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Synthesis and evaluation of phenylcarbamate derivatives as ligands for nicotinic acetylcholine receptors

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Abstract—Phenylcarbamate derivatives were synthesized and evaluated in radioligand binding assays for different nicotinic acetylcholine receptor (nAChR) subtypes. Carbamate derivatives bearing a pyrrolidine or piperidine moiety **8**–**20** exhibited much lower affinity for α7* nAChR than the analogues in the quinuclidine series **21**–**25**, although the same structural elements are present. Furthermore, in contrast to the quinuclidine analogues **21**–**25**, all (*S*)-pyrrolidine derivatives **8**–**12** and the piperidine analogues **15** and **16** exhibited higher affinities for α4β2* nAChR.

1. Introduction

Acetylcholine (ACh) is interacting with two major receptor classes, which can be subdivided into G-protein coupled receptors (muscarinic receptors, mAChRs) and ligand-gated ion channels (nicotinic receptors, nAChRs). Over the past years, neuronal nicotinic acetylcholine receptors are subject of increasing interest being involved in various physiological and pathophysiological processes related to cognition and learning.[1–3] Further on, several nACh receptor subtypes exist in peripheral neurons of autonomic and sensory ganglia, and evidence exists for expression of nAChRs in other tissues and cell types, including lymphocytes, fibroblasts, pulmonary neuroendocrine cells, spermatozoa, keratinocytes, granulocytes, chondrocytes, placenta, and several sensory organs.[4–6] The search and development of ligands for nAChRs were mostly focused on selectivity for α4β2, the most abundant subtype in the CNS. The interest is now growing to develop ligands for α7 and α3-containing subtypes, which are additionally implicated in different diseases of the PNS. Recently, choline, the metabolite of ACh, has been described as a selective activator of α7-type nAChRs involved in neuroprotective activity despite its very low affinity for this receptor subtype ($K_i = 2380\,\mu M$).[7] In the past, acetylcholine and moreover choline have attracted limited interest as lead compounds.[8–12] The structure of choline can be found in a variety of compounds displaying multifarious pharmacological effects, for example, in drugs with antihistaminic and analgesic properties like diphenhydramine and nefopam, respectively, which even display affinities in the micromolar range for neuronal nAChRs.[13] Aryl ether analogues of choline are known as inhibitors of amine oxidase,[14,15] and are also described as compounds with antibacterial, cholesterol level lowering, and germicidal properties.[16] Mono- and poly-substituted pyridyl ether analogues of choline were patented for the use as pesticides.[17] Very recently, Simsek and co-workers[18] showed that several 3-pyridyl ether analogues of choline displayed nanomolar affinities for [^{3}H](-)nicotine sensitive binding sites and antinociceptive properties. Similar analogues of choline, where the amine function is incorporated in a cyclic carbon skeleton are one of the most potent ligands for α4β2 nAChR.[19] Extending choline with an amide moiety to obtain the carbamate function leads to carbacholine, a known muscarinic ligand, whereas the N-methylated analogues MCC and DMCC analogues have been described as nicotinic ACh agonists.[20,21] Carbamates, especially phenylcarbamate derivatives are known as compounds exhibiting a broad pharmacological spectrum, for example, interactions with muscarinic and 5-HT$_3$ receptors,[22,23] local anaesthetic,[24,25] spasmolytic,[26] and analgetic[27] properties, and very recently selective interaction with the α7 subtype of nicotinic acetylcholine receptors (nAChRs).[28,29]

Keywords: Phenylcarbamate; Nicotinic acetylcholine receptor; Epibatidine; MLA (methyllycaconitine).
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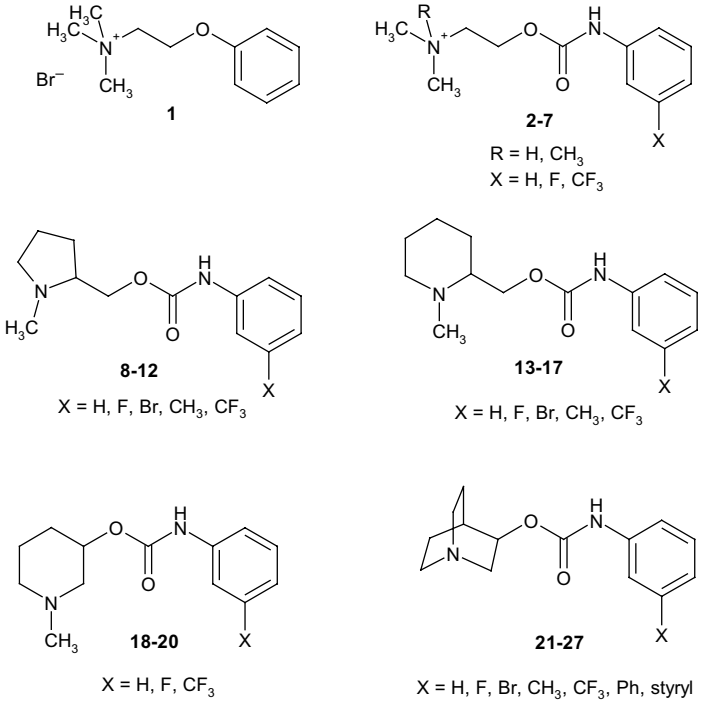
In the course of our investigations, we prepared and evaluated known and novel carbamate derivatives to get more insight into structural requirements for nAChRs, especially for the α7 nAChR. Firstly, we examined the nAChR binding profile of the phenylether of choline **1** (Scheme 1), which has been shown as a powerful ganglion stimulant by Hunt and Renshaw in 1929.[30] Starting from **1**, we were interested to evaluate the binding affinities for several nAChR subtypes observed after the introduction of a carbamate functionality in **1** and related derivatives including their azacyclic analogues (Scheme 1). Since it is known that *ortho* and *para* substitutions at the phenyl moiety in phenylcarbamate derivatives are strongly enhancing the affinity for mAChRs,[21,22] and the *ortho* substitution is also favored for local anaesthetic properties,[23,24] the meta position of the phenyl moiety was chosen for further substitutions (Scheme 1).

