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Combinatorial synthesis of benztropine libraries and their evaluation as monoamine transporter inhibitors†

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A combinatorial synthesis of benztropine analogues is presented. Radical azidonation of 3-benzyloxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester **3** to 3-(1-azidobenzyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester **4** was used as a key step in the synthesis. This step was optimized by adding 10% DMF to the reaction. Reaction of **4** with phenyl magnesium bromide followed by Boc removal and *N*-methylation gave benztropine **1**. Reaction of five-component Grignard reagents with **4** was used to create a two-dimensional library of 25 *N*-normethylbenztropine analogues. Further reaction of this library with five alkyl bromides was carried out to create a three-dimensional library containing 125 compounds. Screening of the libraries towards binding and inhibition of uptake of the human dopamine (hDAT), serotonin (hSERT) and norepinephrine transporters (hNET) was carried out. None of the synthesized compounds were found to be stronger than benztropine, and none were selective for inhibition of binding over monoamine uptake.

Introduction

Combinatorial chemistry represents a series of synthetic techniques that have the potential to facilitate the drug discovery process significantly.[1] Usually, combinatorial chemistry combines multiple reactions and building blocks in order to create many compounds. Both classical synthesis of individual compounds using automated procedures and synthesis of compound mixtures are today classified as combinatorial chemistry,[2] but in the present work combinatorial chemistry describes work with mixtures. Recently, our laboratory has reported a combinatorial method that uses multi-component Grignard reagents to readily create mixed libraries.[3] Due to the versatility of the Grignard reaction, this method can be applied to many interesting targets. We have demonstrated the use of this technique in a two- and three-dimensional screening protocol to discover new phenyltropanes.[4] In the present work the application of this method to benztropine analogues is presented.

Benztropine (**1**) is a well known anti-Parkinsonian drug that has structural similarities to cocaine. Indeed, it has been found that **1**, similarly to cocaine, inhibits the re-uptake of dopamine by binding to the dopamine transporter (DAT).[5] As the ability to inhibit dopamine re-uptake is thought to underlie cocaine's liability in drug abuse, the fact that **1** competes for the same binding site on the DAT as cocaine makes **1** and its analogues potential agents in an anti-cocaine treatment, particularly if compounds can be found that inhibit cocaine's binding without disrupting dopamine transport. Furthermore, interestingly, the behavioural effects of benztropine analogues have been found to be different from those of cocaine, which is another reason why a replacement therapy could work.[6] The search for benztropine analogues with potency and selectivity for the DAT is therefore a worthwhile goal, and in the present work we report a combinatorial approach to benztropine analogues.

The chemical rationale behind the work was that our recently developed radical azidonation reaction[7] could be employed to prepare substituted benzyl ethers,[8] thereby allowing us to prepare libraries of type A (Fig. 1). This synthesis would allow us to prepare alkylphenylmethyl ethers while the classical synthesis of benztropines, by reaction of tropine with diarylcarbinols or diarylmethyl halides, would be difficult or even impossible in the more hindered cases. It is thus interesting to note that while the literature contains hundreds of benztropines containing the diarylmethoxy ether moiety, just a single alkylarylmethyl ether (the hydroxymethyl analogue) has been disclosed. In this paper we present an efficient synthesis of these compounds and their use in preparation of libraries containing both alkylaryl and diaryl benztropines.

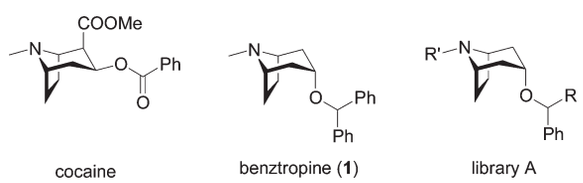

Fig. 1 Cocaine, benztropine and the target library.

Results and discussion

The strategy for the synthesis simply consisted in converting tropine to a benzyl ether that by α-azidonation and substitution could be converted to the desired libraries. To this end, tropine was subjected to demethylation using chloroethyl chloroformate followed by methanolysis, and the resulting amine was protected to give the *N*-Boc derivative **2** in 77% yield from tropine (Scheme 1). Benzylation with NaH/BnBr uneventfully gave **3** in 85% yield.

The radical azidonation of **3** required study in more detail (Table 1). As it turned out, azidonation at the conditions reported originally, which included the use of 3 equivalents of IN_3 (entry 1), did not give a satisfactorily high yield of **4**. An increase in the concentration of reactants (entries 2 and 3) increased the conversion but also led to the formation of byproducts. With an increase in concentration combined with a short reaction time (entries 4 and 5) it was possible to increase the yield somewhat. Change of the solvent to one favouring radical reactions (entry 6) was however counterproductive, presumably because

† Electronic supplementary information (ESI) available: (1) K_i values for the 2D and 3D libraries, (2) ESI and GCMS spectra for sublibraries **I**–**V**, **a**–**e**, and **Z**, and (3) ^{13}C NMR spectra for **3**, **5**, **7**, **8**, **9**, **10**, **12a**, **13a**, **16** and **17**. See http://www.rsc.org/suppdata/ob/b4/b405768f/

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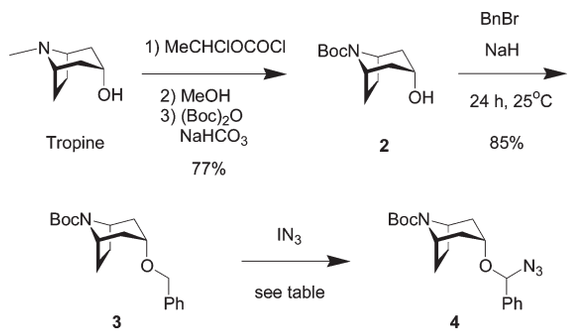
Table 1 Radical azidonation of **3** (Scheme 1). Unless otherwise noted azidonation was performed at reflux (80 °C) using 3 equivalents of IN_3, made *in situ* from premixing 3 equivalents of iodine monochloride (ICl) and 7 equivalents of NaN_3 in MeCN at −10 °C. Yields are isolated yields after chromatography

Entry	Solvent	Additive	Concentration of **3**/M	Time/min	Yield of **4**
1	MeCN	—	0.11	60	52%
2	MeCN	—	0.24	60	51%
3	MeCN	—	0.42	60	43%
4	MeCN	—	0.46	30	59%
5	MeCN	—	0.82	20	58%
6	CCl_4	—	0.15	30	37%
7	MeCN	5% DMF	0.27	40	71%
8	MeCN	10% DMF	0.24	70	73%
9	MeCN	50% DMF	0.26	120	72% (corr.)
10	MeCN	10% DMF (2.2 eq. IN_3)	0.29	300	43% (corr.)
11	MeCN	10% DMA	0.24	120	67% (corr.)
12	MeCN	1.1 eq. 2,6-di-*tert*-butylpyridine	0.31	40	46% (corr.)

(corr.) means that the yield has been corrected by the subtraction of re-isolated starting material from consumed substrate.

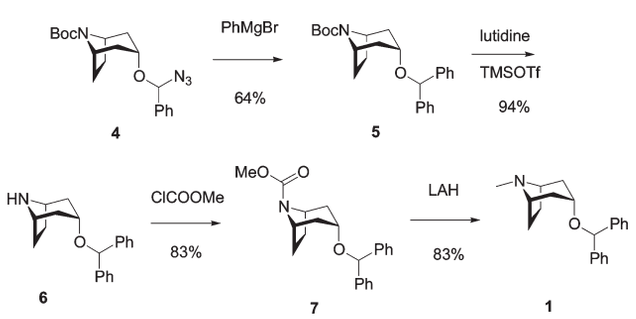


Scheme 1 Synthesis of azidoether **4** from tropine. The conditions investigated for the azidonation are shown in Table 1.

of the necessity to keep azide ions dissolved during the reaction. This observation supports the hypothesis that the reaction leads to a benzylic iodide that is substituted by azide and thus involves an ionic step as well.

