. The troublesome alkyl halides or sulfonates seem to be those containing relatively acidic β-hydrogens or the ones where the elimination forms additional multiple-bond conjugations. It is also important to consider the susceptibility of the latter formed quaternary ammonium salts to the Hofmann elimination (governed by Hofmann's rules).[16]

Many alkyl halides and sulfonates are widely available for use as starting materials, but the less common ones often have to be prepared from the corresponding alcohols. The development of an alternative, one-pot methodology that enables the direct use of primary alcohols as starting materials would, therefore, be particularly advantageous. Looking at the nature of the reactants it soon appears obvious that the alcohols can be activated *in situ* by esterification with tosyl chloride (TsCl), with the DABCO playing the roles of both the base at the beginning and the substrate for the *N*-alkylation in the latter step of the reaction toward the reactive ammonium salts. Here, PEG could not be used as a solvent, because it is an alcohol and thus itself reactive toward tosyl chloride. Therefore, diglyme was used instead. The primary alcohol was first tosylated with tosyl chloride at room temperature in the presence of the DABCO, then K_2CO_3 was added and the mixture was heated for the *N*-alkylation of the DABCO to complete. At this point the phenol was added and the ring-opening reaction promoted by heating at the reflux temperature (Scheme 4). This adaptation enabled the direct synthesis of 1,4-disubstituted piperazines from primary alcohols, DABCO and phenols. This one-pot protocol was first checked on 3-phenylpropanol to give 1-(2-phenoxyethyl)-4-(3-phenylpropyl)piperazine (**3m**) in a 60% yield, which is surprisingly better than the 41% yield obtained from the direct reaction of phenol with **1d** in PEG (Table 1, entry 13).

This protocol was then exemplified by the facile synthesis of compound **8**, a prototype for a series of potential dopamine reuptake inhibitors, which can be considered as ether isosteres

Table 1 Reactions of *N*-alkylated DABCO ammonium salts with phenols and other nucleophiles



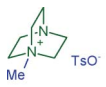
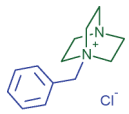
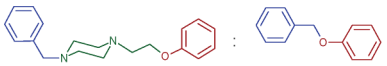
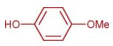
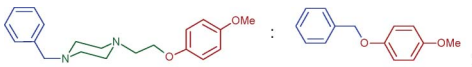
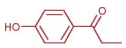
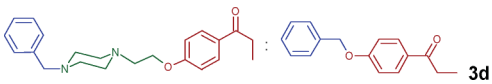
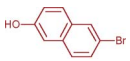
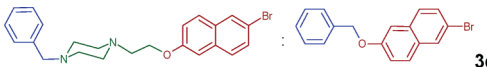
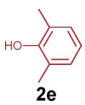
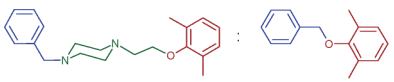
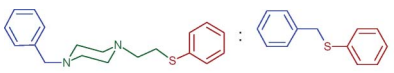
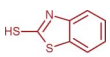
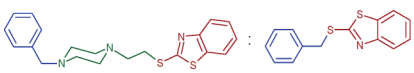
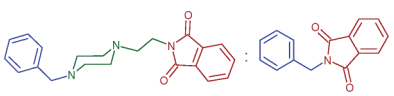
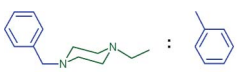
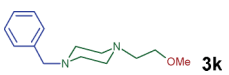
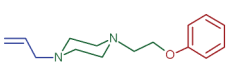
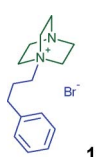
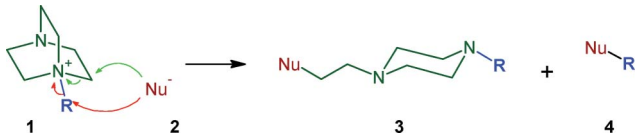
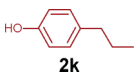
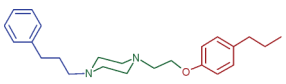
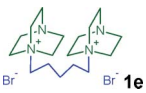
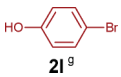
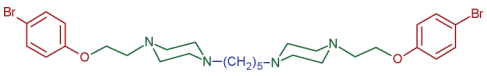
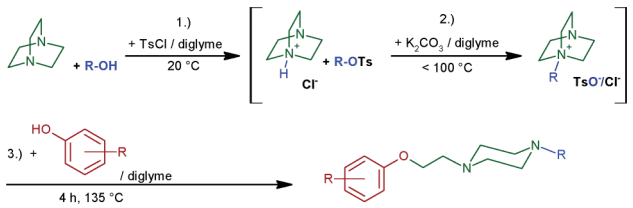
	N-alkyl-DABCO halide or tosylate (**1**)	Nucleophile (**2**; NuH/K_2CO_3, NuK, or NuNa)	Product(s)	Ratio **3** : **4** (isolated yields)[a]
1	 **1a**	 **2a**	 **3a**	100 (63%) : 0[b]
2	 **1b**	 **2a**	 **3b : 4b**	71 (53%) : 29 (22%)
3		 **2b**	 **3c : 4c**	68 (43%) : 32 (16%)
4		 **2c**	 **3d : 4d**	66 (54%) : 34 (29%)
5		 **2d**	 **3e : 4e**	66 (44%) : 34 (19%)
6		 **2e**	 **3f : 4f**	65 (55%) : 35 (26%)
7		 **2f**	 **3g : 4g**	57 (52%) : 43 (25%)[c]
8		 **2g**	 **3h : 4h**	50 (17%) : 50 (19%)[c]
9		 **2h**	 **3i : 4i**	82 (44%) : 18 (9%)[d]
10	$NaBH_4$ **2i**		 **3j : 4j**	62 (41%) : 38[d,e,f]
11	NaOMe **2j**		 **3k**	100 (60%) : 0[d,e]
12	 **1c**	 **2a**	 **3l**	100 (38%) : 0
13	 **1d**	 **2a**	 **3m**	100 (41%) : 0

Table 1 (*Contd.*)

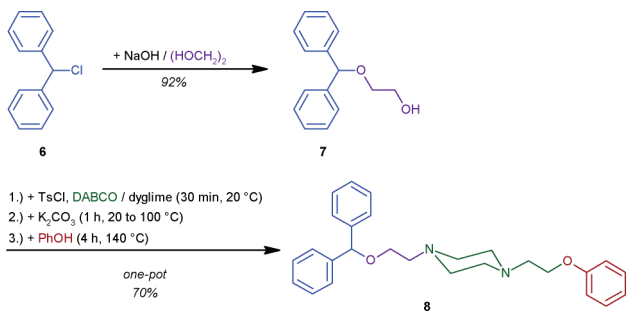


	N-alkyl-DABCO halide or tosylate (**1**)	Nucleophile (**2**; NuH/K_2CO_3, NuK, or NuNa)	Product(s)	Ratio **3** : **4** (isolated yields)[a]
14		 **2k**	 **3n**	100 (77%) : 0
15	 **1e**	 **2l**[g]	 **3o**	100 (62%) : 0

[a] The ratio of products was determined by analyzing the crude reaction mixture extract using ^{1}H NMR spectroscopy. Piperazines **3** were isolated as hydrochlorides. Reactions were conducted for 4 h at 140 °C, unless otherwise specified. [b] The reactions with *N*-methyl-DABCO tosylate were conducted at 150 °C. [c] Reactions with thiols were conducted at a lower temperature (100 °C) due to their higher reactivity. [d] No added base was used in these reactions. [e] Diglyme was used as the solvent for the reactions with NaOMe and $NaBH_4$. [f] Due to its volatility, the toluene formed in the reaction was not isolated, but only identified chromatographically with an HPLC analysis of the reaction mixture and the ratio of products was quantified by ^{1}H NMR. [g] A 1 : 2 ratio of **1e** *vs.* **2l** was used in this experiment.