2. Results and discussion

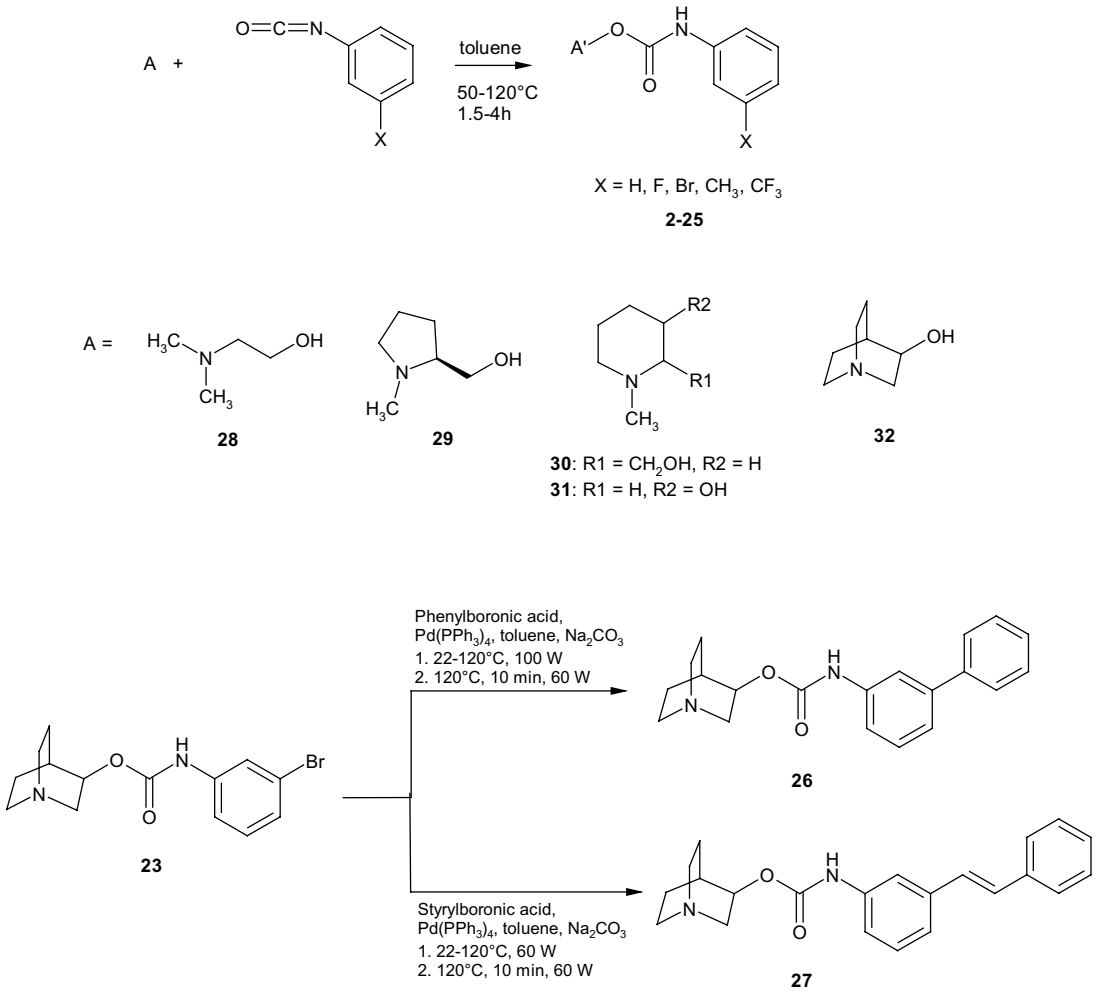
2.1. Chemistry

The phenylether of choline **1** was prepared according to the method of Renshaw and Armstrong.[31] The syntheses of the phenylcarbamate derivatives **2**–**25** including the compounds with different azacyclic cores were carried out under a variety of conditions with regard to the solvent, temperature, and the presence of a catalyst. In summary, equimolar amounts of amino alcohols and the appropriate phenylisocyanate in dry toluene were stirred for 1.5–4 h under argon atmosphere (Scheme 2) to obtain the phenylcarbamate derivatives **2**–**25** in high yields. The reactions were performed under reflux temperature with the exception of derivatives bearing a 3-bromo- or 3-methyl-phenyl (**10**, **11**, **15**, **16**, **23**, **24**) moiety for which we found reduced yields and increased by-products at reflux temperature. Therefore, these compounds were synthesized at max. 50 °C. The addition of a basic catalyst, for example, triethylamine, which is commonly used for the preparation of carbamate derivatives, did not positively influence the yield of the desired products. The derivatives **2** and **5** (DMAE und TMAE phenylcarbamates) were already synthesized by Abood et al.[32] using toluene and a 16 h refluxing period, but were not analytically characterized in detail. The prepared azabicyclic carbamate derivative **23**, also mentioned as a ligand for α7 nAChR in a patent of Astra Laboratories,[28] was used for additional phenyl or styryl substitution at the phenyl moiety (**26**, **27**). Thus, compounds **26** and **27** were prepared by the Suzuki coupling reaction under microwave[33] accelerated conditions in moderate yields, demonstrating a high stability of the azabicyclic carbamate derivatives (**26**, **27**) during reaction (Scheme 2). In contrast to our fast Suzuki method, the biphenyl analogue **26** was synthesized by Naito et al.[22] and Astra Laboratories[28] using biphenyl isocyanate, which was obtained by the addition of phosgene[28] or DPPA[22] (diphenylphosphoryl azide) and triethylamine to 3-aminobiphenyl or biphenyl-3-carboxylic acid, respectively.

The carbamate derivatives **2**–**27** were purified by column chromatography on silica gel. Quaternary salts were prepared by adding methyliodide to the appropriate compounds in acetone and purified by precipitating them out. Compounds **2**–**27** were stable under binding assay conditions using a HEPES salt solution (pH 7.4).



Scheme 1.



Scheme 2.

2.2. In vitro receptor binding

