Bioorganic & Medicinal Chemistry Letters 19 (2009) 87–91

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Carbamoylcholine analogs as nicotinic acetylcholine receptor agonists—Structural modifications of 3-(dimethylamino)butyl dimethylcarbamate (DMABC)

Camilla P. Hansen, Anders A. Jensen *, Thomas Balle, Klaus Bitsch-Jensen, Mohamud M. Hassan, Tommy Liljefors, Bente Frølund *

Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Copenhagen University, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark

ARTICLE INFO

Article history:
Received 1 October 2008
Revised 1 November 2008
Accepted 4 November 2008
Available online 7 November 2008

Keywords:
Carbamoylcholine (CCh)
Nicotinic acetylcholine receptors agonists
$\alpha_4\beta_2$ nAChR
3-(Dimethylamino) butyl dimethylcarbamate

ABSTRACT

Compounds based on the 3-(dimethylamino)butyl dimethylcarbamate (DMABC) scaffold were synthesized and pharmacologically characterized at the $\alpha_4\beta_2$, $\alpha_3\beta_4$, $\alpha_4\beta_4$ and α_7 neuronal nicotinic acetylcholine receptors (nAChRs). The carbamate functionality and a small hydrophobic substituent in the C-3 position were found to be vital for the binding affinity to the nAChRs, whereas the carbamate nitrogen substituents were important for nAChR subtype selectivity. Finally, the compounds were found to be agonists at the $\alpha_3\beta_4$ nAChR.

The nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels mediating the effects of the neurotransmitter acetylcholine (ACh).[1–4] In addition to mediating the fast synaptic response of ACh in postsynaptic terminals, presynaptic nAChRs regulate the activities in the cholinergic synapse and in other important neurotransmitter systems.[5–8] Hence, the receptors are involved in various physiological processes and are implicated in a wide range of neurodegenerative and psychiatric disorders, for example, schizophrenia, depression, epilepsy, Alzheimer's disease and Parkinson's disease. Furthermore, the nAChRs are important targets in smoking cessation.[9–15]

The nAChRs are pentameric assemblies of subunits, which are either heteromeric complexes (composed of α_{2-6} and β_{2-4} or α_9 and α_{10}) or homomeric complexes (α_7 or α_9). The $\alpha_4\beta_2^*$ (the asterisk indicates the possible presence of other subtypes) and the α_7 nAChRs are the major CNS subtypes, whereas the $\alpha_3\beta_4^*$ is the major ganglionic nAChR.[2]

Previously, we have reported the synthesis and pharmacological characterization of several series of carbamoylcholine derived ligands based on the 3-(dimethylamino)butyl dimethylcarbamate (DMABC, **1**, Fig. 1) scaffold.[16–18] Several of these compounds, including compounds **1**–**4** (Fig. 1), were nAChR agonists with pronounced selectivities to the $\alpha_4\beta_2$ subtype over β_4-containing and α_7 nAChRs in binding assays.[16–18] Compound **3** was of particular interest as it was found to be a fairly potent partial $\alpha_4\beta_2$ agonist with negligible activities at the $\alpha_3\beta_4$ and the α_7 nAChRs when studied at these receptors expressed in *Xenopus oocytes*, using the two electrode voltage clamp technique.[17] Our structure–activity relationship (SAR) studies of the DMABC scaffold have so far led to the following major conclusions: (1) A tertiary amino group and one small hydrophobic substituent (such as methyl or ethyl) in the C-3 position are key determinants for high-affinity binding to the nAChRs[16,18] and (2) the nature of the carbamate nitrogen substituents greatly affects the nAChR binding affinities and $\alpha_4\beta_2/\alpha_3\beta_4$ selectivities of the DMABC analogs.[16–18] More specifically, introduction of azetidine rings at the carbamate nitrogen has resulted in highly $\alpha_4\beta_2$ selective compounds displaying nanomolar binding affinities to this receptor, whereas introduction of substituents larger than that (e.g. pyrrolidine, *N*,*N*-diphenyl and *N*,*N*-dipropyl) has led to diminished binding affinities to all nAChRs.[16–18] Smaller substituents at the carbamate nitrogen are well tolerated, yet they result in compounds with decreased $\alpha_4\beta_2$ nAChR selectivity compared to those of **3** and **4**.[16–18] Similar trends were found in a series of DMABC derived esters, where the carbamate nitrogen was replaced by a methine group.[17] However, the decrease in affinity as a result of increasing substituent size, was more pronounced in the ester series than in the carbamate series. The difference was attributed to the sp^3 hybridization of the methine carbon causing a slightly different spatial orientation of the substituents as compared to the sp^2 hybridized carbamate nitrogen.[17]