To further improve the reaction, various additives were added, rationalized from two working hypotheses. The hypothesis that the formation of acid during the reaction was leading to decomposition of the product led us to add a hindered pyridine to the reaction (entry 12), but this was not an advantage compared to the corresponding experiment with no additive. Another hypothesis was that side reactions were occurring in the tropane skeleton, starting with abstraction of a hydrogen atom α to the amine nitrogen. This led to the idea of adding an amide, DMF, that might compete with this abstraction. Indeed, addition of small amounts of DMF led to the best yields (entries 7 and 8), while larger amounts slowed the reaction (entry 9). DMA (dimethylacetamide, entry 11) did not have an effect on the yield of **4**, and the effect of DMF may therefore be due to reaction of one of the methyl hydrogen atoms rather than the hydrogen atom α to the carbonyl group.

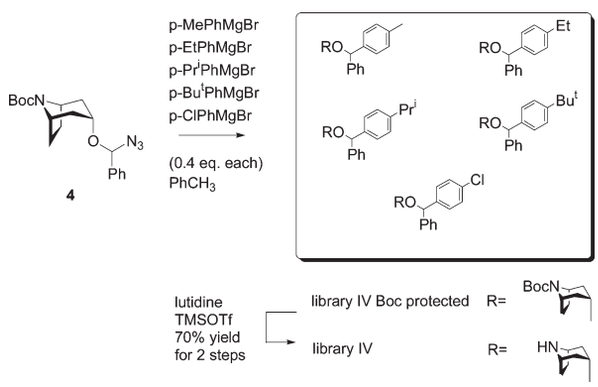
With an efficient preparation of **4** complete, we established its conversion to benztropine (**1**) (Scheme 2). The azidoether **4** was reacted with phenylmagnesium bromide in toluene[8] to give diphenyl derivative **5** in 64% yield. The Boc group was removed



Scheme 2 Synthesis of benztropine from the azidoether **4**.

under conditions[9,10] (lutidine, TMSOTf) selective for its removal in the presence of an acid-sensitive benzhydryl ether, giving **6** in 94% yield. Reaction of this amine with methyl chloroformate in pyridine gave an 83% yield of methyl carbamate **7**, which was reduced to **1** with $LiAlH_4$ in 83% yield.

Now the combinatorial synthesis outlined in Scheme 3 was investigated. Azide **4** was reacted with a 5-component Grignard reagent to give library **IV** in Boc-protected form. After removal of the Boc groups with lutidine/TMSOTf, library **IV** was analysed by ESI mass spectroscopy and GCMS (EI) (see Supplementary material†), both of which showed the presence of all 5 expected compounds. NMR spectroscopy on this library revealed the presence of each of the expected compounds in equimolar amounts.



Scheme 3 Combinatorial synthesis of normethyl benztropine analogues from the azidoether **4**.

This 5-component synthesis (Scheme 3) was repeated with 4 other sets of Grignard reagents to obtain the libraries **I**, **II**, **III** and **V** containing the compounds shown as rows in Table 2. These libraries were characterized with ESI and GC-MS in the same way as library **IV**, confirming, with a single exception (compound **IIe**), the presence of all compounds (see Supplementary material†). Similarly, the reaction was carried out 5 times to create the libraries **a**–**e**, shown as columns in Table 2, so that altogether the 25 compounds shown were made twice in the form of 10 sublibraries of 5 compounds. One of the compounds in the library was the known 4-chlorophenyl analogue **11**, which was included as a positive control. This compound has been reported to have a binding to the DAT from rat brain of 36.8 nM.[11] The remaining compounds were new. It is noteworthy that the library displays a considerable variation its structure and includes both aryl, linear and cycloalkyl derivatives (Table 2).

Screening of the 10 sublibraries towards binding and uptake to hDAT, hSERT and hNET was performed and the measured K_i values are shown in the Supplementary material (Table S1).† None of the 10 libraries showed potent binding to or inhibition

Table 2 Contents of the two-dimensional library contained in the sublibraries **I**–**V** (rows) and **a**–**e** (columns)

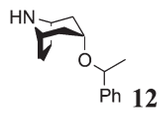
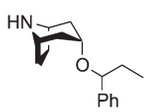
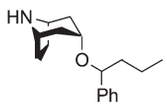
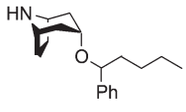
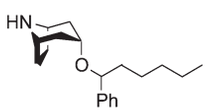
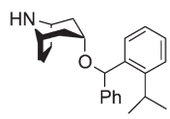
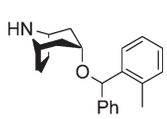
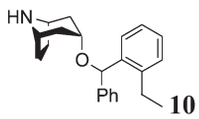
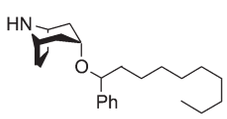
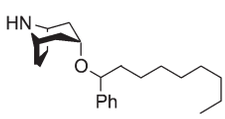
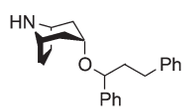
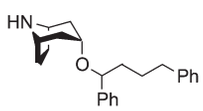
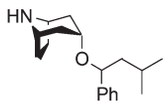
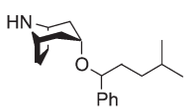
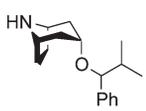
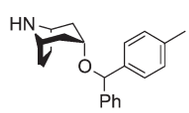
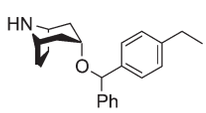
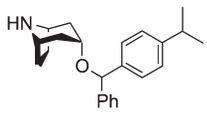
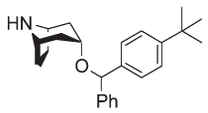
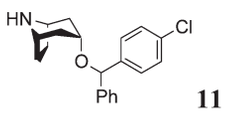
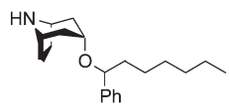
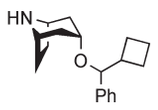
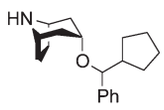
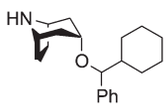
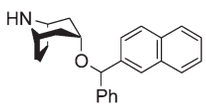
	a	**b**	**c**	**d**	**e**
I	 **12**		 **9**	 **13**	
II			 **10**		
III			 **8**		
IV					 **11**
V					

Table 3 Binding and uptake of **8**–**11** to monoamine transporters

	K_i/nM					
	Binding [^{125}I]RTI-55			Uptake		
	DAT	SERT	NET	[^{3}H]DA	[^{3}H]5-HT	[^{3}H]DA (NET)
Cocaine	741 ± 363	1352 ± 407	1675 ± 477	198 ± 71	493 ± 221	512 ± 249
1	391 ± 132	24945 ± 102	573 ± 166	629 ± 173	22611 ± 3761	940 ± 148
8	927 ± 119	16185 ± 913	1560 ± 255	1095 ± 98	30038 ± 4184	2782 ± 238
9	862 ± 71	7040 ± 266	558 ± 62	690 ± 93	5772 ± 991	823 ± 91
10	11061 ± 1529	5522 ± 936	1106 ± 124	22616 ± 2184	13594 ± 2706	1815 ± 277
11	604 ± 78	4080 ± 380	952 ± 135	1178 ± 340	10380 ± 844	1562 ± 626

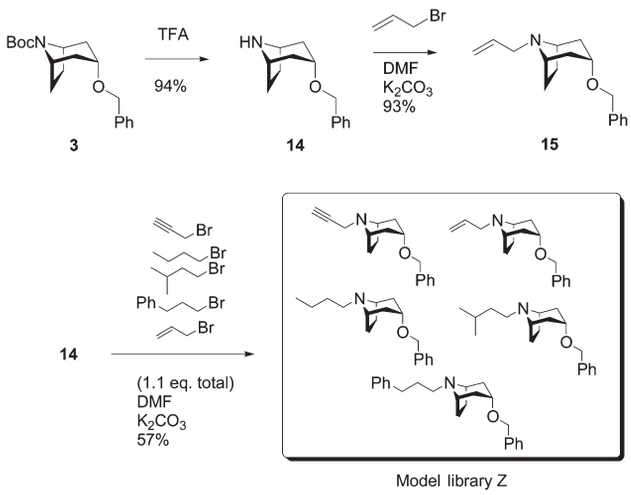
of re-uptake to any of the monoamine transporters, with K_i values of 6–700 nM being the lower limit. It is therefore evident that no extraordinary differences in biological activity appear to exist among the 25 compounds. Thus the significance of changing one phenyl group in the benzhydryl ether moiety appears to be limited. The data indicate that compounds **Ic** and **IIIc** (Table 2) are the more potent compounds in the series towards DAT binding and uptake, that compound **Va** is more potent towards SERT binding and uptake, and that **Ic** is the strongest with regard to net binding and uptake.