Previously described receptor binding assays[13,34–36] were used to evaluate the prepared compounds **1**–**27** for their abilities to compete for [^{3}H]epibatidine and [^{3}H]MLA binding sites in rat forebrain (α4β2*, α7*), pig adrenals (α3β4*) and *Torpedo californica* electroplax ($(\alpha1)_2\beta1\gamma\delta$) membrane fractions (Table 1). The phenylether of choline **1**, evaluated for different nAChRs for the first time, showed nanomolar affinities for neuronal nAChR subtypes with a preference for α4β2* (Table 1). Compound **1** was transformed into an α7* nAChR selective compound with nanomolar affinity when converting it to the corresponding carbamate analogue **5**. Abood and coworkers[32] have reported the ability of **2** and **5** to inhibit the specific binding of [^{3}H]nicotine and [^{3}H]methylcarbamylcholine in rat brain membranes at milli- (for **2**) and micromolar (for **5**) concentrations, but no results were obtained for other nAChR subtypes. Fluorine substitution at position 3 of the phenyl moiety led to a carbamate derivative **6** with slightly reduced affinities for α4β2* and α7* nAChR, but equal subtype selectivity like **5**, whereas the introduction of a trifluoromethyl group enhanced the affinity and subtype selectivity for α7* nAChR. In contrast to the quaternary derivatives **5**–**7**, the tertiary amine analogues **2**–**4** showed dramatically reduced affinities for nAChRs examined, an effect frequently observed for nAChR ligands. Compounds **8**–**27** synthesized with the intention of a penetration through the blood–brain barrier and to study the influence of the azacyclic core, exhibited different binding profiles for diverse nAChR subtypes (Table 1). *N*-Methyl-pyrrolidine derivatives **8**–**12** showed K_i values in the higher nanomolar to lower micromolar range for α4β2* and lower affinity for the α7* subtype (Table 1), which subtype selectivity is contrary to the quaternary ammonium compounds **5**–**7**. Despite of the carbamate moiety, compounds **8**–**12** showed still the subtype profile with affinities in the rank order of $\alpha4\beta2^*>\alpha3\beta4^*>\alpha7^*$, which is mostly found for hitherto existing nAChR ligands. Comparing with their *S*-configurated 2-(aryloxymethyl)pyrrolidine counterparts,[37] which exhibit K_i values in the lower nanomolar range for α4β2*, **8** and **9** showed a ca. 10- and 100-fold, respectively, decreased affinity for α4β2* nAChR. SAR studies within the *N*-methyl-piperidine series **13**–**20** explored the effect of aromatic substitution and the position of the phenylcarbamate moiety at the piperidine ring. Compounds **18**–**20** showed a preference for α7* nAChR with K_i values in the low micromolar range (Table 1) and no effect at α4β2* nAChR, whereas **13**–**17**, displayed a complex pattern of subtype selectivity. Analogues with