Scheme 4 The one-pot protocol for the synthesis of 1,4-disubstituted piperazines directly from primary alcohols.



Scheme 5 Synthesis of a potentially bioactive 1,4-disubstituted piperazine utilizing the one-pot approach by *in situ* primary alcohol activation *via* tosylation.

of Vanoxerine (Scheme 3). The piperazine **8** was prepared in two steps with a 64% overall yield, first by the solvolysis of benzhydryl chloride (**6**) in ethylene glycol to give 2-(benzhydryloxy)ethanol (**7**) followed by the above-described, one-pot protocol for *O*-tosylation, DABCO alkylation and nucleophilic ring-opening with phenol (Scheme 5).

This simple synthetic approach with its modular nature would thus allow the preparation of an interesting library of potentially bioactive compounds. The activity of a variety of 1,4-dialkylpiperazine-based dopamine reuptake inhibitors was already studied,[17] but to the best of our knowledge 1-(2-(benzhydryloxy)ethyl)-4-(2-aryloxyethyl)piperazines, such as represented by **8**, have not yet been evaluated for this activity, though other bioactivities have been claimed for the compounds of this structural class.[18]

Conclusions

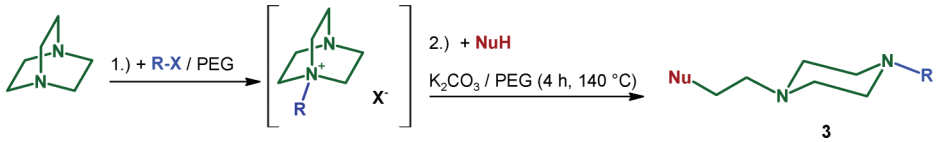
The nucleophilic ring-opening reaction of DABCO-derived quaternary ammonium salts represents a practical synthetic approach to some 1,4-dialkyl piperazines. The reaction conditions are especially convenient when using PEG or diglyme as the solvents. This is of importance when the reaction is applied to the 1-alkyl-1-azoniabicyclo[2.2.2]octanes, because the latter are less reactive than their 1-aryl-substituted counterparts. One-pot modifications enable very simple syntheses of some piperazines, starting from primary alkyl halides, sulfonates or *in situ* activated alcohols, applying DABCO and nucleophilic reagents (phenols, benzenethiols, imides, *etc.*). Several 1-phenoxyethyl-4-alkylpiperazines and related derivatives were synthesized using these simple protocols.

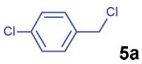
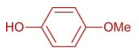
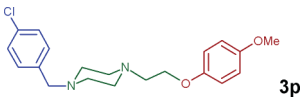
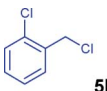
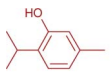
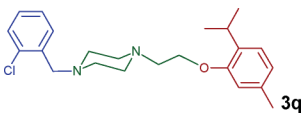
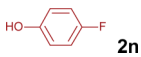
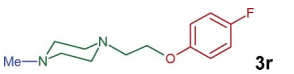
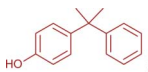
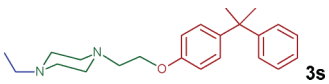
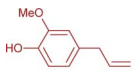
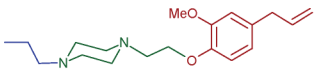
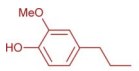
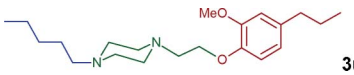
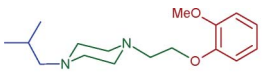
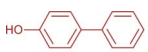
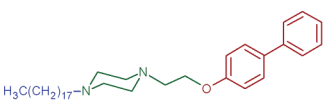
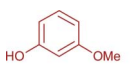
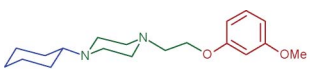
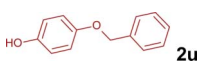
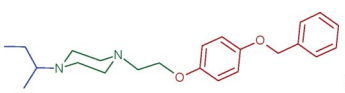
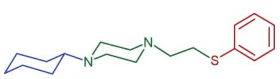
Experimental

General

NMR spectra were recorded at 29 °C on a Bruker Avance DPX 300-MHz spectrometer with tetramethylsilane (TMS) internal standard for DMSO-d_6 and $CDCl_3$, or sodium 3-(trimethylsilyl)-1-propanesulfonate for D_2O. *J* values are given in Hz. The ammonium salts **1** exhibited otherwise seldom observed ^{13}C–^{14}N coupling in the ^{13}C NMR spectra (75 MHz, D_2O), which can however be characteristic for some ammonium compounds with the symmetry of substitution around the nitrogen atom.[19] Melting points are uncorrected and were measured on a Kofler micro hot stage. High-performance liquid chromatography (HPLC) analyses were performed using a Nucleosil C-18 column with an acetonitrile/water mobile phase and UV detection at 254 nm

Table 2 Syntheses of 1,4-disubstituted piperazines from alkyl halides (or tosylate), DABCO and phenols (or benzenethiol) by using a one-pot protocol



	Alkyl halide or tosylate (R–X)	Nucleophile (NuH)	DABCO alkylation conditions	Product **3** (as dihydrochlorides)	Yield (%)
1	 **5a**	 **2b**	15 min, 70 °C	 **3p**	51
2	 **5b**	 **2m**	15 min, 70 °C	 **3q**	50
3	**MeOTs 5c**	 **2n**	25 min, 25 °C	 **3r**	56
4	**CH_3CH_2I 5d**	 **2o**	1 h, 25 °C	 **3s**	31
5	**$CH_3CH_2CH_2Br$ 5e**	 **2p**	1 h, 70 °C	 **3t**	40
6	**$CH_3(CH_2)_4Br$ 5f**	 **2q**	30 min, 100 °C	 **3u**	56
7	**$(CH_3)_2CHCH_2Br$ 5g**	 **2r**	30 min, 100 °C	 **3v**	60
8	**$CH_3(CH_2)_{17}Cl$ 5h**	 **2s**	2 h, 100 °C	 **3w**	79
9	 **5i**	 **2t**	3 h, 90 °C	 **3x**	13
10	**$CH_3CH_2CHBrCH_3$ 5j**	 **2u**	6 h, 90 °C	 **3y**	17
11	 **5i**	 **2f**	3 h, 90 °C	 **3z**	29

or 210 nm (for the detection of alkyl bromides and iodides). MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Potassium carbonate was finely ground and dried at 150 °C for 12 h. Polyethyleneglycol (PEG) with the average molecular mass of 400 was used (PEG400). The ammonium salt **1b** was prepared by the published method.[20] The benzylation products **4b**, **4d** and **4e** were identified by the comparison with authentic samples, while **4c**,[21] **4f**,[21] **4g**,[22] **4h**[23] and **4i**[24] by comparison of their spectroscopic and physical properties with the published data.