The individual compounds **8** (**IIIc**), **9** (**Ic**), **10** (**IIc**) and **11** (**IVe**) (Table 2) were prepared from **4** using the procedure outlined in Scheme 2, and were obtained in 63%, 61%, 59% and 69% yield, respectively, over two steps. Similarly, synthesis of **12** (**Ia**) and **13** (**Id**) was demonstrated through the intermediacy of the corresponding Boc derivatives **12a** and **13a**, which were obtained in 98% and 52% yield from **4**, respectively. The test results from some of these individual compounds are shown in Table 3. Towards the DAT, the two aliphatic compounds **8** and **9** were slightly weaker than benztropine **1** and cocaine, and also slightly weaker than the positive control **11**, an observation that was not displayed in the two-dimensional screening. However, the differences are so small that the two-dimensional screening was unable to detect them, as they are hidden in effects from other compounds. The *o*-ethylbenzhydryl analogue **10** is, however, a remarkably poor inhibitor of the DAT.

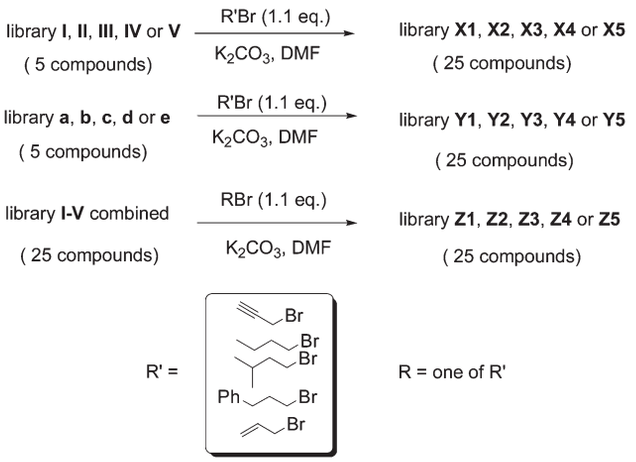
None of the compounds are potent against SERT. The propyl analogue **9** (**Ic**) is the most potent compound for binding to the norepinephrine transporter, being 3 times stronger than the closely related isobutyl analogue **8** (**IIIc**). None of the compounds show any significant selectivity between binding and uptake.

The study was extended to the investigation of the effect of substitution on the nitrogen atom. It was envisaged that this could be carried out by a simple substitution at nitrogen with various alkyl bromides. To investigate the feasibility of this reaction, the model experiments outlined in Scheme 4 were carried out. Compound **3** was deprotected with TFA to give **14**, which was reacted with allyl bromide and potassium carbonate in DMF to give **15** in excellent yield. Consequently the five-component alkylation of **14** was attempted (Scheme 4). Reaction of **14** with a mixture of equimolar amounts (0.22 equivalents each) of propargyl, allyl, isopentyl, phenylpropyl and butyl bromide in the presence of 2 equivalents of K_2CO_3 gave model library **Z**, for which NMR and MS showed that the 5 expected compounds were formed in good yield and in equimolar amounts. There are rate differences in the reaction of these different bromides with **14**, but the fact that only a very slight excess of electrophile is used ensures that products are evenly formed.

Using this chemistry, the two-dimensional library (Table 2) was modified on the nitrogen atom with these 5 electrophiles in order to create the three-dimensional library shown in Fig. 2. The 125 compounds contained were prepared 3 times as 5 sublibraries with 25 compounds either as the layers shown as entries along the Z axis ($\mathbf{Z_1}$–$\mathbf{Z_5}$) or as slices made along the X ($\mathbf{X_1}$–$\mathbf{X_5}$) or Y axes ($\mathbf{Y_1}$–$\mathbf{Y_5}$), respectively. These libraries were



Scheme 4 Model experiments with the synthesis of the *N*-alkylated library.



Scheme 5 Synthesis of libraries $\mathbf{X_1}$ to $\mathbf{Z_5}$.

synthesized as shown in Scheme 5. The libraries $\mathbf{X_1}$–$\mathbf{X_5}$ were made by carrying out *N*-alkylation with the 5 bromides of the libraries **I**–**V** individually. Similarly, the libraries $\mathbf{Y_1}$–$\mathbf{Y_5}$ were obtained from 5 reactions of each of libraries **a** to **e** with the 5 electrophiles. Finally the libraries $\mathbf{Z_1}$–$\mathbf{Z_5}$ were obtained by mixing libraries **I**–**V** and reacting them with one of the 5 bromides (Scheme 5). Characterization of these 25-membered sublibraries could not be as good as in the smaller libraries, but the products were subjected to GCMS, which revealed masses corresponding to the presence of 20 or more of the expected compounds in each library. With this documentation, and due to the similarity of the model compound **14** and the library members of Table 2 in the vicinity of the nitrogen, it is reasonable to assume that the expected 125 compounds were synthesized 3 times.

The 15 libraries were then screened and the results are shown in Table S2 (see Supplementary material†).

From the data it was clear that the difference in binding among the 125 analogues appeared limited, or at least no compound was significantly more potent than others in the 6 assays. According to the test results from the **Z**-libraries it appeared that the *N*-butyl analogues ($\mathbf{Z_1}$) were more potent. Therefore the compounds **16** ($\mathbf{X_1}$, $\mathbf{Y_3}$, $\mathbf{Z_1}$) and **17** ($\mathbf{X_3}$, $\mathbf{Y_3}$, $\mathbf{Z_1}$) were chosen for individual synthesis. These compounds were prepared from **9** by alkylation with butyl bromide and isopentyl bromide (respectively) and K_2CO_3 in DMF. Testing of these two compounds showed that they had no particularly strong inhibitory effect (Table 4); compound **16** had a K_i of 1604 nM towards the DAT, while **17** was weaker. The biological activities of each compound are close to the average of the **X** and **Y** libraries.

It is surprising that we find a relatively low potency of benztropines compared to previous studies. For example, compound **11** has been reported to inhibit the DAT with a K_i of 36 nM,[11] while we find a 20-fold higher value. This discrepancy is likely to be due to two differences: 1) that previous studies were