fluorine and trifluoromethyl substituents (**14**, **17**) demonstrated poor receptor binding affinities. Surprisingly, the unsubstituted compound **13** was found to show selectivity towards α3β4*. Only **15** and **16** being the most potent analogues in the piperidine series for α4β2* nAChR gave a similar subtype profile like their pyrrolidine analogues **8**–**12**. The quinuclidine analogues **21** and **26**, already developed for SAR studies on muscarinic receptors[22] and also claimed together with **22**–**24** as α7 selective compounds in a patent of Astra Laboratories[28] were examined for different nAChR subtypes. Like the phenylcarbamate derivatives **5**–**7** compounds **21**–**25** exhibit remarkable selectivity for α7* versus α4β2*. Bulkier groups at the phenyl moiety reduce affinity for α7* and subtype selectivity, which can be strongly observed in the styryl analogue **27**. It is interesting that carbamate derivatives bearing a pyrrolidine or piperidine moiety **8**–**20** possess much lower affinity for α7* nAChR than the analogues in the quinuclidine series **21**–**25**, although the same structural elements are present, like a basic nitrogen, which can be protonated providing a cationic center, a carbamate moiety, and a π-electron system. Furthermore, in contrast to the quinuclidine analogues **21**–**25**, all (*S*)-pyrrolidine derivatives **8**–**12** and the piperidine analogues **15** and **16** exhibited higher affinities for α4β2* nAChR. It seems that the carbamate moiety together with a certain spatial distance between the oxygen and the nitrogen of the choline fragment in these derivatives, are crucial for the interaction with the α7* nAChR. The favorite distance between the choline oxygen and nitrogen can probably be fulfilled in the azabicyclic core of, for example, the quinuclidine moiety or the acyclic variant. We also investigated the binding affinities for the α3β4* subtype. Table 1 reveals that with exception of **23** all phenylcarbamate derivatives examined show K_i values in the micromolar range for the ganglionic subtype. Compared with the pyrrolidine and piperidine series a higher affinity for α3β4* is observed for the quinuclidine derivatives **21**–**26**. As indicated in Table 1, the 3-bromophenyl carbamate derivatives **10**, **15**, **23** showed the most interesting binding profiles. Within the bromo analogues, **23** is the most potent compound for α7* with a K_i value of 273 nM, whereas the (*S*)-pyrrolidine analogue **10** showed the highest affinity for α4β2* (K_i = 526 nM), both compounds displaying contrary profiles of subtype selectivity. The highest affinity for α3β4* nAChR was also obtained for **23**, whereas **10** and **15** exhibited similar, but a ca. 9-fold lower affinity for the ganglionic subtype. None of the phenylcarbamate derivatives examined showed activity for the muscle type nAChR. Interestingly, 3-quinuclidinole, the compound used for the synthesis of **21**–**25** and which can be considered as a rigid choline derivative, displayed K_i values in the mircomolar range for different neuronal nAChRs with similar affinities for α4β2* and α7* nAChRs.

3. Conclusion

We demonstrated that phenylcarbamate derivatives led to compounds with different subtype selectivity for nAChRs. Compounds **5**–**7**, together with their quinuclidine analogues **21**–**25**, displayed highest affinities and subtype selectivity for α7*. Surprisingly, all (*S*)-pyrrolidine derivatives **8**–**12** and the piperidine analogues **15** and **16** exhibited higher affinities and subtype selectivity for α4β2* nAChR. The position of the phenylcarbamate moiety at the piperidine ring within the *N*-methyl-piperidine series **13**–**20** influenced the subtype selectivity towards α7* and α3β4* nAChRs. The difference in subtype selectivity among the phenylcarbamate derivatives could be discussed on the basis of the spatial distance of the nitrogen and oxygen of the choline substructure incorporated.

4. Experimental

4.1. General procedures

Each starting material was obtained from commercial suppliers with the exception of styrylboronic acid, which was synthesized according to Brown and Gupta.[38] Standard vacuum techniques (argon atmosphere) were used in handling of air sensitive materials. Melting points were determined on a Büchi Melting Point B-545 and are uncorrected. Solvents were dried and freshly distilled before use according to literature procedures. IR spectra were obtained on a Perkin–Elmer 1310 IR spectrometer; liquids were run as films, solids as KBr pellets. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker DRX 500 at 298 K. Chemical shifts (δ) are reported in ppm (J values in Hz) and are referenced to the solvent (^{1}H NMR: δ/ppm = 7.24 for chloroform, 2.49 for dimethylsulfoxid, 3.35, 4.78 for methanol; ^{13}C NMR: δ/ppm = 77.0 for chloroform, 39.7 for dimethylsulfoxid, 49.3 for methanol). Mass spectra were measured with a MS-50 (Kratos) or MAT 95 (Thermo Quest). Column chromatography was carried out on Merck silica gel 60 (flash chromatography). Reactions were monitored by thin-layer chromatography (TLC) by using plates of silica gel Merck silicagel-60F_{254}. Elemental microanalyses were performed internally. Microwave irradiation was carried out using the CEM-Discover microwave synthesis system (CEM GmbH, Kamp-Lintfort, Germany).

4.2. General procedure for the preparation of phenylcarbamates 2–4, 8–25

Equimolar amounts of the amino alcohols **28**–**32** and appropriate phenylisocyanate were stirred in toluene (10 mL) under argon atmosphere at 50–120 °C for 1.5–4 h. The solvent was evaporated and the resulting oily residue was purified by flash chromatography on a small amount of silica gel (max. 50 g) eluting with CH_2Cl_2/MeOH (95:5).

4.2.1. Trimethyl-(2-phenoxy-ethyl)-ammonium bromide (1). (2-Bromo-ethoxy)-benzene (771.0 mg, 3.8 mmol) and trimethylamine (0.08 mL, 3.7 mmol) in toluene (2.5 mL) were condensed in a pressure bottle and allowed to stand 48 h. Then the mixture was heated to 50 °C for 1 h. The crude product was separated and crystallized from ethanol to give the bromide salt (756.6 mg,

Table 1. Radioligand binding affinities of compounds **1**–**27**, 3-quinuclidinole **32**, epibatidine and nicotine for different nAChR subtypes