* Corresponding authors. Tel.: +45 35336491; fax: +45 35336040 (A.A.J.); tel.: +45 35336494; fax: +45 35336040 (B.F.).
E-mail addresses: aaj@farma.ku.dk (A.A. Jensen), bfr@farma.ku.dk (B. Frølund).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.11.011

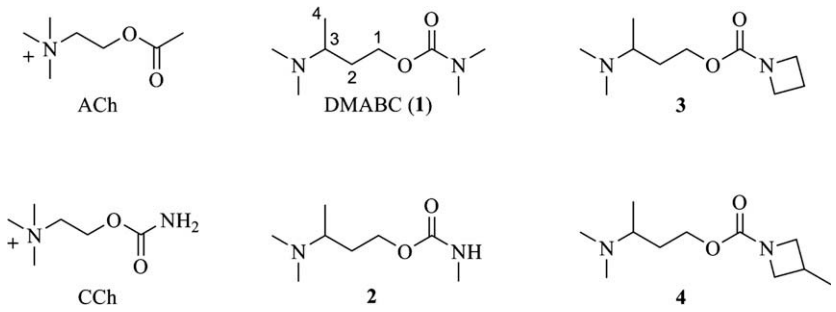

Figure 1. Acetylcholine (ACh), carbamoylcholine (CCh) and examples of the DMABC series, compounds **1**, **2**, **3** and **4**.

In the present study, we thoroughly probe the carbamate functionality of the DMABC scaffold (**5**–**10**, Fig. 2) and continue to explore the SARs of the C-3 position by substitution of the methyl group with small or planar substituents (**11a**–**d**, Fig. 2). Furthermore, we present a series of carbamate N-substituted DMABC analogs (**12a**–**e**, Fig. 2), as homology modeling studies revealed a rather spacious area in the binding pocket possibly allowing the introduction of larger substituents in one of the carbamate nitrogen positions while keeping one methyl group (Fig. 3).

Finally, we report a series of analogs with one hydrogen substituent on the carbamate nitrogen in order to further investigate the $\alpha_4\beta_2/\alpha_3\beta_4$ selectivity exhibited by compound **2** (**13a**–**e**, Fig. 2).[16,18]

Compound **5** was synthesized from 5-oxohexanoic acid by amidation followed by reductive amination, whereas **6a**–**b** were formed in Horner–Wadsworth–Emmons reactions from 3-dimethylamino-butan-1-ol.[19] Compounds **7**, **12a,b,e** and **13a**–**e** were synthesized according to standard carbamate formation procedures[16–18,20] from 3-dimethylamino-butan-1-ol and the appropriate thiocarbamoyl chloride, amine, carbamoyl chloride or isocyanate. Similar procedures were employed to obtain compounds **8** and **11a**–**d** using the appropriately 3-substituted aminothiol or aminoalcohols and dimethylcarbamoyl chloride. Compounds **12c**–**d** were formed in palladium cross coupling reactions of **2** and the arylchloride[21,22], while the ureas **9** and **10** were synthesized from 4-oxopentanoic acid using a modified Curtius reaction with diphenyl phosphorazidate (DPPA) and the appropriate amine followed by reductive amination.[23] All new compounds were characterized by ^{1}H NMR, ^{13}C NMR and CHN analysis.