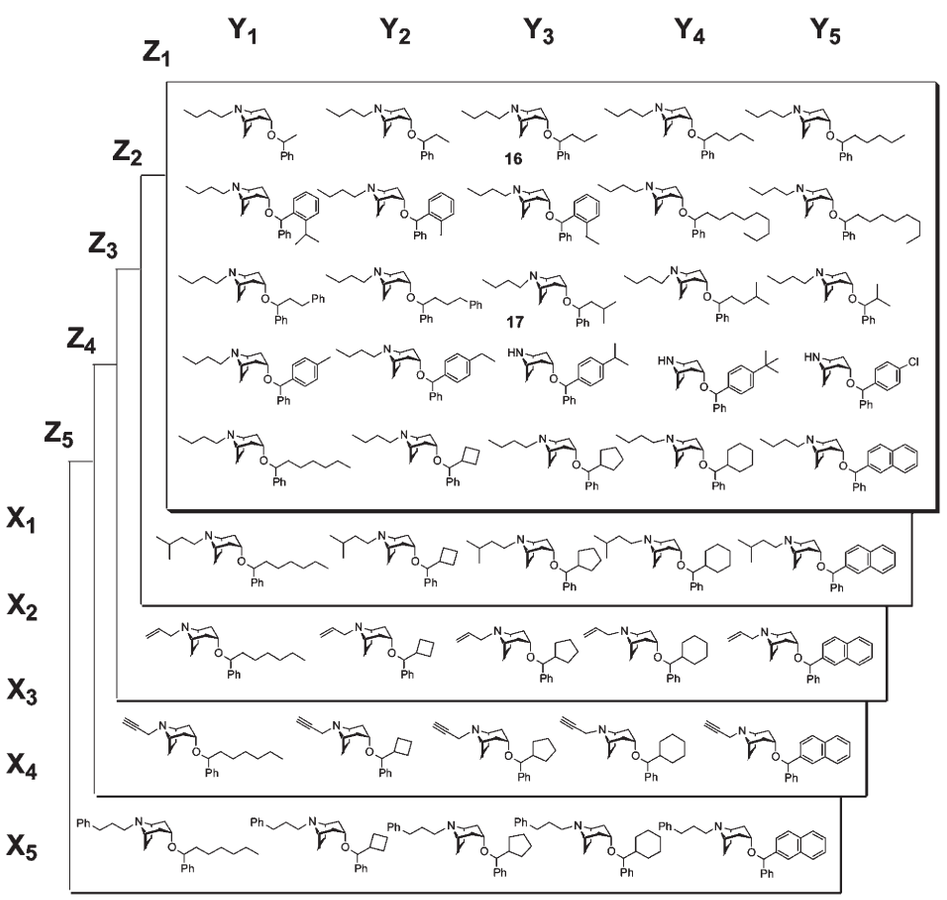


Fig. 2 The three-dimensional library.

Table 4 K_i values for binding and uptake at hDAT, hSERT or hNET

	K_i/nM					
	Binding [^{125}I]RTI-55			Uptake		
	DAT	SERT	NET	[^{3}H]DA	[^{3}H]5-HT	[^{3}H]DA (NET)
16	1604	5149	3857	2173	4698	13570
17	3641	6235	3784	8403	18257	24919

made with brain homogenates while we used a cloned transporter, and 2) prior work was performed with the monoamine transporters from rat while we used human transporters. It is well known that discrepancies can be observed between the work made with brain homogenates and cloned transporters, possibly due to the presence of other material in the homogenates affecting the assay. However, for cocaine the difference between the two test systems is not as large. Also for benztropine (**1**) itself the difference is not as large.

The binding of **1** to DAT gave a K_i of 197 nM using rat homogenates and 412 nM with monkey brain homogenates,[12] which is not far from the value of 391 nM we find for **1**. Therefore the discrepancies we find for **11** and other compounds are compound specific and therefore appear to be associated with differences in specific interaction of these compounds with the transporters from the two species. A closer comparison of the effects of these compounds with cloned human and rat transporter might be worthwhile. Secondly, it is noted that no significant selectivity between binding and uptake is was observed in the studied compounds.

In summary, we have developed a new combinatorial synthesis of benztropine analogues employing radical azidonation as the key step. The azidonation reaction was improved by addition of 10% DMF. Our approach can also be employed to combinatorial synthesis of analogues of other benzhydryl ethers, of which the pharmaceutical literature contains many. We found that substitution of one phenyl group in benztropine with many other functionalities did not improve (and in most cases did not decrease) inhibition and uptake of hDAT, hSERT or hNET. The results show somewhat surprisingly that the two phenyl groups in **1** are not necessary and may be replaced with little effect. Our results also confirm the results from others that, in many cases, changes in the *N*-substituents do not change the effect on the transporter.

Experimental

Cell culture

Cells stably expressing hSERT, hDAT or hNET were produced by transfecting COS-7 cells with hSERT/hDAT/hNET inserted in the pIRES vector (BD Biosciences Clontech) also bearing a Blasticidin resistance gene. Cells were cultured in DMEM (BioWhitaker) supplemented with 10% FCS (Gibco Life Technologies), 1% Penicillin/Streptomycin (BioWhitaker) and 10 μg mL^{-1} of Blasticidin (Cayla) for negative selection of nontransfected cells. After 14 days of selection Blasticidin was adjusted to 2 μg mL^{-1} in the culture medium and cells were subcultured under this selection regime and grown at 37 °C, 5% CO_2, and 95% humidity.

Uptake assay

For the uptake assay stably transfected cells were seeded in 96 well microplates (Nunc) and grown at 37 °C, 5% CO_2, and 95% humidity for two days. Before the IC_{50} assay the medium was aspired and the cells were washed in PBSCM (137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2HPO_4, 1.4 mM KH_2PO_4, 0.1 mM $CaCl_2$, 1 mM $MgCl_2$, pH 7.4) on a BioTek ELX50 microplate washer, and the dilution series of the drug in PBSCM supplemented with 30–100 nM tritiated 5-HT (Perkin-Elmer Life Sciences) or DA (Amersham Biosciences), applied to the cells adhering to the bottom of the microplate wells to initiate uptake. Accumulation of 5-HT or DA was allowed to proceed for 10 min at 20 °C and the assay was terminated by aspiration of the uptake media and washing with PBSCM. Scintillant (MicroScint 20 from Packard Bell) was used to solubilise cells, and accumulated radioactivity was quantifed on a Packard Topcounter. Concentration of substrate was quantified by liquid scintillation counting on an Packard Tri-Carb.

Binding assay

Membrane preparations for the binding assay were produced by scraping the stably transfected cells from cell culture dishes (Nunc), pelleting the cells in ice-cold PBSCM by centrifugation, homogenising the cells in ice-cold Harvest Buffer I (150 mM NaCl, 50 mM Tris, 20 mM EDTA) using a Ultra-Turrax (Janke & Kunkel AG) for 60 s. The membrane was pelleted by centrifugation at 12000 g for 10 min at 4 °C and washed in ice-cold Harvest Buffer I, the membrane pelleted again and the membrane pellet resuspended in PBSCM, briefly using the Ultraturrax. Membrane preperations were aliquoted into 2 mL portions and stored at −80 °C until use. The concentration of total protein in the membrane preparation was determined with a MicroBCA kit (Pierce).

A concentration of 5 μg per well of membrane preparation was used with the nominated concentration of drug of interest in combination with 0.1–0.25 nM [^{125}I]-RTI-55. Membrane and ligands were incubated for 1 h at 20 °C. Using a Filtermate Cell-harvester (Packard), membranes were captured on GF/B 96-well filterplates (Packard) presoaked with 0.5% polyethyleneimine (Merck) and washed thrice with ice-cold water. The filter in each well was dissolved in 40 μL Microscint 20 and scintillation counts were determined with a Packard Topcounter. Precise concentration of radioligand was quantified by liquid scintillation counting on a Packard Tri-Carb.

3α-Hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (2)[13]

To a solution of tropine (prepared from azeotropically distilling a mixture of tropine hydrate in toluene (4.98 g, 35.3 mmol)) in 1,2-dichloroethane (12 mL) was added dropwise 1-chloroethyl chloroformate (6.3 mL, 58.39 mmol) at 0 °C. The mixture obtained was refluxed for 1 h and then concentrated *in vacuo*. The residue was dissolved in MeOH (15 mL), refluxed for 45 min and concentrated *in vacuo* again. The residue was taken into acetone (15 mL) and water (15 mL) and stirred for 1 h. $NaHCO_3$ (11.80 g, 141.2 mmol) and $(Boc)_2O$ (16.5 g, 75.53 mmol) were added. The mixture was stirred overnight and concentrated *in vacuo* in order to remove acetone. The aqueous phase was extracted with $CHCl_3$ (4 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (CH_2Cl_2/EtOAc, 6:1, R_f = 0.2) gave the desired product (6.14 g, 77%) as a colourless solid. M.p. 141.5 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.16 (1H, br. s, H-3), 4.09 (2H, br. s, H-1,5), 2.14–1.66 (8H, m, H_2-2,4,6,7), 1.41 (9H, s, $C(CH_3)_3$, Boc) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 153.6 (C=O, Boc), 79.3 ($C(CH_3)_3$, Boc), 65.3 (C-3), 53.3/52.4* (C-1,5), 38.8/38.3* (C-2,4), 28.7 ($(CH_3)_3C$, Boc), 28.7/28.1* (C-6,7) ppm.