Compd (Ster.)	R	X	[^{3}H]epibatidine α4β2*, rat brain K_i (nM) (±SEM)[a]	[^{3}H]MLA α7*, rat brain K_i (nM) (±SEM)[a]	[^{3}H]epibatidine α3β4*, pig adrenal K_i (nM) (±SEM)[a]	[^{3}H]epibatidine $(\alpha1)_2\beta1\gamma\ \delta$, Torpedo calif. K_i (nM) (±SEM)[a]
1			22.3 (4.3)	196 (9.19)	135 (11)	697 (22)
2	H	H	>20,000	12,836 (2,762)	n.d.	n.d.
3	H	F	>20,000	11,000[b]	23,157[b]	>20,000
4	H	CF_3	>20,000	>20,000	n.d.	n.d.
5	CH_3	H	835 (0.7)	38.9 (2.9)	2200 (45)	>20,000
6	CH_3	F	1412 (17)	62 (5)	2500 (35)	n.d.
7	CH_3	CF_3	6000 (23)	29 (3)	3800 (120)	>20,000
8 (S)		H	1100 (223)	5853[b]	2582 (211)	>20,000
9 (S)		F	1633 (62)	15,000[b]	13,443[b]	>20,000
10 (S)		Br	526 (19)	10,810[b]	6146 (294)	n.d.
11 (S)		CH_3	1248 (126)	14,108[b]	6000[b]	n.d.
12 (S)		CF_3	1050 (103)	13,000[b]	7790[b]	>20,000
13 (RS)		H	>20,000	15,000[b]	6100[b]	>20,000
14 (RS)		F	>20,000	22,000[b]	11,392[b]	>20,000
15 (RS)		Br	3770 (79)	27,000[b]	6357[b]	n.d.
16 (RS)		CH_3	175 (12)	31,800[b]	14,392[b]	>20,000
17 (RS)		CF_3	>20,000	13,000[b]	>20,000	>20,000
18 (RS)		H	>20,000	3600 (230)	23,712[b]	>20,000
19 (RS)		F	>20,000	2600 (155)	6963[b]	>20,000
20 (RS)		CF_3	>20,000	4400 (167)	17,303[b]	>20,000
21 (RS)		H	3084 (132)	44 (2.3)	1627 (123)	>20,000
22 (RS)		F	4203 (98)	37.3 (5)	1581 (22)	>20,000
23 (RS)		Br	2988 (66)	273 (25)	715 (33)	n.d.
24 (RS)		CH_3	2695 (90)	321 (3.5)	1478 (78)	n.d.
25 (RS)		CF_3	1718 (67)	173 (23)	1200 (66)	>20,000
26 (RS)		Ph	7772[b]	1135 (431)	1448 (66)	n.d.
27 (RS)		styryl	5350[b]	6100[b]	5976[b]	n.d.
32 (RS)			5924 (642)	7761[b]	14,604[b]	n.d.
(−)-epibatidine			0.008 (0.001)	4 (0.3)	0.05 (0.003)	2.0 (0.1)
(−)-nicotine			0.84 (0.13)	130 (15)	73.4 (10.1)	n.d.

n.d. = not determined.
[a] Values are the mean from at least $n = 3$ to 5 independent assays.
[b] Values are the mean from $n = 2$.
* Naturally expressed nAChRs.

2.9 mmol, 78.0%). Mp: 167–169 °C. IR (KBr) 3014, 2934, 1600, 1586, 1480 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 (t, $J = 7.3$ Hz, 2H), 7.00 (m, 3H), 4.45 (m, 2H), 3.29 (m, 2H), 3.19 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.51, 129.70, 121.50, 114.85, 64.28, 61.65, 53.30. MS (EI) *m/z* (%) = 180.0 (100) [M$^+$]. Anal. Calcd for $C_{11}H_{18}NOBr$ (260.17): C, 50.78; H, 6.97; N, 5.38. Found: C, 50.67; H, 6.94; N, 5.37.

4.2.2. Phenyl-carbamic acid 2-dimethylamino-ethyl ester (2). The synthesis was done according to the general method with 2-dimethylamino-ethanol **28** (0.24 mL, 2.4 mmol) and phenylisocyanate (0.26 mL, 2.4 mmol). The final product was obtained as yellowish oil (200.6 mg, 1.0 mmol, 40.0%), which crystallized on standing. Mp: 163–165 °C. IR (KBr) 3223, 3110, 3044, 1728, 1596, 1545, 1442 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.48 (d, $J = 7.9$ Hz, 2H), 7.29 (t, $J = 7.6$ Hz, 2H), 6.96 (t, $J = 7.4$ Hz, 1H), 4.53 (m, 2H), 3.85 (m, 2H), 3.27 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) 152.64, 138.89, 128.92, 122.88, 118.54, 69.52, 61.60, 57.69, 49.64. MS (EI) *m/z* (%) = 209.30 (100) [M+H]$^+$.