The nAChR binding properties of compounds **5**–**13e** were determined in a [^{3}H]epibatidine binding assay to heteromeric $\alpha_4\beta_2$, $\alpha_3\beta_4$ and $\alpha_4\beta_4$ nAChRs stably expressed in HEK293 cells and in a [^{3}H]MLA binding assay to tsA-201 cells transiently expressing the α_7/5-HT$_{3A}$ chimera.[17] The functional properties of the compounds

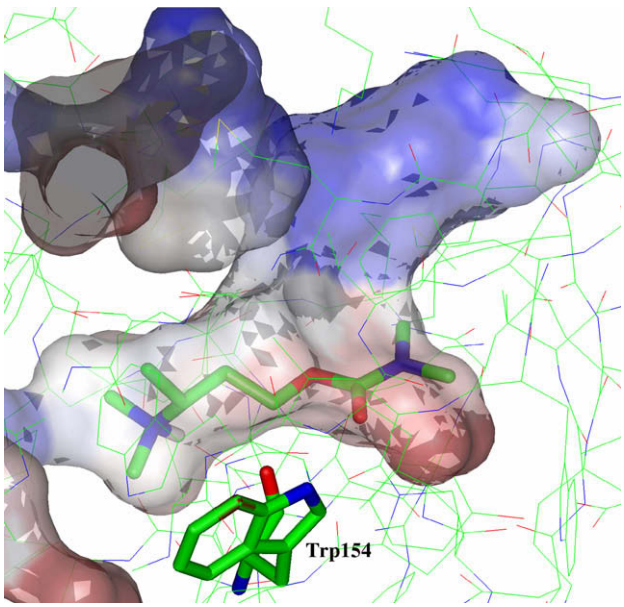

Figure 3. Compound **1** docked in the binding pocket of the homology model of the $\alpha_4\beta_2$ receptor.[17,32] The displayed PASS[33]-contour shows the cavities in the protein structure. A red color signifies deep burial in the protein whereas the blue area is closer to the surface.

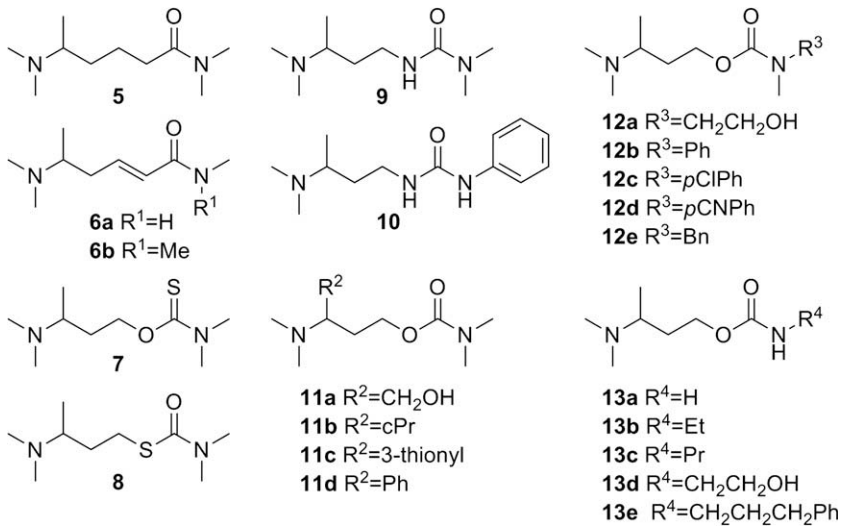

Figure 2. The newly synthesized DMABC analogs cPx, cyclopropyl; Bn, benzyl.

at the $\alpha_3\beta_4$ nAChR-HEK 293 cell line were determined in the FLIPR Membrane Potential™ (FMP) assay.[17] The pharmacological experiments were conducted as described in the literature.[17] The binding affinities of compounds **1**, **5**–**13e** to the $\alpha_4\beta_2$, $\alpha_3\beta_4$ and $\alpha_4\beta_4$ nAChRs and to the α_7/5-HT_{3A} chimera are given in Table 1. The functional characteristics of these compounds at the $\alpha_3\beta_4$ nAChR are given in Table 2 together with those of acetylcholine and compound **2**.