(* The spectrum showed two rotamers.) HRMS (ES): calculated for $C_{12}H_{21}NO_3Na$ (M + Na): 250.1419. Found: *m/z* 250.1396.

3-Benzyloxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (3)

A solution of 3α-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (**2**, 3.30 g, 14.7 mmol) in dry DMF (20 mL) was cooled to 0 °C. NaH (2.81 g, 58.6 mmol, 50%) was added with continuous stirring. The cooling bath was removed and stirring was continued at room temperature for 1 h. A solution of BnBr (3.48 mL, 29.30 mmol) in dry DMF (5 mL) was added and the mixture was stirred overnight. 1 M HCl was added until a neutral pH value was obtained. The mixture was extracted with Et_2O (3 × 25 mL). The combined organic phases were dried ($MgSO_4$), evaporated *in vacuo* and the residue was purified by chromatography (DCM/EtOAC, 100 : 1, R_f = 0.28) to give the product (3.94 g, 85%) as a colourless solid. M.p. 61.5 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35–7.26 (5H, m, Ph–H), 4.49 (2H, s, O–CH_2–Ph), 4.17 (2H, m, H-1,5), 3.71 (1H, br. s, H-3), 2.17–1.85 (8H, m, H_2-2,4,6,7), 1.46 (9H, s, $(CH_3)_3$, Boc) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz) δ = 153.7 (C=O, Boc), 139.2 (C(Ph)), 128.5; 127.5; 127.2 (CH(Ph)), 79.2 ($C(CH_3)_3$, Boc), 72.8 (O–CH_2–Ph), 70.9 (C-3), 53.4/52.6* (C-1.5), 35.7/34.6* (C-2,4), 28.8 ($(CH_3)_3$C, Boc), 28.8/28.1* (C-6,7) ppm. (* The spectrum showed two rotamers.) HRMS (ES); calculated for $C_{19}H_{27}NO_3Na$ (M + Na): 340.1889. Found: *m/z* 340.1885.

3-(1-Azidobenzyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (4)

A solution of iodine monochloride (131 mg, 0.81 mmol) in dry CH_3CN (1 mL) was cooled to −10 °C. NaN_3 (122 mg, 1.88 mmol) was added with continuous stirring. After 15 min, the cooling bath was removed and DMF (0.1 mL) and 3α-benzyloxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (**3**, 85 mg, 0.27 mmol) were added. The mixture was refluxed for 70 min (monitored by TLC) and then cooled to room temperature. CH_2Cl_2 (10 mL) was added and the mixture was washed with a solution of 5% $Na_2S_2O_3$ (10 mL). This procedure resulted in the brown organic phase becoming yellow and the colourless water phase becoming orange. The water phase was extracted with DCM (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography (pentane/EtOAc, 10 : 1, R_f = 0.26) to give the product (69 mg, 73%) as a clear colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.45–7.36 (5H, m, Ph–H), 5.39 (1H, s, O–CHN_3–Ph), 4.19 (2H, br. s, H-1,5), 4.13 (1H, t, H-3, *J* = 4.4 Hz), 2.22–1.78 (8H, m, H_2-2,4,6,7), 1.46 (9H, s, $(CH_3)_3$, Boc) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz) δ = 153.6 (C=O, Boc), 137.5 (C(Ph)), 129.3; 129.2; 128.9 (CH(Ph)), 91.5 (O–CHN_3–Ph), 79.4 ($C(CH_3)_3$, Boc), 72.4 (C-3), 53.1/52.3* (C-1,5), 37.2/36.4* (C-2,4), 35.3/34.4* (C-6,7), 28.7/28.0 ($(CH_3)_3$C, Boc) ppm. (* The spectrum showed two rotamers.) HRMS (ES); calculated for $C_{19}H_{26}N_4O_3Na$ (M + Na): 381.1904. Found: *m/z* 381.1903. IR (film) ν = 3444, 2978, 2103, 1694, 1652, 1548 cm^{-1}.

Preparation of single-component Grignard reagents

Mg turnings (20 mmol) were suspended in dry Et_2O (10 mL) in a two necked round bottomed flask fitted with a reflux condenser. The halide (10 mmol) was added at such a rate that the mixture kept refluxing. After addition the mixture was refluxed for 2 h. The Grignard reagent was taken out using a syringe and titrated before use in order to determine the concentration.

Preparation of multiple-component Grignard reagents

Mg turnings (20 mmol) were suspended in dry Et_2O (10 mL) in a two necked round bottomed flask fitted with a reflux condenser. Several different halides were added dropwise one by one in mole-equivalent amounts (10 mmol total) at such a rate that the solution kept refluxing. After addition the mixture was refluxed for 2 h. The Grignard reagent was taken out using a syringe and titrated before use.

Titration of Grignard reagents

To a solution of menthol (156 mg, 1 mmol) and 1,10-phenanthroline (5 mg) in dry THF (10 mL), the Grignard reagent was added dropwise through a syringe. The equivalence point was read when the mixture turned pink and the colour lasted for a minimum of 1 min.[14]

Substitution of azide by single-component Grignard reagents

The reactions were carried out by dissolving approximately 100 mg (0.3 mmol) of 3-(Azidophenylmethoxy)-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (**4**) in 3 mL of dry toluene. A freshly prepared ether solution of the desired Grignard reagents (2 equivalents) was slowly added with continuous stirring at room temperature. The addition caused the clear colourless solution to become yellow. After stirring for 1 h the reactions were quenched by adding 1 mL of saturated NH_4Cl and 1 mL of water. The mixtures were extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, evaporated *in vacuo* and purified by chromatography.

3-Benzhydryloxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (5)

Chromatography (pentane/EtOAc, 15 : 1, R_f = 0.25) gave the product **5** (76 mg, 64%) as a colourless solid. M.p. 92.4 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.30–7.13 (10H, m, Ph–H), 5.36 (1H, s, O–CH–$(Ph)_2$), 4.09 (2H, m, H-1,5), 3.61 (1H, s, H-3), 2.17–1.83 (8H, m, H_2-2,4,6,7), 1.38 (9H, s, $(CH_3)_3$, Boc) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 153.3 (C=O, Boc), 142.7 (C(Ph)), 128.2; 127.2; 126.7 (CH(Ph)), 81.0 (O–CH–$(Ph)_2$), 78.9 ($C(CH_3)_3$, Boc), 69.8 (C-3), 53.1/52.3* (C-1,5), 35.6/34.8* (C-2,4), 28.4/27.7* ($(CH_3)_3$C, Boc), 28.4/27.7* (C-6,7) ppm. (* The spectrum showed two rotamers.) HRMS (ES); calculated for $C_{25}H_{31}NONa$ (M + Na): 416.2206. Found: *m/z* 416.2202.

3-(1-Phenylethoxy)-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (12a)

Chromatography (pentane/EtOAc, 20 : 1, R_f = 0.39), gave the product **12a** (99 mg, 91%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.29–7.20 (5H, m, Ph–H), 4.44 (1H, q, O–CH(Me)–Ph, *J* = 6.4 Hz), 4.11 (2H, br. s, H-1,5), 3.48 (1H, br. s, H-3), 2.19–1.63 (8H, m, H_2-2,4,6,7), 1.40 (9H, s, $(CH_3)_3$, Boc), 1.35 (3H, d, CH_3, *J* = 6.4 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 153.3 (C=O, Boc), 144.2 (C(Ph)), 128.2; 127.1; 126.0 (CH(Ph)), 78.8 ($C(CH_3)_3$, Boc), 74.9 (O–CH(Me)–Ph), 69.3 (C-3), 53.1/52.3* (C-1,5), 37.0/36.1* (C-2,4), 34.2/33.4* (C-6,7), 28.4/27.8* ($(CH_3)_3$C, Boc), 24.4 (CH_3). (* The spectrum showed two rotamers.) HRMS (ES), Calculated for $C_{20}H_{29}NO_3Na$ (M + Na): 354.2045. Found: *m/z* 354.2045.