Synthesis of quaternary ammonium salts from DABCO

1-Methyl-1,4-diazabicyclo[2.2.2]octan-1-ium tosylate (1a). To a solution of DABCO (4.49 g, 40 mmol) in THF (60 mL) a solution of methyl *p*-toluenesulfonate (7.52 g, 40 mmol) in diisopropyl ether (40 mL) was added over the course of 1 h while stirring in an ice bath. After stirring for 2 h at rt, the precipitated product was filtered, washed with diisopropyl ether (3 × 15 mL) and dried under vacuum to give a hygroscopic white solid (10.50 g, 87%): mp 142–144 °C; IR (KBr) ν_{max}/cm^{-1} 1468, 1227, 1208, 1200, 1128; ^{1}H NMR (D_2O) δ 2.32 (s, 3H), 2.91 (s, 3H), 3.06 (t, J = 7.5, 6H),

3.24 (t, J = 7.5, 6H), 7.31 (d, J = 8.1, 2H), 7.65 (d, J = 8.2, 2H); ^{13}C NMR (D_2O) δ 20.9, 44.6, 51.90 (t, J = 4.5), 54.3 (t, J = 3.4), 125.8, 129.9, 140.3, 142.8; MS (ESI) m/z 127 ([M – TsO]$^+$), 120; HRMS (ESI) calcd for $C_7H_{15}N_2$ [M – TsO]$^+$ 127.1235, found 127.1237.

1-Allyl-1,4-diazabicyclo[2.2.2]octan-1-ium bromide (1c). To a solution of DABCO (6.17 g, 55 mmol) in THF (100 mL) allyl bromide (4.41 mL, 50 mmol) was slowly added while stirring at rt. An oil immediately started precipitating and then slowly solidified. The product was filtered, larger chunks crushed and washed with acetone (3 × 25 mL). The product was dried under vacuum to give a white solid (11.48 g, 98%): mp 117–121 °C; IR (KBr) ν_{max}/cm^{-1} 1644, 1464, 1430, 1400, 1373, 1323; ^{1}H NMR (D_2O) δ 3.19 (t, J = 7.5, 6H), 3.41 (t, J = 7.5, 6H), 3.90 (d, J = 7.5, 2H), 5.63–5.75 (m, 2H), 5.99 (m, 1H); ^{13}C NMR (D_2O) δ 44.7, 52.5 (t, J = 3.3), 67.0 (t, J = 3.3), 124.2, 129.5; MS (ESI) m/z 153 ([M – Br]$^+$); HRMS (ESI) calcd for $C_9H_{17}N_2$ [M – Br]$^+$ 153.1392, found 153.1386.

1-(3-Phenylpropyl)-1,4-diazabicyclo[2.2.2]octan-1-ium bromide (1d). A solution of DABCO (6.17 g, 55 mmol) and 3-phenylpropyl bromide (10.00 g, 50 mmol) in THF (60 mL) was left standing at rt for 3 days. The formed precipitate was then filtered and washed with ethyl acetate (3 × 10 mL) and petroleum ether (20 mL). The product was dried under vacuum to give a white crystalline product (14.59 g, 94%): mp 223–226 °C; Anal. Calcd for $C_{15}H_{23}N_2Br$: C 57.88, H 7.45, N 9.00. Found: C 58.01, H 7.72, N 8.96%; IR (KBr) ν_{max}/cm^{-1} 1599, 1495, 1456, 1416, 1385; ^{1}H NMR (D_2O) δ 2.02 (m, 2H), 2.66 (t, J = 7.4, 2H), 3.11 (t, J = 7.4, 6H), 3.18 (m, 2H), 3.27 (t, J = 7.4, 6H), 7.26–7.33 (m, 3H), 7.35–7.42 (m, 2H); ^{13}C NMR (D_2O) δ 23.4, 32.0, 44.6, 52.6 (t, J = 3.3), 64.3 (t, J = 3.1), 127.1, 129.1, 129.4, 140.9; MS (EI) m/z 231 ([M – Br]$^+$, 44), 217 (55), 117 (29), 91 (100), 70 (49).

1,1′-(Pentane-1,5-diyl)bis(1,4-diazabicyclo[2.2.2]octan-1-ium) dibromide (1e). A solution of DABCO (10.41 g, 90 mmol) and 1,5-dibromopentane (6.90 g, 30 mmol) in methanol (180 mL) was left stirring for 24 h at rt. The reaction mixture was then evaporated *in vacuo* to give a yellow resin, which was first triturated with warm acetone (100 mL), the acetone was then decanted and the resin dissolved in a minimal amount of propan-2-ol (30 mL). To this solution acetone (100 mL) was slowly added to precipitate the crude product. This was again triturated with warm acetone and decanted. The residue was dried under vacuum to give a yellowish product in the form of large chunks of solid (13.30 g, 98%): mp 210–214 °C; IR (KBr) ν_{max}/cm^{-1} 1634, 1620, 1464, 1100, 1057; ^{1}H NMR (D_2O) δ 1.43 (m, 2H), 1.86 (m, 4H), 3.19 (t, J = 7.4, 12H), 3.30 (m, 4H), 3.42 (t, J = 7.4, 12H); ^{13}C NMR (D_2O) δ 21.4, 23.2, 44.7, 52.6 (t, J = 3.3), 64.5 (t, J = 3.2); MS (ESI) m/z 407, 373, 375 ([M – Br]$^+$), 329 ([M – 2Br + Cl]$^+$), 222, 165, 147; HRMS (ESI) calcd for $C_{17}H_{34}N_4Cl$ [M – 2Br + Cl]$^+$ 329.2472, found 329.2480.

Synthesis of piperazines from *N*-alkyl-DABCO salts

General procedure. A slurry of 1-alkyl-1,4-diazabicyclo-[2.2.2]octan-1-ium halide or tosylate (5 mmol of **1a–d** or 2.5 mmol of **1e**), phenol (5 mmol) and K_2CO_3 (350 mg, 2.5 mmol) in PEG (3 mL) was stirred for 4 h at 140 °C (see Table 1 for exceptions). The reaction mixture was then diluted with water (60 mL), extracted with ethyl acetate (60 mL), and the extract was washed with NaOH(aq) (1 M, 2 × 30 mL) and water (30 mL). A sample of ethyl acetate solution was analyzed with ^{1}H NMR and HPLC to determine the ratio of products. The piperazine product was generally obtained by extraction in 0.5 M HCl(aq) (25 mL) and evaporation of the aqueous extract *in vacuo*. The residue was azeotropically dried by the repeated evaporation *in vacuo* from portions of propan-2-ol (2 × 10 mL). Piperazine products that precipitated as hydrochlorides insoluble in water were isolated by filtration instead. Neutral benzylated products **4** (when using **1b** as the starting material) were obtained by evaporating the leftover ethyl acetate solution and further purification by recrystallization or chromatography.