The observed pharmacological profiles of compounds **5**–**13e** at the heteromeric nAChRs exhibit similar trends when grouping the compounds according to their structural resemblance, that is as non-carbamates (**5**–**10**), carbamates with C-3 carbon substitutions (**11a**–**d**) and carbamates with carbamate nitrogen substitutions (**12a**–**13e**). In the following, the SARs are thus discussed within these groups unless specifically mentioned below. None of the compounds displayed significant affinity for the homomeric α_7 receptor which is in agreement with all previously synthesized compounds in the DMABC series.[16–18]

Exchanging the carbonyl oxygen of **1** with a sulfur atom (compound **7**) had detrimental effects on the binding affinity to all heteromeric nAChRs (Table 1). A similar effect has been observed for cytisine and thiocytisine, where the latter exhibited a 7- and 15-fold reduction in binding affinity to the $\alpha_4\beta_2$ and the α_7 nAChRs, respectively, compared to cytisine.[24] Sulfur is not as electronegative as oxygen and in addition, the optimal direction and length of hydrogen bonding to sulfur differ from those of hydrogen bonding to oxygen.[25] The decreased nAChR binding affinity of compound **7** and thiocytisine, compared to **1** and cytisine, thus indicate that the hydrogen bonding properties of the carbonyl oxygen is critical for binding and support the existence of a water-mediated hydrogen bond in this region of the binding pocket.[17,26]

Replacement of the ether-like oxygen in **1** with methylene, methine, sulfur or nitrogen (giving compounds **5**, **6b**, **8** and **9**, respectively) also resulted in ligands with significantly impaired binding affinities to all heteromeric nAChRs (Table 1). The observed decreases in binding affinity likely arise from several factors. Firstly, the hydrogen bonding properties of the carbonyl group are essential, as observed for compound **7**, and these will be affected by substitutions of the neighboring oxygen atom. Secondly, the degree of flexibility in the carbon chain is important. Compounds **5**, **6b**, **8** and **9** are all more rotationally restricted than **1**, which most likely affects the ability of the compounds to adopt the bioactive conformations. Thirdly, the most detrimental decrease in binding affinity compared to compound **1** was observed for urea **9**. This may partly be explained by the cost of desolvating the NH group of **9** in the absence of compensatory hydrogen bonding partners in the receptor.

The binding affinities displayed by compounds **11a**–**11d** were in concordance with observations made for previous C-3 substituted analogs.[16] Introduction of aromatic groups in the C-3 position (compounds **11c** and **11d**) led to decreased binding affinities to all heteromeric nAChRs compared to **1**, and although these ring systems were planar, the effect of aromatic substitution was comparable to the effect of a previously reported cyclohexyl substituent.[16] Analogously, the cyclopropyl analog (**11b**) displayed similar binding affinities to the nAChRs as the isopropyl analog.[16] Interestingly, introducing a hydroxymethyl group in the C-3

Table 1
Binding characteristics of the DMABC analogs at stable HEK293 cell lines expressing rat $\alpha_4\beta_2$, $\alpha_3\beta_4$, and $\alpha_4\beta_4$ nAChRs and at tsA201 cells transiently expressing the α_7/$5HT_{3A}$ chimera