3-(1-Phenylpentyloxy)-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (13a)

Chromatography (pentane/EtOAc, 20 : 1, R_f = 0.29), gave the product **13a** (120 mg, 52%) as a colourless solid. M.p. 71.6 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.34–7.23 (5H, m, Ph–H), 4.27 (1H, t, *J* = 6.8 Hz, O–CH(Bu)–Ph), 4.14 (2H, br. s, H-1,5), 3.46 (1H, br. s, H-3), 2.21–1.85 (8H, m, H_2-2,4,6,7), 1.72–1.52 (4H, m, CH_2–CH_2 butyl), 1.42 (9H, s, $(CH_3)_3$, Boc), 1.30 (2H, q, *J* = 5.6 Hz, CH_2–CH_3 butyl), 0.86 (3H, t, *J* = 5.6 Hz, CH_3 butyl) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz) δ = 153.6 (C=O, Boc), 143.5 (C(Ph)), 128.4; 127.4; 127.0 (CH(Ph)), 80.0 (O–CH(Bu)–Ph), 79.1 ($C(CH_3)_3$, Boc), 69.6 (C-3), 53.3/52.6* (C-1,5), 38.7 (CH_2), 37.6/35.9* (C-2,4), 34.1/33.4* (C-6,7), 28.7/28.2* ($(CH_3)_3$C, Boc), 28.2 (CH_2), 22.9 (CH_2), 14.2

(CH_3) ppm. (* The spectrum showed two rotamers.) HRMS (ES); calculated for $C_{23}H_{35}NO_3Na$ (M + Na): 396.2518. Found: *m*/*z* 396.2515.

Synthesis of *N*-Boc-protected libraries I–V and a–e

The reactions were carried out by dissolving approximately 200 mg (0.6 mmol) of 3-(azidophenylmethoxy)-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (**4**) in 5 mL of dry toluene. A freshly prepared ether solution of the desired multiple-component Grignard reagents (2 equivalents) were slowly added (*ca.* 2 h) with continuous stirring at room temperature. The halides used in the Grignard reactions were mixed according to Table 2. The additions of the Grignard reagents caused a colour change from colourless to yellow. After the additions the reactions were quenched by adding 1 mL saturated solution of NH_4Cl and 1 mL of water. The mixtures were extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$ and evaporated to dryness. The crude compound was used without further purification.

Deprotection of a single amine compound

The Boc-protected compound (0.6 mmol) was dissolved in CH_2Cl_2 (5 mL). 2,6-Lutidine (8 eq.) and TMSOTf (5 eq.) were added at 0 °C. The reaction was allowed to reach room temperature over 45 min. After stirring for another 10 min (monitored by TLC) the reaction was quenched by adding a saturated solution of $NaHCO_3$ (8 mL) and extracted with DCM (3 × 10 mL). The dried ($MgSO_4$) organic layer was evaporated *in vacuo* and the residue was purified by chromatography (MeOH, 2% Et_3N) to give the product as clear colourless oil.

3-Benzhydryloxy-8-azabicyclo[3.2.1]octane (6)[15]

R_f = 0.29 (MeOH, 2% Et_3N). Yield 94%. ^1H NMR ($CDCl_3$, 200 MHz) δ = 7.31–7.10 (10H, m, Ph–H), 5.35 (1H, s, O–CH–$(Ph)_2$), 3.57 (1H, br. s, H-3), 3.44 (2H, br. s, H-1,5), 3.01 (1H, br. s, NH), 2.25–1.66 (8H, m, H_2-2,4,6,7) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 142.9 (C(Ph)), 128.2; 127.1; 126.7 (CH(Ph)), 80.7 (O–CH–$(Ph)_2$), 69.6 (C-3), 53.5 (C-1,5), 36.8 (C-2,4), 29.1 (C-6,7) ppm. HRMS (ES); calculated for $C_{20}H_{23}NONa$ (M + Na): 294.1853. Found: *m*/*z* 294.1858.

3-(3-Methyl-1-phenylbutoxy)-8-azabicyclo[3.2.1]octane (8)

R_f = 0.28 (MeOH, 2% Et_3N). Yield 63% (2 steps). ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.17 (5H, m, Ph–H), 4,31 (1H, br. s, NH), 4.26 (1H, dd, *J* = 5.2 Hz, *J* = 7.6 Hz, O–CH(Ph)–CH_2), 3.52 (2H, br. s, H-1,5), 3.37 (1H, t, *J* = 4.4 Hz, H-3), 2.01–1.73 (8H, m, H_2-2,4,6,7), 1.65–1.62 (2H, m, CH_2 isobutyl), 1.29 (1H, sep, CH_2–CH–$(CH_3)_2$, *J* = 5.2), 0.86 (6H, t, CH_3–CH–CH_3, *J* = 5.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 143.8 (C(Ph)), 128.5; 127.5; 127.0 (CH(Ph)), 78.0 (O–CH–Ph), 69.1 (C-3), 54.1; 53.9 (C-1,5), 48.5 (2H, CH_2 isobutyl), 40.0; 38.5 (C-2,4), 29.0; 28.7 (C-6,7), 24.6 (CH), 23.5 (CH_3), 22.5 (CH_3) ppm. HRMS (ES); calculated for $C_{18}H_{28}NO$ (M + H): 274.2177. Found: *m*/*z* 274.2171.

3-(1-Phenylbutoxy)-8-azabicyclo[3.2.1]octane (9)

R_f = 0.28 (MeOH, 2% Et_3N). Yield 61% (2 steps). ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.14 (5H, m, Ph–H), 4.20 (1H, dd, O–CH–Ph, *J* = 5.2 Hz, *J* = 7.6 Hz), 3.41 (2H, br. s, H-1,5), 3.36 (1H, t, *J* = 4.4 Hz, H-3), 2.35 (1H, br. s, NH), 2.19–2.15 (2H, m, CH_2), 1.88–1.61 (8H, m, H_2-2,4,6,7), 1.51–1.09 (2H, m, CH_2), 0.83 (3H, t, CH_3, *J* = 7,6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 143.6 (C(Ph)), 128.2; 127.1; 126.8 (CH(Ph)), 79.2 (O–CH–Ph), 69.4 (C-3), 53.9; 53.7 (C-1,5), 41.1; 40.8 (C-2,4), 39.0 (CH_2), 29.4; 29.1 (C-6,7), 19.1 (CH_2), 14.2 (CH_3) ppm. HRMS (ES); calculated for $C_{17}H_{26}NO$ (M + H): 260.2014. Found: *m*/*z* 260.2010.

3-[(2-Ethylphenyl)phenylmethoxy]-8-azabicyclo[3.2.1]octane (10)

R_f = 0.28. Yield 59% (2 steps). ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.50–7.08 (9H, m, Ph–H), 5.57 (1H, s, O–CH–Ph), 3.56 (1H, br. s, H-3), 3.42 (2H, br. s, H-1,5), 2.65 (1H, br. s, NH), 2.64–2.45 (2H, m, CH_2), 1.92–1.61 (8H, m, H_2-2,4,6,7), 0.98 (3H, t, CH_3, *J* = 7.6 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 142.7; 141.6; 139.8 (C(Ph)), 128.8; 128.3; 127.9; 127.7; 127.5; 127.2; 126.1 (CH(Ph)), 77.6 (O–CH–Ph), 69.7 (C-3), 53.9; 53.7 (C-1,5), 37.8; 36.5 (C-2,4), 29.5; 29.2 (C-6,7), 25.1 (CH_2), 15.0 (CH_3) ppm. HRMS (ES); calculated for $C_{22}H_{28}NO$ (M + H): 322.2171. Found: *m*/*z* 322.2171.