4.2.3. (3-Fluoro-phenyl)-carbamic acid 2-dimethylamino-ethyl ester (3). The synthesis was done according to the general method with 2-dimethyl-ethanol **28** (1.0 mL, 10 mmol) and *m*-fluoro-phenylisocyanate (1.08 mL, 10 mmol). The product was obtained as yellowish oil (1341.0 mg, 5.9 mmol, 63.2%), which crystallized on standing. Mp: 55–56 °C. IR (KBr) 2957, 2823, 2776, 1732, 1607, 1557 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.38 (dt, $J = 12$ Hz, $J = 2.2$ Hz, 1H), 7.29 (dt, $J = 6.9$ Hz, $J = 8.2$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 6.79 (dt, $J = 2.3$ Hz, $J = 8.1$ Hz, 1H), 4.16 (m, 2H), 2.52 (m, 2H), 2.17 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.47 (d, $J = 239.6$ Hz), 153.54, 141.26 (d, $J = 11.2$ Hz), 130.45 (d, $J = 9.4$ Hz), 114.07 (d, $J = 2.0$ Hz), 108.80 (d, $J = 20.8$ Hz), 104.95 (d, $J = 26.26$ Hz), 62.13, 57.69, 45.38. MS (EI) *m/z* (%) = 226.9 (100) [M$^+$]. Anal. Calcd for $C_{11}H_{15}FN_2O_2$ (226.25): C, 58.40; H, 6.68; N, 12.38. Found: C, 57.92; H, 6.82; N, 12.31.

4.2.4. (3-Trifluoromethyl-phenyl)-carbamic acid 2-dimethylamino-ethyl ester (4). The synthesis was done according to the general method with 2-dimethyl-ethanol **28** (1.0 mL, 10 mmol) and *m*-trifluoromethyl-phenylisocyanate (1.40 mL, 10 mmol). The final product was obtained as yellowish oil (2245.4 mg, 8.1 mmol, 61.0%), which crystallized on standing. Mp: 75–78 °C. IR (KBr) 2958, 2825, 2777, 1733, 1608, 1559 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.38 (dt,

J = 2.2 Hz, J = 11.7 Hz, 1H), 7.28 (dt, J = 6.7, J = 8.1 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 6.78 (dt, J = 2.2 Hz, J = 8,1 Hz, 1H), 4.15 (m, 2H), 2.50 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.53, 141.21, 130.42, 129.72 (q, J = 31.5 Hz), 124.21 (q, J = 270.9 Hz), 123.13, 120.62, 119.24 (q, J = 3.49 Hz), 62.12, 57.69, 45.37. MS (EI) m/z (%) = 277.4 (100) $[M+H]^+$. Anal. Calcd for $C_{12}H_{15}F_3N_2O_2$ (276.26): C, 52.17; H, 5.47; N, 10.14. Found: C, 51.71; H, 5.81; N, 9.44.

4.2.5. Trimethyl-(2-phenylcarbamoyloxy-ethyl)-ammonium iodide (5). Phenyl-carbamic acid 2-dimethylamino-ethyl ester **2** (150 mg, 7.2 mmol) and methyl iodide (0.06 mL, 9.3 mmol) were stirred in acetone (3.5 mL) under argon atmosphere at room temperature for 12 h. The crude product was filtered, washed twice with diethyl ether (5 mL) and dried to give a white crystalline solid (121.5 mg, 3.6 mmol, 48.2%). Mp: 132–133 °C. IR (KBr) 3121, 2970, 2770, 1741, 1595, 1537, 1441 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 9.70 (s, 1H), 7.46 (d, J = 7.9 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 4.52 (m, 2H), 3.68 (m, 2H), 3.16 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.76, 138.82, 128.94, 122.92, 118.53, 64.28, 58.08, 53.25. MS (EI) m/z (%) = 223.2 (100) $[M^+]$. Anal. Calcd for $C_{12}H_{19}N_2O_2I$ (350.20): C, 41.16; H, 5.47; N, 8.00. Found: C, 41.18; H, 5.47; N, 7.96.

4.2.6. Trimethyl-[2-(3-Fluoro-phenylcarbamoyloxy)-ethyl]-ammonium iodide (6). (3-Fluoro-phenyl)-carbamic acid 2-dimethylamino-ethyl ester **3** (111.2 mg, 5.0 mmol) and methyl iodide (0.08 mL, 6.5 mmol) were stirred in acetone (5 mL) under argon atmosphere at room temperature for 12 h. The crude product was filtered, washed twice with diethyl ether (5 mL) and dried to yield a white crystalline solid (179.2 mg, 4.8 mmol, 99.0%). Mp: 113 °C. IR (KBr) 3220, 3060, 3010, 2900, 1740, 1595, 1530, 1471 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 9.94 (s, 1H), 7.39 (d, J = 11.7 Hz, 1H), 7.33 (dt, J = 6.9 Hz, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 6.84 (dt, J = 2.1 Hz, J = 8.5 Hz), 4.53 (m, 2H), 3.69 (m, 2H), 3.16 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.43 (d, J = 241.3 Hz), 152.67, 140.75 (d, J = 11.2 Hz), 130.65 (d, J = 9.72 Hz), 114.31, 109.99 (d, J = 20.95 Hz), 105.84 (d, J = 23.44 Hz), 64.30, 58.33, 53.23. MS (EI) m/z (%) = 241.2 (100) $[M^+]$. Anal. Calcd for $C_{12}H_{18}FN_2O_2I$ (368.19): C, 39.15; H, 4.93; N, 7.61. Found: C, 39.19; H, 4.89; N, 7.58.