Compound	$\alpha_4\beta_2$	$\alpha_3\beta_4$	$\alpha_4\beta_4$	α_7/$5HT_{3A}$	Compound	$\alpha_4\beta_2$	$\alpha_3\beta_4$	$\alpha_4\beta_4$	α_7/$5HT_{3A}$
1[a]	0.02 [7.7 ± 0.04]	0.42 [6.4 ± 0.06]	0.15 [6.8 ± 0.04]	>1000 [<3]	**11d**	35 [4.5 ± 0.04]	35 [4.5 ± 0.05]	6.6 [5.2 ± 0.05]	~1000 [~3]
5	1.1 [5.0 ± 0.05]	~300 [~3.5]	72 [4.1 ± 0.02]	>1000 [<3]	**12a**	1.6 [5.8 ± 0.05]	14 [4.8 ± 0.04]	3.9 [5.4 ± 0.05]	>1000 [<3]
6a	6.6 [5.2 ± 0.05]	24 [4.6 ± 0.05]	4.6 [5.3 ± 0.01]	>1000 [<3]	**12b**	9.8 [5.0 ± 0.03]	12 [4.9 ± 0.03]	3.4 [5.5 ± 0.05]	~1000 [~3]
6b	0.29 [6.5 ± 0.04]	6.3 [5.2 ± 0.06]	2.5 [5.6 ± 0.02]	>1000 [<3]	**12c**	12 [4.9 ± 0.03]	14 [4.9 ± 0.04]	3.9 [5.4 ± 0.06]	~1000 [~3]
7	1.5 [5.8 ± 0.05]	4.9 [5.3 ± 0.04]	6.9 [5.2 ± 0.05]	>1000 [<3]	**12d**	23 [4.6 ± 0.04]	25 [4.6 ± 0.03]	9.5 [5.0 ± 0.03]	~1000[~3]
8	1.6 [5.8 ± 0.03]	~100 [~4]	19 [4.7 ± 0.04]	>1000 [<3]	**12e**	0.13 [6.9 ± 0.05]	1.4 [5.8 ± 0.05]	0.42 [6.4 ± 0.06]	~1000 [~3]
9	~100 [~4]	~1000 [~3]	~100 [~4]	>1000 [<3]	**13a**	1.9 [5.7 ± 0.06]	3.2[5.5 ± 0.04]	2.1 [5.7 ± 0.05]	>1000 [<3]
10	~300 [~3.5]	~1000 [~3]	~300 [~3.5]	>1000 [<3]	**13b**	0.036 [7.4 ± 0.05]	12 [4.9 ± 0.05]	0.79 [6.1 ± 0.04]	>1000 [<3]
11a	3.6 [5.4 ± 0.04]	~100 [~4]	18 [4.7 ± 0.06]	>1000 [<3]	**13c**	0.048 [7.3 ± 0.05]	4.9 [5.3 ± 0.03]	1.6 [5.8 ± 0.04]	>1000 [<3]
11b	6.5 [5.2 ± 0.04]	40 [4.4 ± 0.01]	3.8 [5.4 ± 0.05]	>1000 [<3]	**13d**	0.20 [6.7 ± 0.06]	2.2 [5.7 ± 0.05]	8.1 [5.1 ± 0.01]	>1000 [<3]
11c	41 [4.4 ± 0.03]	45 [4.4 ± 0.04]	3.2 [5.5 ± 0.05]	~1000 [~3]	**13e**	0.091 [7.0 ± 0.04]	38 [4.4 ± 0.05]	1.4 [5.8 ± 0.04]	~1000 [~3]

The K_i values are given in μM with the pK_i ± SEM values in brackets.
[a] Binding data for compound **1** is from Ref. 17.

Table 2
Functional characteristics of the DMABC analogs at the stable $\alpha_3\beta_4$-HEK293 cell line in the FMP assay

Compound	EC_{50} [pEC_{50} ± SEM]	R_{max} ± SEM	Compound	EC_{50} [pEC_{50} ± SEM]	R_{max} ± SEM
ACh	19 [4.7 ± 0.03]	—	**11c**[a]	>1000 [<3]	n.d.
1	12 [4.9 ± 0.03]	107 ± 5	**11d**[a]	>1000 [<3]	n.d.
2	170 [3.8 ± 0.04]	103 ± 5	**12a**	160 [3.8 ± 0.05]	82 ± 5
5[a]	>1000 [<3]	n.d.	**12b**	51 [4.3 ± 0.04]	37 ± 4
6a	150 [3.8 ± 0.05]	96 ± 2	**12c**	28 [4.5 ± 0.04]	22 ± 5
6b	91 [4.0 ± 0.04]	89 ± 5	**12d**[a]	>1000 [<3]	n.d.
7	53 [4.3 ± 0.04]	67 ± 2	**12e**	6.7 [5.2 ± 0.03]	69 ± 5
8	430 [3.4 ± 0.03]	31 ± 4	**13a**	57 [4.2 ± 0.03]	93 ± 3
9[b]	>3000 [<2.5]	n.d.	**13b**	55 [4.3 ± 0.04]	96 ± 4
10[b]	>3000 [<2.5]	n.d.	**13c**	95 [4.0 ± 0.02]	69 ± 3
11a[b]	>3000 [<2.5]	n.d.	**13d**[c]	~300[~3.5]	n.d.
11b[a]	>1000 [<3]	n.d.	**13e**[a]	>1000 [<3]	n.d.