1-Methyl-4-(2-phenoxyethyl)piperazine dihydrochloride (3a). White crystalline powder (930 mg, 63%); mp 241–245 °C, dec.; IR (KBr) ν_{max}/cm^{-1} 1595, 1494, 1452, 1416, 1240; ^{1}H NMR (D_2O) δ 3.02 (s, 3H), 3.40–4.10 (m, 10H), 4.40 (t, J = 4.8, 2H), 7.04 (m, 3H), 7.37 (m, 2H); ^{13}C NMR (D_2O) δ 43.3, 49.4, 50.5, 56.1, 61.8, 115.1, 122.5, 130.4, 157.5; MS (ESI) m/z 221 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{13}H_{21}N_2O$ [M – HCl_2]$^+$ 221.1654, found 221.1660.

1-Benzyl-4-(2-phenoxyethyl)piperazine dihydrochloride (3b). Off-white crystalline powder (970 mg, 53%); mp 204–208 °C; IR (KBr) ν_{max}/cm^{-1} 1602, 1587, 1495, 1460, 1422; ^{1}H NMR (D_2O) δ 3.63–3.95 (m, 10H), 4.45 (t, J = 4.7, 2H), 4.53 (s, 2H), 7.03–7.15 (m, 3H), 7.43 (m, 2H), 7.57 (m, 5H); ^{13}C NMR (D_2O) δ 48.3, 49.4, 56.1, 61.0, 61.7, 115.1, 122.6, 127.8, 129.9, 130.4, 131.1, 131.7, 157.5; MS (ESI) m/z 297 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{19}H_{25}N_2O$ [M – HCl_2]$^+$ 297.1967, found 297.1973.

1-Benzyl-4-(2-(4-methoxyphenoxy)ethyl)piperazine dihydrochloride (3c). White crystalline powder (860 mg, 43%); mp 186–189 °C; IR (KBr) ν_{max}/cm^{-1} 1619, 1512, 1458, 1444, 1232; ^{1}H NMR (D_2O) δ 3.55–3.82 (m, 10H), 3.69 (s, 3H), 4.28 (t, J = 4.6, 2H), 4.44 (s, 2H), 6.91 (AA′BB′, 4H), 7.48 (m, 5H); ^{13}C NMR (D_2O) δ 48.3, 49.4, 56.2, 56.3, 60.9, 62.4, 115.6, 116.4, 127.7, 129.9, 131.1, 131.7, 151.9, 154.2; MS (ESI) m/z 327 ([M – HCl_2]$^+$), 198, 196, 158, 141, 77; HRMS (ESI) calcd for $C_{20}H_{27}N_2O_2$ [M – HCl_2]$^+$ 327.2073, found 327.2071.

1-(4-(2-(4-Benzylpiperazin-1-yl)ethoxy)phenyl)propan-1-one dihydrochloride (3d). White crystalline powder (1150 mg, 54%); mp 200–204 °C; IR (KBr) ν_{max}/cm^{-1} 1680, 1601, 1458, 1260, 1227; ^{1}H NMR (DMSO-d_6) δ 1.07 (t, J = 7.2, 3H), 2.98 (q, J = 7.2, 2H), 3.55 (m, 2H), 3.66 (m, 2H), 3.76 (m, 4H), 4.45 (bs, 2H), 4.54 (t, J = 4.2, 2H), 7.11 (AA′XX′, J = 9.0, 2H), 7.46 (m, 3H), 7.69 (m, 2H), 7.96 (AA′XX′, J = 9.0, 2H), 12.56 (bs, 2H), 11.00–13.00 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 8.2, 30.8, 46.9, 48.1, 54.1, 57.9, 62.5, 114.5, 128.7, 129.1, 129.5, 129.9, 130.1, 131.4, 160.9, 198.8; MS (ESI) m/z 353 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{22}H_{29}N_2O_2$ [M-HCl_2]$^+$ 353.2229, found 353.2229.

1-Benzyl-4-{2-[(6-bromonaphthalen-2-yl)oxy]ethyl}piperazine dihydrochloride (3e). Colorless scales (1100 mg, 44%): mp 232–236 °C; Anal. Calcd for $C_{23}H_{25}BrN_2O$ ×2HCl: C 55.44, H 5.46, N 5.62. Found: C 55.33, H 5.48, N 5.50%; IR (KBr) ν_{max}/cm^{-1} 1628, 1590, 1499, 1442, 1366, 1255, 1206; MS (ESI) m/z 428, 427 ([M – HCl_2]$^+$), 425; HRMS (ESI) calcd for $C_{23}H_{26}BrN_2O$ [M – HCl_2]$^+$ 425.1228, found 425.1238. The dihydrochloride salt had a low solubility in D_2O, $CDCl_3$ and DMSO. The NMR analysis was therefore performed on the free-base amine: ^{1}H NMR ($CDCl_3$) δ 2.51 (m, 4H), 2.64 (m, 4H), 2.87 (t, J = 5.9, 2H), 3.51 (s, 2H), 4.19

(t, J = 5.9, 2H), 7.08 (d, J = 2.4, 1H), 7.15 (dd, J = 2.4, 9.0, 1H), 7.20–7.34 (m, 5H), 7.47 (dd, J = 1.9, 8.8, 1H), 7.56 (d, J = 8.8, 1H), 7.61 (d, J = 9.0, 1H), 7.89 (d, J = 1.9, 1H); ^{13}C NMR ($CDCl_3$) δ 41.0, 53.0, 53.7, 57.1, 63.0, 106.7, 117.0, 120.0, 127.0, 128.2, 128.3, 128.4, 129.2, 129.56, 129.60, 130.0, 133.0, 138.1, 157.0.

1-Benzyl-4-[2-(2,6-dimethylphenoxy)ethyl]piperazine dihydrochloride (3f). White crystalline powder (1100 mg, 55%); mp 205–209 °C; Anal. Calcd for $C_{21}H_{28}N_2O{\times}2HCl{\times}\frac{1}{2}H_2O$: C 62.07, H 7.69, N 6.89. Found: C 62.34, H 7.95, N 7.23%; IR (KBr) ν_{max}/cm^{-1} 1478, 1454, 1431, 1412, 1373, 1330, 1195; ^{1}H NMR (D_2O) δ 2.20 (s, 6H), 3.63–3.90 (m, 10H), 4.19 (t, J = 4.9, 2H), 4.47 (s, 2H), 6.97–7.07 (m, 3H), 7.51 (s, 5H); ^{13}C NMR (D_2O) δ 16.1, 48.3, 49.6, 57.1, 61.0, 65.3, 125.5, 127.8, 129.6, 129.9, 131.2, 131.3, 131.7, 155.0; MS (ESI) m/z 325 ([M – HCl_2]$^+$), 196, 158, 141, 77; HRMS (ESI) calcd for $C_{21}H_{29}N_2O$ [M – HCl_2]$^+$ 325.2280, found 325.2274.