4.2.7. Trimethyl-[2-(3-trifluoromethyl-phenylcarbamoyloxy)-ethyl]-ammonium iodide (7). (3-Trifluoromethyl-phenyl)-carbamic acid 2-dimethylamino-ethyl ester **4** (131.5 mg, 4.8 mmol) and methyl iodide (0.08 mL, 6.2 mmol) were stirred in acetone (5 mL) under argon atmosphere at room temperature for 12 h. The crude product was filtered, washed twice with diethyl ether (5 mL) and dried to give a white crystalline solid (173.5 mg, 4.1 mmol, 87.0%). Mp: 172–173 °C. IR (KBr) 3197, 3075, 3015, 2957, 1729, 1595, 1556, 1503 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.91 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 4.55 (m, 2H), 3.70 (m, 2H), 3.16 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.79, 139.78, 130.27, 129.72 (q, J = 31.5 Hz), 124.21 (q, J = 270.9 Hz), 123.13, 120.62, 119.24 (q, J = 3.49 Hz), 114.45, 64.18, 58.45, 53.22. MS (EI) m/z (%) = 291.3 (100) $[M^+]$. Anal. Calcd for $C_{13}H_{18}F_3N_2O_2I$ (418.20): C, 37.34; H, 4.34; N, 6.70. Found: C, 37.35; H, 4.39; N, 6.73.

4.2.8. Phenyl-carbamic acid (*S*)-1-methyl-pyrrolidin-2-ylmethyl ester (8). The synthesis was done according to the general method with (*S*)-(−)-1-methyl-2-pyrrolidinylmethanol **29** (0.25 mL, 2.1 mmol) and phenylisocyanate (0.2 mL, 2.1 mmol). The final product was obtained as colorless oil (345.8 mg, 1.48 mmol, 69%). IR (film): 2954, 2789, 1716, 1600, 1531 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 7.4 Hz, 2H), 6.97 (t, J = 7.4 Hz, 1H), 4.06 (dd, J = 4.9 Hz, J = 10.9 Hz, 1H), 3.98 (dd, J = 5.7 Hz, J = 11.0 Hz, 1H), 2.90–2.97 (m, 1H), 2.38–2.46 (m, 1H), 2.31 (s, 3H), 2.12–2.20 (m, 1H), 1.84–1.92 (m, 1H), 1.62–1.69 (m, 2H), 1.53–1.60 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.70, 139.33, 128.8, 122.43, 118.36, 66.25, 63.70, 57.06, 41.19, 28.24, 22.56. MS (EI) m/z (%) = 235.3 (100) $[M+H]^+$. Anal. Calcd for $C_{13}H_{18}N_2O_2$ (234.30): C, 64.64; H, 7.74; N, 11.96. Found: C, 63.23; H, 7.73; N, 11.550.

4.2.9. (3-Fluoro-phenyl)-carbamic acid (*S*)-1-methyl-pyrrolidin-2-ylmethyl ester (9). The synthesis was done according to the general method with (*S*)-(−)-1-methyl-2-pyrrolidinylmethanol **29** (0.24 mL, 2 mmol) and *m*-fluoro-phenylisocyanate (0.23 mL, 2 mmol). The final product was obtained as colorless oil (386.6 mg, 1.53 mmol, 77.4%). IR (film): 2957, 2793, 1718, 1609, 1540 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.38 (d, J = 12 Hz, 1H), 7.25–7.32 (m, 1H), 7.22 (d, J = 8.2 Hz, 1H), 6.78 (t, J = 8.2 Hz, 1H), 4.08 (dd, J = 4.9 Hz, J = 10.9 Hz, 1H), 3.98 (dd, J = 5.7 Hz, J = 11.0 Hz, 1H), 2.88–2.97 (m, 1H), 2.38–2.45 (m, 1H), 2.32 (s, 3H), 2.11–2.19 (m, 1H), 1.84–1.93 (m, 1H), 1.62–1.72 (m, 2H), 1.52–1.60 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.45 (d, J = 239.3 Hz), 153.59, 141.24 (d, J = 11.0 Hz), 130.46 (d, J = 9.72 Hz), 114.11, 108.83 (d, J = 20.95 Hz), 104.98 (d, J = 26.68 Hz), 66.38, 63.63, 57.03, 41.15, 28.18, 22.56. MS (EI) m/z (%) = 253.3 (100) $[M+H^+]$. Anal. Calcd for $C_{13}H_{17}FN_2O_2$ (252.29): C, 61.89; H, 6.79; N, 11.10. Found: C, 60.24; H, 6.74; N, 10.91.

4.2.10. (3-Bromo-phenyl)-carbamic acid (*S*)-1-methyl-pyrrolidin-2-ylmethyl ester (10). The synthesis was done according to the general method with (*S*)-(−)-1-methyl-2-pyrrolidinylmethanol **29** (0.24 mL, 2 mmol) and *m*-bromo-phenylisocyanate (0.25 mL, 2 mmol). The final product was obtained as colorless oil (610 mg, 1.94 mmol, 97%), which crystallized on standing. Mp: 49 °C. n_D^{20} = 1.3295. IR (KBr) 2942, 2857, 1714, 1596 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.23 (s, 1H), 7.10–7.16 (m, 2H), 6.78 (s, 1H), 4.22 (dd, J = 4.4 Hz, J = 11.0 Hz, 1H), 4.10 (dd, J = 4.7 Hz, J = 11.4 Hz, 1H), 3.07 (dt, J = 1.9 Hz, J = 7.9 Hz, 1H), 2.42–2.47 (m, 1H), 2.39 (s, 3H), 2.20–2.25 (dt, J = 7.3 Hz, J = 9.5 Hz, 1H), 1.82–1.93 (m, 1H), 1.63–1.82 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.25,

139.20, 130.26, 126.35, 122.73, 121.45, 117.0, 66.30, 64.12, 57.50, 41.15, 27.84, 22.68. MS (EI) *m/z* (%) = 312.1 (20) [M^+], 314.0 (19) [M+2]. Anal. Calcd for $C_{13}H_{17}BrN_2O_2$ (313.202): C, 49.85; H, 5.47; N, 8.94; found C, 49.01; H, 5.57; N, 8.54.