The EC_{50} values are given in μM (with the pEC_{50} ± SEM values in brackets), and the R_{max} values are given in % of the R_{max} of ACh.
n.d., not determined.
[a] Significant agonist responses were observed at concentrations higher than 300 μM.
[b] Significant agonist responses were observed at concentrations higher that 1 mM.
[c] The EC_{50} value for this compound is an estimate.

position (**11a**) led to a 120- to 240-fold decrease in nAChR binding affinity compared to **1**, whereas the binding affinity of the corresponding ethyl analog was much less affected (e.g. by a factor of 7 at the $\alpha_4\beta_2$ nAChR).[18] The two substituents are almost equivalent in size which indicates that polar C-3 substituents are disfavored.

Introduction of aromatic groups like phenyl (**12b**), *p*-chlorophenyl (**12c**) and *p*-cyanophenyl (**12d**) at the carbamate nitrogen of the DMABC scaffold gave rise to compounds with markedly decreased binding affinities to all heteromeric nAChRs as compared to **1**, which was convergent with earlier observations.[16–18] However, unlike any other compounds in the DMABC series, compounds **12b–d** displayed a slight preference (2- to 3-fold) for the $\alpha_4\beta_4$ nAChR over the $\alpha_4\beta_2$ subtype. Interestingly, the benzyl analog **12e** had considerably higher binding affinities to all heteromeric nAChRs compared to those of **12a–d**. In particular, the compound exhibited nanomolar binding to the $\alpha_4\beta_2$ nAChR which, together with the nanomolar $\alpha_4\beta_2$ binding affinity displayed by **13e**, suggests that the receptor has a narrow hydrophobic pocket extending outwards from the orthosteric site. Hence, the spacious area, which was observed in the homology modeling of the $\alpha_4\beta_2$ nAChR (Fig. 3), seems to be a little narrower than initially anticipated, and a ligand might require a linker moiety between the carbamate nitrogen and an aromatic group in order to accommodate this area of the receptor.

In the above-mentioned compounds both carbamate nitrogen positions were substituted and only one analog with a mono substituted carbamate (compound **2**) has previously been synthesized and analyzed. This compound displayed low nanomolar binding affinity to the $\alpha_4\beta_2$ nAChR (K_i = 13 nM) and a high degree of $\alpha_4\beta_2/\alpha_3\beta_4$ selectivity (770-fold).[18] Replacement of the methyl group at the carbamate nitrogen in **2** with ethyl or propyl groups (analogs **13b** and **13c**), resulted in ligands with binding profiles very similar to **2**, although the compounds did not exhibit the same level of $\alpha_4\beta_2/\alpha_3\beta_4$ selectivity (Table 1). The unsubstituted analog **13a** and hydrophilic hydroxyethyl derivative **13d** both displayed a decreased binding affinity to the $\alpha_4\beta_2$ nAChR (Table 1). Accordingly, binding affinity to and selectivity for the nAChRs are not greatly affected when the carbamate nitrogen has one, fairly small, hydrophobic substituent. However, increasing the size of the substituent leads to decreased binding affinity for the $\alpha_4\beta_2$ and the $\alpha_3\beta_4$ nAChR, as exhibited by the phenylpropyl analog **13e**.

Finally, compounds **5–13e** displayed agonistic properties at the $\alpha_3\beta_4$ nAChR in the FMP assay (Table 2), which confirmed the observations of earlier studies in which DMABC derived compounds were found to be agonists at the $\alpha_4\beta_2$ and the $\alpha_3\beta_4$ nAChRs.[16–18] As can be seen from Tables 1 and 2, the rank order of agonist potencies displayed by compounds **5–13e** at the $\alpha_3\beta_4$ nAChR was in good agreement with the rank order of their binding affinities at this receptor.