3-[(4-Chlorophenyl)phenylmethoxy]-8-azabicyclo[3.2.1]octane (11)[11]

R_f = 0.28. Yield 69% (2 steps). ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.22–7.15 (9H, m, Ph–H), 5.29 (1H, s, O–CH–Ph), 4.36 (1H, br. s, NH), 3.55 (1H, t, H-3, *J* = 3.2 Hz), 3.41 (2H, br. s, H-1,5), 2.18–1.61 (8H, m, H_2-2,4,6,7) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 142.4; 141.6 (C(Ph)), 133.0 (C(Ph–Cl), 128.6; 128.5; 128.2; 127.6; 126.8 (CH(Ph)), 80.3 (O–CH–Ph), 69.7 (C-3), 54.0; 53.7 (C-1,5), 36.7; 36.4 (C-2,4), 29.0; 28.2 (C-6,7) ppm. HRMS (ES); calculated for $C_{20}H_{23}ClNO$ (M + H): 328.1468. Found: *m*/*z* 328.1468.

3-Benzyloxy-8-azabicyclo[3.2.1]octane (14)

3α-Benzyloxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (**3**, 238 mg, 0.75 mmol) was dissolved in DCM (2 mL), and TFA (2 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction was quenched by adding a saturated solution of $NaHCO_3$ (8 mL) and extracted with DCM (3 × 10 mL). The dried ($MgSO_4$) organic layer was evaporated *in vacuo*. Purification by chromatography (MeOH, 2% Et_3N, R_f = 0.12) gave the product (153 mg, 94%) as a clear colourless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.30 (5H, m, Ph–H), 4.46 (1H, s, O–CH_2–Ph), 3.67 (1H, br. t, *J* = 4.4 Hz, H-3), 3.49 (2H, br. s, H-1,5), 2.31 (1H, br. s, NH), 2.21–1.73 (8H, m, H_2-2,4,6,7) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 139.4 (C(Ph)), 128.5; 127.4; 127.2 (CH(Ph)), 72.8 (O–CH_2–Ph), 70.6 (C-3), 54.0 (C-1,5), 37.1 (C-2,4), 29.6 (C-6,7) ppm. HRMS (ES); calculated for $C_{14}H_{20}NO$ (M + H): 218.1546. Found: *m*/*z* 218.1545.

3-(1-Phenylethoxy)-8-azabicyclo[3.2.1]octane (12)

Chromatography (MeOH, 2% Et_3N, R_f = 0.31) gave the product (55 mg, 57% over 2 steps) as a clear colourless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.17 (10H, m, Ph–H), 4.37 (1H, q, *J* = 6.4 Hz, O–CH–Ph), 3.40 (1H, s, H-3), 3.37 (2H, m, H-1,5), 1.95 (1H, br. s, NH), 2.17–1.69 (8H, m, H_2-2,4,6,7), 1.29 (3H, d, *J* = 6.4 Hz, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 136,7 (C(Ph)), 128.5; 127.3; 126.3 (CH(Ph)), 74.8 (O–CH–$(Ph)_2$), 69.6 (C-3), 54.0 (C-1,5), 38.9; 36.2 (C-2,4), 29.8; 29.5 (C-6,7), 24.8 (CH_3) ppm. HRMS (ES); calculated for $C_{15}H_{21}NONa$ (M + Na): 254.1521. Found: *m*/*z* 254.1525.

Compound library

The crude library from the multicomponent Grignard reaction (0.5 mmol) was dissolved in DCM (5 mL). 2,6-Lutidine (8 eq.) and TMSOTf (5 eq.) were added at 0 °C. The reaction was allowed to reach room temperature over 1 h. The reaction was quenched by adding a saturated solution of $NaHCO_3$ (8 mL) and extracted with DCM (3 × 10 mL). The dried ($MgSO_4$) organic layer was evaporated *in vacuo* and purified by chromatography (MeOH, 2% Et_3N) to give the library as a clear colourless or yellow oil in a yield of 56–70% over 2 steps.

8-Allyl-3-benzyloxy-8-azabicyclo[3.2.1]octane (15)

3-Benzyloxy-8-azabicyclo[3.2.1]octane (72 mg, 0.33 mmol) was dissolved in dry DMF (3 mL). K_2CO_3 (91 mg, 0.66 mmol) and

allyl bromide (31 μL, 0.37 mmol) were added. The reaction was stirred at room temperature for 1 h. The reaction was quenched by addition of water (10 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) organic layer was evaporated *in vacuo* and purified by chromatography (MeOH/DCM, 2:1, R_f = 0.32) to give the product (79 mg, 93%) as a clear colourless oil. ^{1}H NMR (CD_3OD, 400 MHz) δ = 7.31–7.23 (5H, m, Ph–H), 5.91 (1H, m, vinyl), 5.21 (2H, m, vinyl), 4.43 (2H, s, O–CH_2–Ph), 3.62 (1H, m, H-3), 3.26 (2H, m, H-1,5), 3.07 (2H, d, allyl, J = 6.4 Hz), 2.14–1.91 (8H, m, H_2-2,4,6,7) ppm. ^{13}C NMR (CD_3OD, 100 MHz) δ = 139.2 (C(Ph)), 134.1 (CH vinyl) 128.1; 127.2 (CH(Ph)), 118.4 (CH_2 vinyl), 71.7 (O–CH_2–Ph), 70.4 (C-3), 58.3 (allyl), 54.9 (C-1,5), 35.0 (C-2,4), 25.3 (C-6,7), 24.8 (CH_3) ppm. HR-MS (ES); calculated for $C_{15}H_{21}NONa$ (M + Na): 258.1858. Found: *m/z* 258.1850.

3-Benzhydryloxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid methyl ester (7)

To a solution of 3-benzhydryloxy-8-azabicyclo[3.2.1]octane (**6**, 45 mg, 0.15 mmol) in pyridine (0.5 mL) was added dropwise methyl chloroformate (0.1 mL) at 0 °C. The addition caused the clear colourless solution to be red. After stirring for additionally 30 min at room temperature (monitored by TLC) the reaction was quenched by addition of water (5 mL). 1 M HCl was added until a neutral pH value was obtained. The mixture was extracted with DCM (3 × 10 mL). The dried ($MgSO_4$) organic layer was evaporated *in vacuo* and the residue was purified by chromatography (pentane/EtOAc, 8:1, R_f = 0.24), to give the product (44 mg, 83%) as a clear colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.30–7.12 (10H, m, Ph–H), 5.36 (1H, s, O–CH–$(Ph)_2$), 4.17 (2H, m, H-1,5), 3.63 (1H, s, H-3), 3.60 (3H, s, Me), 2.19–1.66 (8H, m, H_2-2,4,6,7) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 154.0 (C=O), 142.6 (C(Ph)), 128.2; 127.2; 126.7 (CH(Ph)), 81.0 (O–CH–$(Ph)_2$), 69.7 (C-3), 52.7 (Me), 52.7/52.0* (C-1,5), 35.8/35.0* (C-2,4), 28.6/27.8* (C-6,7) ppm. (* The spectrum showed two rotamers.) HR-MS (ES); calculated for $C_{22}H_{25}NO_3Na$ (M + Na): 374.1729. Found: *m/z* 374.1732.

3-Benzhydryloxy-8-methyl-8-azabicyclo[3.2.1]octane (benztropine, 1)[16]

$LiAlH_4$ (108 mg, excess) was suspended in dry Et_2O (3 mL). 3-Benzhydryloxy-8-azabicyclo[3.2.1]octane-8-carboxylic acid methyl ester (33 mg, 0.094 mmol) was added and the mixture was refluxed for 2 h. Adding a saturated solution of NH_4Cl until all the $LiAlH_4$ was deactivated quenched the reaction. The mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) organic layer was evaporated *in vacuo* and the residue was purified by chromatography (pentane/EtOAc, 5:1, R_f = 0.38), to give the product (24 mg, 83%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.31–7.14 (10H, m, Ph–H), 5.34 (1H, s, O–CH–$(Ph)_2$), 3.50 (1H, s, H-3), 3.01 (2H, m, H-1,5), 2.19 (3H, s, Me), 2.10–1.81 (8H, m, H_2-2,4,6,7) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz) δ = 143.4 (C(Ph)), 128.5; 127.4; 127.0 (CH(Ph)), 80.9 (O–CH–$(Ph)_2$), 69.4 (C-3), 60.4 (CH_3), 40.7 (C-1,5), 36.6 (C-2,4), 26.0 (C-6,7) ppm. HRMS (ES); calculated for $C_{21}H_{25}NONa$ (M + Na): 308.2015. Found: *m/z* 308.2014.