1-Benzyl-4-[2-(phenylthio)ethyl]piperazine dihydrochloride (3g). White crystalline powder (1000 mg, 52%); mp 188–192 °C, dec.; Anal. Calcd for $C_{19}H_{24}N_2S{\times}2HCl$: C 59.21, H 6.80, N 7.27. Found: C 58.98, H 6.99, N 7.20%; IR (KBr) ν_{max}/cm^{-1} 1581, 1482, 1439, 1402, 1372; ^{1}H NMR (D_2O) δ 3.36 (m, 2H), 3.47 (m, 2H), 3.67 (m, 8H), 4.50 (s, 2H), 7.35–7.63 (m, 10H); ^{13}C NMR (D_2O) δ 27.8, 48.4, 49.2, 55.9, 60.9, 127.8, 128.4, 129.9, 130.1, 131.1, 131.3, 131.7, 132.8; MS (ESI) m/z 313 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{19}H_{25}N_2S$ [M – HCl_2]$^+$ 313.1738, found 313.1747.

2-{[2-(4-Benzylpiperazin-1-yl)ethyl]thio}benzo[*d*]thiazole dihydrochloride (3h). White crystalline powder (365 mg, 17%); mp 191–195 °C; IR (KBr) ν_{max}/cm^{-1} 1457, 1428, 1403, 1372; ^{1}H NMR (D_2O) δ 3.52–3.73 (m, 12H), 4.42 (s, 2H), 7.33 (t, J = 7.6, 1H), 7.39–7.56 (m, 6H), 7.69 (d, J = 8.0, 1H), 7.79 (d, J = 8.0, 1H); ^{13}C NMR (D_2O) δ 48.5, 49.4, 56.1, 60.90, 60.94, 121.1, 122.2, 125.6, 127.2, 127.7, 129.9, 131.1, 131.7, 135.3, 152.2, 166.9; MS (ESI) m/z 370 ([M – HCl_2]$^+$), 203, 196, 158, 141, 113; HRMS (ESI) calcd for $C_{20}H_{24}N_3S_2$ [M – HCl_2]$^+$ 370.1406, found 370.1402.

2-[2-(4-Benzylpiperazin-1-yl)ethyl]isoindoline-1,3-dione dihydrochloride (3i). Gray crystalline powder (920 mg, 44%); mp 196–199 °C; IR (KBr) ν_{max}/cm^{-1} 1710, 1435, 1421, 1402, 1389; ^{1}H NMR (D_2O) δ 3.53–3.86 (m, 10H), 4.05 (t, J = 5.8, 2H), 4.42 (s, 2H), 7.45 (m, 5H), 7.75 (s, 4H); ^{13}C NMR (D_2O) δ 32.6, 48.4, 49.3, 55.1, 60.9, 124.1, 127.7, 129.9, 131.1, 131.5, 131.7, 135.5, 170.3; MS (ESI) m/z 350 ([M – HCl_2]$^+$), 196, 158, 141; HRMS (ESI) calcd for $C_{21}H_{24}N_3O_2$ [M – HCl_2]$^+$ 350.1869, found 350.1866.

1-Allyl-4-(2-phenoxyethyl)piperazine dihydrochloride (3l). White crystalline powder (600 mg, 38%); mp 193–198 °C; IR (KBr) ν_{max}/cm^{-1} 1599, 1495, 1444, 1416, 1401; ^{1}H NMR (D_2O) δ 3.60–3.91 (m, 10H), 3.95 (d, J = 6.9, 2H), 4.46 (t, J = 4.8, 2H), 5.69 (m, 2H), 5.96 (m, 1H), 7.09 (m, 3H), 7.42 (m, 2H); ^{13}C NMR (D_2O) δ 48.2, 49.5, 56.2, 59.3, 61.7, 115.1, 122.6, 124.8, 128.6, 130.4, 157.5; MS (ESI) m/z 247 ([M – HCl_2]$^+$), 205, 164, 99; HRMS (ESI) calcd for $C_{15}H_{23}N_2O$ [M – HCl_2]$^+$ 247.1810, found 247.1820.

1-(2-Phenoxyethyl)-4-(3-phenylpropyl)piperazine dihydrochloride (3m). White crystalline powder (1183 mg, 41%); mp 203–206 °C; IR (KBr) ν_{max}/cm^{-1} 1597, 1497, 1452, 1292, 1246; ^{1}H NMR (D_2O) δ 2.12 (m, 2H), 2.77 (t, J = 7.4, 2H), 3.31 (m, 2H), 3.62–3.92 (m, 10H), 4.44 (t, J = 4.8, 2H), 7.04–7.16 (m, 3H), 7.29–7.47 (m, 7H); ^{13}C NMR (D_2O) δ 25.4, 32.0, 48.9, 49.4, 56.2, 56.8, 61.7, 115.1, 122.6, 127.1, 129.0, 129.3, 130.4, 140.7, 157.5; MS (ESI) m/z 325 ([M – HCl_2]$^+$), 319, 293, 282, 236; HRMS (ESI) calcd for $C_{21}H_{29}N_2O$ [M – HCl_2]$^+$ 325.2280, found 325.2281.

1-(3-Phenylpropyl)-4-[2-(4-propylphenoxy)ethyl]piperazine dihydrochloride (3n). White crystalline powder (1700 mg, 77%); mp 193–197 °C; Anal. Calcd for $C_{24}H_{34}N_2O{\times}2HCl{\times}1/3H_2O$: C 64.71, H 8.30, N 6.29. Found: C 64.76, H 8.66, N 6.54%; IR (KBr) ν_{max}/cm^{-1} 1609, 1510, 1450, 1374, 1237; ^{1}H NMR (DMSO-d_6) δ 0.87 (t, J = 7.3, 3H), 1.55 (m, 2H), 2.06 (m, 2H), 2.49 (m, 2H), 2.66 (t, J = 7.7, 2H), 3.44–3.91 (m, 12H), 4.42 (d, J = 4.5, 2H), 6.93 (AA′XX′, J = 8.4, 2H), 7.12 (AA′XX′, J = 8.4, 2H), 7.17– 7.35 (m, 5H), 12.34 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 13.4, 24.2, 24.6, 31.8, 36.3, 47.8, 48.5, 54.5, 55.2, 62.2, 114.5, 126.0, 128.1, 128.3, 129.1, 134.9, 140.4, 155.4; MS (ESI) m/z 367 ([M – HCl_2]); HRMS (ESI) calcd for $C_{24}H_{35}N_2O$ [M – HCl_2]$^+$ 367.2749, found 367.2763.