In conclusion, the present SAR study has provided us with new information on the structural requirements for binding of the DMABC class of compounds to the heteromeric β_2- and β_4-containing nAChRs. In addition, the critical ligand–protein interactions upon binding have been validated.

Both oxygens in the carbamate moiety of the DMABC scaffold appear to be crucial for binding to the nAChRs as substitution of these with other atoms leads to ligands with greatly reduced binding affinities. Hence, the hydrogen bonding properties of the carbamate functionality as well as the degree of flexibility in the carbon chain provided by the ether-like oxygen must be important. In addition, the presence of a small hydrophobic group, preferably a methyl group, at the C-3 carbon is essential for proper receptor binding, given that small hydrophilic or planar substituents in this position induces a shift from nanomolar to micromolar binding at the heteromeric nAChRs. This observation is in agreement with previous studies[16–18] where bulkier C-3 substituents were investigated.

Furthermore, the present study confirms that the carbamate nitrogen substituents greatly affect the binding properties and subtype selectivities of the DMABC analogs. Compounds with small hydrophobic substituents, whether they are mono- or disubstituted with, for example, methyl or ethyl groups, display nanomolar binding affinities to the $\alpha_4\beta_2$ nAChR in addition to exhibit marked selectivities for this receptor. Hydrophilic carbamate nitrogen substituents, on the other hand, are unfavorable as are aromatic groups directly attached to the carbamate nitrogen. However, the binding properties of **12e** and **13e** suggest that larger groups (such as for example aromatic groups) might be allowed as substituents in one of the carbamate nitrogen positions, if they are attached to a linker. The possibility of introducing a linker between two ligands (making a bivalent ligand) or between a ligand and a receptor specific group (such as a larger hydrophobic group that recognizes a hydrophobic pocket somewhere on the receptor) is intriguing and has been explored by various groups in the nAChR system[27,28] as well as other neurotransmitter systems.[29–31] Thus, the linker approach will be an interesting path to pursue in future studies.

Finally, the DMABC analogs presented in this study were shown to be agonists at the $\alpha_3\beta_4$ nAChR like all other compounds in the series to date.[16–18] Based on the resemblance with compounds **3** and **4** which in previous studies exhibited agonistic properties at the $\alpha_4\beta_2$ nAChR, the reported analogs are most likely agonists at this receptor as well, although this remains to be determined.

Acknowledgments

Drs. James W. Patrick and David J. Julius are thanked for providing the nAChR and 5-HT_{3A} receptor cDNAs. Drs. Ken Kellar and Yingxian Xiao are thanked for giving us the $\alpha_3\beta_4$ and $\alpha_4\beta_4$ nAChR cell lines and Dr. Joe Henry Steinbach for providing us with the $\alpha_4\beta_2$-HEK293 cell line Shahrokh Padrah is thanked for his technical assistance. This work was supported by the Lundbeck Foundation, the Carlsberg Foundation and the Danish Medical Research Council.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.11.011.

References and notes

1. Gotti, C.; Zoli, M.; Clementi, F. *Trends Pharmacol. Sci.* **2006**, *27*, 482.
2. Jensen, A. A.; Frølund, B.; Liljefors, T.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2005**, *48*, 4705.
3. Karlin, A. *Nat. Rev. Neurosci.* **2002**, *3*, 102.
4. Le Novère, N.; Changeux, J. P. *J. Mol. Evol.* **1995**, *40*, 155.
5. Girod, R.; Barazangi, N.; McGehee, D.; Role, L. W. *Neuropharmacology* **2000**, *39*, 2715.
6. Kenny, P. J.; File, S. E.; Neal, M. J. *J. Neurochem.* **2000**, *75*, 2409.
7. Seth, P.; Cheeta, S.; Tucci, S.; File, S. E. *Pharmacol. Biochem. Behav.* **2002**, *71*, 795.
8. Wonnacott, S.; Soliakov, L.; Wilkie, G.; Redfern, P.; Marshall, D. *Drug Dev. Res.* **1996**, *38*, 149.
9. Feret, B.; Orr, K. *Formulary* **2006**, *41*, 265.
10. Fujita, M.; Ichise, M.; Zoghbi, S. S.; Liow, J.-S.; Ghose, S.; Vines, D. C.; Sangare, J.; Lu, J.-Q.; Cropley, V. L.; Iida, H.; Kim, K. M.; Cohen, R. M.; Bara-Jimenez, W.; Ravina, B.; Innis, R. B. *Ann. Neurol.* **2006**, *59*, 174.
11. Gotti, C.; Clementi, F. *Prog. Neurobiol.* **2004**, *74*, 363.
12. Marini, C.; Guerrini, R. *Biochem. Pharmacol.* **2007**, *74*, 1308.
13. Oddo, S.; LaFerla, F. M. *J. Phys. (Paris)* **2006**, *99*, 172.
14. Paterson, D.; Nordberg, A. *Prog. Neurobiol.* **2000**, *61*, 75.
15. Rollema, H.; Chambers, L. K.; Coe, J. W.; Glowa, J.; Hurst, R. S.; Lebel, L. A.; Lu, Y.; Mansbach, R. S.; Mather, R. J.; Rovetti, C. C.; Sands, S. B.; Schaeffer, E.; Schulz, D. W.; Tingley, F. D., III; Williams, K. E. *Neuropharmacology* **2007**, *52*, 985.