Synthesis of model library Z

3-Benzyloxy-8-azabicyclo[3.2.1]octane (**14**, 110 mg, 0.51 mmol) was dissolved in dry DMF (3 mL), and K_2CO_3 (140 mg, 1.02 mmol) was added. Five alkyl bromides (1-bromobutane, 1-bromo-3-methyl-butane, 3-bromopropene, 3-bromopropyne, (3-bromopropyl)benzene) were added in mole-equivalent amounts (0.56 mmol total). The mixture was stirred at room temperature overnight. The reaction was quenched by addition of water (10 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) organic layer was evaporated *in vacuo* and the residue was purified by chromatography (MeOH/DCM, 2:1, R_f = 0.29), to give the product (82 mg, 57%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.08 (30H, m, Ph–H), 5.89–5.79 (1H, m, R_3), 5.11–5.02 (2H, m, R_3), 4.39 (10H, s, O–CH_2–Ph), 3.55 (5H, br. s, H-3), 3.11–3.10 (10H, m, H-1,5), 2.93 (2H, d, R_3, J = 6.4 Hz), 2.58 (1H, t, J = 8.0 Hz, R_4), 2.32–2.21 (6H, m, CH_2 R_5), 2.04–1.70 (40H, m, H_2-2,4,6,7), 1.56–1.17 (12H, m, CH_2 R_1, CH_2 R_2, CH_2 R_4), 0.85 (3H, t, CH_3 R_1, J = 7.6 Hz), 0.83 (6H, d, J = 6.4 Hz, CH_3 R_2) ppm. HRMS (ES); found: *m/z* 256.1; 258.1; 274.2; 288.2; 336.1.

Synthesis of libraries X_1–X_5 and Y_1–Y_5

One library of **I**–**V** or **a**–**e** (approx. 100 mg, 0.5 mmol) was dissolved in dry DMF (5 mL), and 2 eq. K_2CO_3 were added. Five alkyl bromides (1-bromobutane, 1-bromo-3-methylbutane, 3-bromopropene, 3-bromopropyne, (3-bromopropyl)benzene) were added in mole-equivalent amounts (1.1 eq. total). The mixtures were stirred at room temperature for 40 h. The reactions were quenched by addition of water (10 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) organic layers was evaporated to dryness. The libraries were synthesized in 70–90% yield.

Synthesis of libraries Z_1–Z_5

Libraries **I** to **V** were combined (approx. 100 mg, 0.3 mmol) and dissolved in dry DMF (5 mL), divided into 5 equal portions and 2 eq. K_2CO_3 were added to each reaction. Five alkyl bromides (1-bromobutane, 1-bromo-3-methylbutane, 3-bromopropene, 3-bromopropyne, (3-bromopropyl)benzene) were added separately to the five reactions in 1.1 mole-equivalent amounts. The five mixtures were stirred at room temperature until TLC analysis showed that the reactions were finished (1–40 h). The reactions were quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) organic layers was evaporated to dryness. The libraries were synthesized in 71–88% yield.

8-Butyl-3-(3-methyl-1-phenylbutoxy)-8-azabicyclo[3.2.1]octane (16)

R_f = 0.18. Yield 71%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.15 (5H, m, Ph–H), 4.27 (1H, dd, J = 5.2 Hz, J = 8.0 Hz, O–CH(Ph)–CH_2), 3.30 (1H, br. s, H-3), 3.07 (2H, br. s, H-1,5), 2.27–2.22 (2H, m, N–CH_2), 2.07–1.73 (8H, m, H_2-2,4,6,7), 1,69–1.62 (2H, m, CH_2 isobutyl), 1.55–1.51 (1H, m, CH isobutyl), 1.41–1.21 (4H, m, CH_2 butyl), 0.86 (6H, t, CH_3 isobutyl, J = 6.4 Hz), 0.83 (3H, t, J = 7.2 Hz, CH_3 butyl) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 144.0 (C(Ph)), 128.2; 127.1; 126.8 (CH(Ph)), 77.5 (O–CH–Ph), 69.2 (C-3), 58.3; 57.9 (C-1,5), 51.7 (N–CH_2), 48.5 (CH_2 isobutyl), 39.5; 37.3 (C-2,4), 31.1 (CH_2 butyl), 26.2; 26.0 (C-6,7), 24.3; 23.4 (CH_3 isobutyl), 22.3 (CH isobutyl), 21.0 (CH_2 butyl), 14.1 (CH_3 butyl) ppm. HRMS (ES); calculated for $C_{22}H_{35}NO$ (M + H): 330.2757. Found: *m/z* 330.2784.

8-(3-Methylbutyl)-3-(3-methyl-1-phenylbutoxy)-8-azabicyclo-[3.2.1]octane (17)

R_f = 0.20. Yield 62%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28–7.14 (5H, m, Ph–H), 4.26 (1H, dd, J = 5.2 Hz, J = 8.0 Hz, O–CH(Ph)–CH_2), 3.30 (1H, br. s, H-3), 3.07 (2H, br. s, H-1,5), 2.28–2.24 (2H, m, N–CH_2), 2.09–1.73 (8H, m, H_2-2,4,6,7), 1.70–1.60 (2H, m, CH_2 isobutyl), 1.55–1.45 (2H, m, CH isobutyl, CH 3-methylbutyl), 1.33–1.24 (2H, m, CH_2 3-methylbutyl), 0.86 (6H, t, CH_3 isobutyl, J = 6,4 Hz), 0.82 (6H, t, J = 7.2 Hz, CH_3 3-methylbutyl) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 144.0 (C(Ph)), 128.2; 127.1; 126.8 (CH(Ph)), 77.5 (O–CH–Ph), 69.2 (C-3), 58.3; 57.9 (C-1,5), 50.1 (N–CH_2), 48.5 (CH_2 isobutyl), 39.5; 37.8 (C-2,4), 37.2 (CH_2 3-methylbutyl), 26.8 (CH 3-methylbutyl), 26.2; 26.0 (C-6,7), 24.3; 23.4 (CH_3

isobutyl), 22.8 (CH_3 3-methylbutyl), 22.3 (CH isobutyl) ppm. HRMS (ES), Calculated for $C_{23}H_{37}NO$ (M + H): 344.2953. Found: *m/z* 344.2981.

Synthesis of [^{125}I]-RTI-55 {[^{125}I]-(1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester}

The synthesis of [^{125}I]-RTI-55 was published by Swahn *et al.*[17] We modified the radiosynthesis as follows: to a Nunc vial coated with 100 µg of iodogen was added 50 µL (0.5 mg mL^{-1}) of the trimethyltin precursor ((1*R*,2*S*,3*S*,5*S*)-3-(4-trimethylstannylphenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester)) prepared according to the literature,[17] and 40 µL of 0.02 N HCl. The mixture was transferred to the vial containing 74 MBq [^{125}I]iodide in 20 µL 0.01 M NaOH (Amersham Biosciences, IMS30) and back to the iodogen vial. The mixture was allowed to react in the dark for 30 min at room temperature. The [^{125}I]RTI-55 was purified by preparative HPLC (Macherey-Nagel Nucleosil 100–5 C18 4.6 × 250 mm, eluent: 375 mL MeOH, 1 mL Et_3N and sterile water was added to a total volume of 500 mL, retention time = 15 min) and a typical radiochemical yield of 50–70% was obtained. The fraction containing the desired product was evaporated immediately to avoid decomposition and reformulated in H_2O/EtOH/MeCN in the ratio 1 : 1 : 0.1, in a concentration of approximately 20 MBq mL^{-1}). A typical radiochemical purity of more than 95% was obtained (analytical HPLC conditions: Waters Nova-Pak C-18 3.9 × 150 mm, eluent: 4% TEA in H_2O/MeOH 35 : 65, flow: 1 mL min^{-1}, retention time = 7.1 min).

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