1,5-bis{4-[2-(4-Bromophenoxy)ethyl]piperazin-1-yl}pentane tetrahydrochloride (3o). Off-white crystalline powder (975 mg, 62%); mp 235–242 °C, dec.; Anal. Calcd for $C_{29}H_{42}Br_2N_4O_2{\times}4HCl{\times}H_2O$: C 43.41; H 6.03; N 6.98. Found: C 43.21, H 5.85, N 7.00%; IR (KBr) ν_{max}/cm^{-1} 1490, 1459, 1447, 1413, 1373, 1235; ^{1}H NMR (D_2O) δ 1.45 (m, 2H), 1.82 (m, 4H), 3.30 (t, J = 8.1, 4H), 3.55–3.90 (m, 20H), 4.38 (t, J = 4.8, 4H), 6.94 (AA′XX′, J = 9.0, 4H), 7.49 (AA′XX′, J = 9.0, 4H); ^{13}C NMR (D_2O) δ 23.1, 23.3, 49.0, 49.4, 56.1, 56.9, 62.1, 114.1, 117.0, 132.9, 156.8; MS (ESI) m/z 641, 639, 637 ([M – H_3Cl_4]$^+$), 355, 353, 321, 320, 319; HRMS (ESI) calcd for $C_{29}H_{43}Br_2N_4O_2$ [M – H_3Cl_4]$^+$ 637.1753, found 637.1752.

1-Benzyl-4-ethylpiperazine dihydrochloride (3j). A mixture of **1b** (1.23 g, 5 mmol) and $NaBH_4$ (0.39 g, 10 mmol) in diglyme (10 mL) was stirred for 6 h under reflux. A sample of the reaction mixture was analyzed with ^{1}H NMR and HPLC to determine the ratio of **3j** and toluene (**4j**) formed. The reaction mixture was diluted with water (80 mL), extracted with ethyl acetate (60 mL), washed with water (3 × 50 mL), the organic phase was back extracted with 0.5 M HCl(aq) (25 mL) and this aqueous solution evaporated *in vacuo*. The residue was recrystallized from ethanol to give a white crystalline solid (525 mg, 41%): mp 247–250 °C (lit.[25] 250 °C, dec.); IR (KBr) ν_{max}/cm^{-1} 1638 (br), 1474, 1457, 1449, 1441, 1420; ^{1}H NMR (D_2O) δ 1.40 (t, J = 7.3, 3H), 3.40 (q, J = 7.3, 2H), 3.46–3.95 (m, 8H), 4.54 (s, 2H), 7.59 (m, 5H); ^{13}C NMR (D_2O) δ 9.0, 48.5, 48.6, 52.8, 60.9, 127.9, 129.9, 131.1, 131.7.

1-Benzyl-4-(2-methoxyethyl)piperazine dihydrochloride (3k). A mixture of **1b** (1.23 g, 5 mmol) and $NaOCH_3$ (0.55 g, 10 mmol) in diglyme (10 mL) was stirred for 4 h at 140 °C. A sample of the reaction mixture was analyzed with ^{1}H NMR. The product was isolated as described above to give a white crystalline solid (920 mg, 60%): mp 193–196 °C, dec.; IR (KBr) ν_{max}/cm^{-1} 1604, 1498, 1455, 1379; ^{1}H NMR (D_2O) δ 3.41 (s, 3H), 3.54 (t, J = 5.0, 2H), 3.62–3.79 (m, 8H), 3.82 (t, J = 5.0, 2H), 4.52 (s, 2H), 7.56 (m, 5H); ^{13}C NMR (D_2O) δ 48.3, 49.2, 56.3, 58.9, 60.9, 65.5, 127.9, 129.9, 131.1, 131.7; MS (ESI) m/z 235 ([M – HCl_2]$^+$), 214, 196, 158, 141; HRMS (ESI) calcd for $C_{14}H_{23}N_2O$ [M – HCl_2]$^+$ 235.1810, found 235.1800.

Synthesis of piperazines using a one-pot procedure from alkyl halides or tosylates, DABCO and phenols

General procedure. DABCO (720 mg, 6.25 mmol) was dissolved in PEG (3 mL) by applying heat, if necessary. The alkyl halide or tosylate (5 mmol) was added to the solution at rt and the homogenous mixture was stirred under the conditions described in Table 2 (generally until the reaction monitoring indicated the consumption of the alkylating reagent). The phenol (5 mmol) and K_2CO_3 (415 mg, 3 mmol) was added and the reaction continued for 4 h at 140 °C. The reaction mixture was then diluted with water (60 mL) and the piperazine product was isolated as described in the general procedure for the synthesis of piperazines from *N*-alkyl-DABCO salts.

1-(4-Chlorobenzyl)-4-[2-(4-methoxyphenoxy)ethyl]piperazine dihydrochloride (3p). White crystalline powder (1100 mg, 51%): mp 211–216 °C; IR (KBr) ν_{max}/cm^{-1} 1600, 1508, 1464, 1444; ^{1}H NMR (D_2O) δ 3.65–3.87 (m, 10H), 3.83 (s, 3H), 4.41 (t, J = 4.8, 2H), 4.53 (s, 2H), 7.03 (AA′BB′, 4H), 7.56 (AA′BB′, 4H); ^{13}C NMR (D_2O) δ 48.4, 49.4, 56.2, 56.3, 60.1, 62.4, 115.6, 116.3, 126.5, 129.9, 133.2, 136.6, 151.9, 154.2; MS (ESI) m/z 361 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{20}H_{26}ClN_2O_2$ [M – HCl_2]$^+$ 361.1683, found 361.1690.

1-(2-Chlorobenzyl)-4-(2-(2-isopropyl-5-methylphenoxy)ethyl)-piperazine dihydrochloride (3q). White crystalline powder (1150 mg, 50%); mp 188–191 °C; Anal. Calcd for $C_{23}H_{31}ClN_2O$×2HCl: C 60.07, H 7.23, N 6.09. Found: C 60.01, H 7.51, N 5.99%; IR (KBr) ν_{max}/cm^{-1} 1611, 1577, 1506, 1445, 1414; ^{1}H NMR (D_2O) δ 1.17 (d, J = 6.9, 6H), 2.32 (s, 3H), 3.25 (sept, J = 6.9, 1H), 3.65–3.87 (m, 10H), 4.42 (t, J = 4.8, 2H), 4.61 (s, 2H), 6.90 (s, 1H), 6.94 (d, J = 7.8, 1H), 7.28 (d, J = 7.8, 1H), 7.45–7.65 (m, 4H); MS (ESI) m/z 387 ([M – HCl_2]$^+$), 345; HRMS (ESI) calcd for $C_{23}H_{32}ClN_2O$ [M – HCl_2]$^+$ 387.2203, found 387.2200. The dihydrochloride salt dissolved poorly in D_2O or DMSO. The ^{13}C NMR analysis was therefore performed on the free-base amine: ^{13}C NMR ($CDCl_3$) δ 21.5, 23.0, 26.7, 53.4, 54.0, 57.6, 59.4, 66.6, 112.6, 121.4, 126.1, 126.7, 128.3, 129.6, 130.9, 134.3, 134.5, 136.1, 136.5, 156.0.