16. Jensen, A. A.; Mikkelsen, I.; Frølund, B.; Frydenvang, K.; Brehm, L.; Jaroszewski, J. W.; Bräuner-Osborne, H.; Falch, E.; Krogsgaard-Larsen, P. *Eur. J. Pharmacol.* **2004**, *497*, 125.
17. Hansen, C. P.; Jensen, A. A.; Christensen, J. K.; Balle, T.; Liljefors, T.; Frølund, B. *J. Med. Chem.* [Epub 11-07-2008].
18. Jensen, A. A.; Mikkelsen, I.; Frølund, B.; Bräuner-Osborne, H.; Falch, E.; Krogsgaard-Larsen, P. *Mol. Pharmacol.* **2003**, *64*, 865.
19. Langlois, N.; Rojas-Rousseau, A.; Gaspard, C.; Werner, G. H.; Darro, F.; Kiss, R. *J. Med. Chem.* **2001**, *44*, 3754.
20. Albrecht, R.; Gutsche, K.; Kessler, H. J.; Schröder, E. *J. Med. Chem.* **1970**, *13*, 733.
21. Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.
22. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.
23. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
24. Imming, P.; Klaperski, P.; Stubbs, M. T.; Seitz, G.; Gündisch, D. *Eur. J. Med. Chem.* **2001**, *36*, 375.
25. Platts, J. A.; Howard, S. T.; Bracke, B. R. F. *J. Am. Chem. Soc.* **1996**, *118*, 2726.
26. Celie, P. H. N.; van Rossum-Fikkert, S. E.; van Dijk, W. J.; Brejc, K.; Smit, A. B.; Sixma, T. K. *Neuron* **2004**, *41*, 907.
27. Zheng, G.; Zhang, Z.; Pivavarchyk, M.; Deaciuc, A. G.; Dwoskin, L. P.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6734.
28. Dwoskin, L. P.; Joyce, B. M.; Zheng, G.; Neugebauer, N. M.; Manda, V. K.; Lockman, P.; Papke, R. L.; Bardo, M. T.; Crooks, P. A. *Biochem. Pharmacol.* **2007**, *74*, 1271.
29. Morphy, R.; Rankovic, Z. *J. Med. Chem.* **2005**, *48*, 6523.
30. Tejada, F. R.; Nagy, P. I.; Xu, M.; Wu, C.; Katz, T.; Dorsey, J.; Rieman, M.; Lawlor, E.; Warrier, M.; Messer, W. S. *J. Med. Chem.* **2006**, *49*, 7518.
31. Choi, S. K.; Green, D.; Ho, A.; Klein, U.; Marquess, D.; Taylor, R.; Turner, S. D. *J. Med. Chem.* **2008**, *51*, 3609.
32. Le Novère, N.; Grutter, T.; Changeux, J. P. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3210.
33. Brady, G. P.; Stouten, P. F. W. *J. Comput. Aided Mol. Des.* **2000**, *14*, 383.