1-[2-(4-Fluorophenoxy)ethyl]-4-methylpiperazine dihydrochloride (3r). White crystalline powder (870 mg, 56%); mp 192–195 °C; IR (KBr) ν_{max}/cm^{-1} 1630, 1512, 1472, 1456, 1252, 1206; ^{1}H NMR (D_2O) δ 3.09 (s, 3H), 3.58–4.12 (m, 8H), 3.80 (t, J = 4.7, 2H), 4.44 (t, J = 4.7, 2H), 7.00–7.20 (m, 4H); ^{13}C NMR (D_2O) δ 43.4, 49.5, 50.5, 56.2, 62.4, 116.4, 116.6 (d, J = 14.7), 153.7 (d, J = 2.0), 158.1 (d, J = 236.8); MS (ESI) m/z 239 ([M – HCl_2]$^+$), 202, 160; HRMS (ESI) calcd for $C_{13}H_{20}FN_2O$ [M – HCl_2]$^+$ 239.1560, found 239.1553.

1-Ethyl-4-{2-[4-(2-phenylpropan-2-yl)phenoxy]ethyl}piperazine hydrochloride (3s). White crystalline powder (665 mg, 31%); mp 207–211 °C; IR (KBr) ν_{max}/cm^{-1} 1610, 1511, 1447 (br), 1245, 1186; ^{1}H NMR (D_2O) δ 1.64 (t, J = 7.3, 3H), 1.70 (s, 6H), 3.64 (q, J = 7.3, 2H), 3.75–4.20 (m, 10H), 4.50 (t, J = 4.3, 2H), 7.12 (d, J = 8.7, 2H), 7.26–7.43 (m, 7H); ^{13}C NMR (D_2O) δ 10.6, 32.2, 43.8, 49.8, 51.0, 54.4, 57.7, 63.6, 116.3, 127.6, 128.5, 129.8, 130.1, 146.0, 152.6, 157.1; MS (ESI) m/z 353 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{23}H_{33}N_2O$ [M – HCl_2]$^+$ 353.2593, found 353.2588.

1-[2-(4-Allyl-2-methoxyphenoxy)ethyl]-4-propylpiperazine dihydrochloride (3t). Off-white crystalline powder (790 mg, 40%); mp 170–174 °C; IR (KBr) ν_{max}/cm^{-1} 1638, 1594, 1513, 1462, 1450; ^{1}H NMR (D_2O) δ 1.05 (t, J = 7.3, 3H), 1.85 (m, 2H), 3.34 (m, 4H), 3.46–4.24 (m, 8H), 3.83 (t, J = 4.3, 2H), 3.90 (s, 3H), 4.45 (t, J = 4.3, 2H), 5.12 (m, 2H), 6.03 (m, 1H), 6.82–7.10 (m, 3H); ^{13}C NMR (D_2O) δ 10.4, 17.5, 39.4, 48.8, 49.3, 56.2, 58.9, 62.7, 113.2, 114.4, 116.0, 121.5, 135.7, 138.6, 144.9, 148.8 (1 signal is hidden); MS (ESI) m/z 319 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{19}H_{31}N_2O_2$ [M – HCl_2]$^+$ 319.2386, found 319.2371.

1-[2-(2-Methoxy-4-propylphenoxy)ethyl]-4-pentylpiperazine dihydrochloride (3u). White crystalline powder (1180 mg, 56%); mp 180–184 °C; IR (KBr) ν_{max}/cm^{-1} 1594, 1516, 1468, 1455, 1419; ^{1}H NMR (D_2O) δ 0.93 (m, 6H), 1.41 (m, 4H), 1.56 (m, 2H), 1.83 (m, 2H), 2.57 (t, J = 7.5, 2H), 3.36 (m, 2H), 3.45–4.20 (m, 8H), 3.83 (t, J = 4.5, 2H), 3.92 (s, 3H), 4.45 (t, J = 4.5, 2H), 6.89 (dd, J = 1.2, 8.1, 1H), 7.01 (d, J = 1.2, 1H), 7.04 (d, J = 8.1, 1H); ^{13}C NMR (D_2O) δ 13.4, 21.8, 23.4, 24.6, 28.1, 37.2, 48.8, 49.3, 56.2, 57.5, 62.8, 113.3, 114.3, 121.4, 138.6, 144.6, 148.6 (2 signals hidden); MS (ESI) m/z 349 ([M – HCl_2]$^+$), 183; HRMS (ESI) calcd for $C_{21}H_{37}N_2O_2$ [M – HCl_2]$^+$ 349.2855, found 349.2855.

1-Isobutyl-4-[2-(2-methoxyphenoxy)ethyl]piperazine dihydrochloride (3v). White crystalline powder (1100 mg, 60%); mp 186–190 °C; IR (KBr) ν_{max}/cm^{-1} 1596, 1499, 1461, 1373, 1262, 1252; ^{1}H NMR (D_2O) δ 1.06 (d, J = 6.6, 6H), 2.22 (m, 1H), 3.22 (d, J = 7.2, 2H), 3.45–4.05 (m, 8H), 3.83 (t, J = 4.8, 2H), 3.92 (s, 3H), 4.47 (t, J = 4.8, 2H), 7.02–7.18 (m, 4H); ^{13}C NMR (D_2O) δ 19.7, 23.8, 49.2, 49.3, 56.3, 62.6, 62.7, 64.5, 113.2, 114.5, 122.2, 123.5, 146.8, 148.9; MS (ESI) m/z 293 ([M – HCl_2]$^+$); HRMS (ESI) calcd for $C_{17}H_{29}N_2O_2$ [M – HCl_2]$^+$ 293.2229, found 293.2227.

1-[2-(Biphenyl-4-yloxy)ethyl]-4-octadecylpiperazine dihydrochloride (3w). White fluffy powder (2400 mg, 79%); mp 160–190 °C, wax-like transition; IR (KBr) ν_{max}/cm^{-1} 2917, 2851, 1606, 1522, 1489, 1470; MS (ESI) m/z 535 ([M – HCl_2]$^+$), 473, 413, 345; HRMS (ESI) calcd for $C_{36}H_{59}N_2O$ [M – HCl_2]$^+$ 535.4627, found 535.4639. The dihydrochloride salt had a low solubility in D_2O, $CDCl_3$ or DMSO. The NMR analysis was therefore performed on the free-base amine: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.4, 3H), 1.26 (m, 30H), 1.47 (m, 2H), 2.32 (t, J = 7.7, 2H), 2.37–2.75 (m, 8H), 2.83 (t, J = 5.8, 2H), 4.14 (t, J = 5.8, 2H), 6.96 (d, J = 8.6, 2H), 7.28 (m, 1H), 7.39 (t, J = 7.5, 2H), 7.52 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 27.1, 27.8, 29.5, 29.8, 29.8–29.9 (overlaping peaks), 29.9, 32.1, 53.4, 53.9, 57.5, 59.1, 66.2, 115.1, 126.8, 126.9, 128.3, 128.9, 134.0, 141.0, 158.6.

1-Cyclohexyl-4-[2-(3-methoxyphenoxy)ethyl]piperazine dihydrochloride (3x). White crystalline powder (250 mg, 13%); mp 203–207 °C; IR (KBr) ν_{max}/cm^{-1} 1614, 1601, 1580, 1489, 1456, 1160; ^{1}H NMR (D_2O) δ 1.10–1.59 (m, 5H), 1.70 (m, 1H), 1.95 (m, 2H), 2.16 (m, 2H), 3.42 (m, 1H), 3.49–4.25 (m, 8H), 3.80 (t, J = 4.8, 2H), 3.85 (s, 3H), 4.45 (t, J = 4.8, 2H), 6.67 (t, J = 2.3, 1H), 6.72 (m, 2H), 7.35 (t, J = 8.2, 1H); ^{13}C NMR (D_2O) δ 24.7, 24.8, 27.0, 45.8, 49.7, 56.0, 56.1, 61.8, 66.9, 101.7, 107.6, 108.1, 131.1, 158.8, 160.7; MS (ESI) m/z 319 ([M – HCl_2]$^+$), 237, 196, 118, 77; HRMS (ESI) calcd for $C_{19}H_{31}N_2O_2$ [M – HCl_2]$^+$ 319.2386, found 319.2390.

1-{2-[4-(Benzyloxy)phenoxy]ethyl}-4-*sec*-butylpiperazine dihydrochloride (3y). Off-white crystalline powder (380 mg, 17%): mp 197–202 °C; IR (KBr) ν_{max}/cm^{-1} 1635, 1508, 1456, 1381, 1231;

^{1}H NMR (D_2O) δ 0.94 (t, J = 7.4, 3H), 1.31 (d, J = 6.6, 3H), 1.55 (m, 1H), 1.82 (m, 1H), 3.40 (m, 1H), 3.48–3.76 (m, 10H), 4.24 (t, J = 4.2, 2H), 4.93 (s, 2H), 6.90 (m, 4H), 7.32 (m, 5H); ^{13}C NMR (D_2O) δ 9.8, 12.9, 23.8, 45.7, 49.6, 56.1, 62.7, 65.0, 71.3, 116.3, 117.0, 128.5, 128.8, 129.2, 137.1, 152.3, 153.1; MS (ESI) m/z 369 ([M – HCl_2]), 313; HRMS (ESI) calcd for $C_{23}H_{33}N_2O_2$ [M – HCl_2]$^+$ 369.2542, found 369.2545.

1-Cyclohexyl-4-[2-(phenylthio)ethyl]piperazine dihydrochloride (3z). White crystalline powder (540 mg, 29%); mp 200–207 °C, dec.; Anal. Calcd for $C_{18}H_{28}N_2S$×2HCl×1/4H_2O: C 56.61, H 8.05, N 7.33. Found: C 56.66, H 8.27, N 7.27%; IR (KBr) ν_{max}/cm^{-1} 1586, 1483, 1455, 1439, 1401; ^{1}H NMR (D_2O) δ 1.03–1.52 (m, 5H), 1.63 (d, J = 12.6, 1H), 1.88 (d, J = 12.9, 2H), 2.08 (d, J = 11.1, 2H), 3.26–3.48 (m, 5H), 3.55–3.87 (m, 8H), 7.35–7.57 (m, 5H); ^{13}C NMR (D_2O) δ 26.9, 27.0, 29.2, 30.0, 48.1, 51.7, 58.1, 69.0, 130.6, 132.3, 133.5, 135.0; MS (ESI) m/z 305 ([M – HCl_2]$^+$), 214; HRMS (ESI) calcd for $C_{18}H_{29}N_2S$ [M – HCl_2]$^+$ 305.2051, found 305.2041.

Synthesis of piperazines using a one-pot procedure from primary alcohols, DABCO and phenols

2-(Benzhydryloxy)ethanol (7). To a stirred mixture of NaOH (4.00 g, 95 mmol) in ethylene glycol (100 mL) at rt was added dropwise a solution of benzhydryl chloride (**6**; 13.30 mL, 75 mmol) in THF (60 mL) at such a rate that the mixture was kept clear and homogenous. The addition required about 90 min. The mixture was left stirring for an additional 4 h and then heated up to 60 °C for 30 min. Then the mixture was diluted with water (500 mL), extracted with diisopropyl ether (100 mL), the extract washed with water (300 mL) and evaporated *in vacuo* to give a yellowish oil. The latter was dissolved in methanol (40 mL), diluted with water (15 mL) and the solution left overnight at −15 °C. The crystallized product was filtered, washed with methanol/water (1 : 1, 3 × 30 mL) and dried to give white crystals (15.73 g, 92%): mp 59–61 °C (lit.[26] 69 °C, from EtOH); IR (KBr) ν_{max}/cm^{-1} 1634br, 1494, 1453, 1117, 1066; ^{1}H NMR ($CDCl_3$) δ 2.09 (bs, 1H), 3.59 (t, J = 4.5, 2H), 3.78 (m, J = 4.5, 2H), 5.41 (s, 1H), 7.21–7.38 m, 10H).

One-pot procedure for the synthesis of 8. To an ice-bath cooled stirring solution of DABCO (720 mg, 6.25 mmol) and alcohol (5.5 mmol) in diglyme (6 mL) *p*-toluenesulfonyl chloride (1050 mg, 5.5 mmol) was added portion-wise allowing the temperature of the reaction mixture to stay below 20 °C. The mixture was then left stirring at rt for 30 min. K_2CO_3 (860 mg, 6.25 mmol) was added and the mixture was stirred for an additional 10 min at 100 °C. The phenol (5 mmol) was then added at this temperature and the mixture heated for 4 h at 140 °C. The cooled mixture was then diluted with water (60 mL) and the piperazine product **8** was isolated as described in the general procedure for the synthesis of piperazines from *N*-alkyl-DABCO salts.

1-[2-(Benzhydryloxy)ethyl]-4-(2-phenoxyethyl)piperazine dihydrochloride (8). White crystalline powder (1710 g, 70%); mp 168–170 °C; IR (KBr) ν_{max}/cm^{-1} 1597, 1492, 1468, 1450, 1242; ^{1}H NMR (D_2O) δ 3.63 (t, J = 4.9, 2H), 3.65–3.88 (m, 10H), 3.92 (t, J = 4.9, 2H), 4.45 (t, J = 4.7, 2H), 5.64 (s, 1H), 7.05–7.17 (m, 3H), 7.35–7.54 (m, 12H); ^{13}C NMR (D_2O) δ 49.1, 49.2, 56.1, 56.6, 61.7, 62.5, 84.3, 115.1, 122.6, 127.2, 128.7, 129.4, 130.4, 141.5, 157.5; MS (ESI) m/z 417 ([M – HCl_2]$^+$), 167; HRMS (ESI) calcd for $C_{27}H_{33}N_2O_2$ [M – HCl_2]$^+$ 417.2542, found 417.2534.

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