4.2.11. (3-Methyl-phenyl)-carbamic (*S*)-1-methyl-pyrrolidin-2-ylmethyl ester (11). The synthesis was done according to the general method with (*S*)-(−)-1-methyl-2-pyrrolidinylmethanol **29** (0.24 mL, 2 mmol) and *m*-tolylisocyanate (0.26 mL, 2 mmol). The final product was obtained as colorless oil (206 mg, 0.83 mmol, 42%). Mp: 62 °C. $n_D^{20} = 1.3295$. IR (KBr) 3053, 2854, 2798, 1710, 1565 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.11–7.17 (m, 2H), 6.84 (d, $J = 6.9$ Hz, 1H), 6.67 (s, 1H), 4.22 (dd, $J = 4.4$ Hz, $J = 11.0$ Hz, 1H), 4.05 (dd, $J = 4.7$ Hz, $J = 11.4$ Hz, 1H), 3.08 (dt, $J = 1.9$ Hz, $J = 8.2$ Hz, 1H), 2.43–2.48 (m, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.20–2.26 (dt, $J = 7.6$ Hz, $J = 9.5$ Hz, 1H), 1.88–1.93 (m, 1H), 1.64–1.81 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.54, 138.97, 137.77, 128.84, 124.21, 119.17, 115.64, 66.03, 64.23, 57.54, 41.16, 27.88, 22.68, 21.47. MS (EI) *m/z* (%) = 248.1 (20) [M^+]. Anal. Calcd for $C_{14}H_{20}N_2O_2$ (248.33): C, 67.71; H, 8.05; N, 11.28. Found: C, 67.21; H, 8.12; N, 10.65.

4.2.12. (3-Trifluoromethyl-phenyl)-carbamic acid (*S*)-1-methyl-pyrrolidin-2-ylmethyl ester (12). The synthesis was done according to the general method with (*S*)-(−)-1-methyl-2-pyrrolidinylmethanol **29** (0.19 mL, 1.7 mmol) and *m*-trifluoromethyl-phenylisocyanate (0.23 mL, 1.7 mmol). The final product was obtained as colorless oil (382.0 mg, 1.3 mmol, 76.4%). IR (film): 2956, 2794, 1715, 1604, 1552 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.51 (d, $J = 8.2$ Hz, 1H), 7.39 (t, $J = 8.2$ Hz, 1H), 7.29 (d, $J = 7.9$ Hz, 1H), 6.89 (s, 1H), 4.23 (dd, $J = 4.3$ Hz, $J = 11.2$ Hz, 1H), 4.12 (dd, $J = 4.7$ Hz, $J = 11.1$ Hz, 1H), 3.06–3.11 (m, 1H), 2.43–2.49 (m, 1H), 2.40 (s, 3H), 2.20–2.29 (m, 1H), 1.89–1.97 (m, 1H), 1.72–1.84 (m, 1H), 1.64–1.71 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.34, 138.48, 131.51 (q, $J = 32.4$ Hz), 129.55, 123.84 (q, $J = 272.5$ Hz), 121.50, 119.96 (q, $J = 3.8$Hz), 115.25, 66.34, 64.15, 57.52, 41.14, 27.85, 22.69. MS (EI) *m/z* (%) = 303.5 (100) $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}F_3N_2O_2$ (302.30): C, 55.63; H, 5.67; N, 9.27. Found: C, 54.97; H, 5.73; N, 9.38.

4.2.13. Phenyl-carbamic acid 1-methyl-piperidin-2-ylmethyl ester (13). The synthesis was done according to the general method with 2-hydroxymethyl-*N*-methylpiperidine **30** (0.26 mL, 2.0 mmol) and phenylisocyanate (0.188 mL, 2.0 mmol). The final product was obtained as yellowish oil (484.3 mg, 1.9 mmol, 96.8%). IR (film): 2939, 2857, 2805, 2266, 1938, 1711, 1601, 1556, 1500, 1444 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.58 (s, 1H), 7.46 (d, $J = 7.5$ Hz, 2H), 7.25 (t, $J = 7.6$ Hz, 2H), 6.97 (t, $J = 7.4$ Hz, 1H), 4.14 (dd, $J = 4.1$Hz, $J = 11.4$ Hz, 1H), 4.07 (dd, $J = 4.7$ Hz, $J = 11.4$ Hz, 1H), 2.71–2.78 (m, 1H), 2.22 (s, 3H), 2.03–2.09 (m, 1H), 2.00 (dt, $J = 3.1$, $J = 11.6$, 1H), 1.61–1.71 (m, 2H), 1.49–1.55 (m, 1H), 1.40–1.48 (m, 1H), 1.29–1.39 (m, 1H), 1.16–1.26 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.69, 139.32, 128.81, 122.44, 118.33, 65.83, 62.37, 56.51, 43.26, 28.74, 25.35, 23.66. MS (EI) *m/z* (%) = 249.4 (100) $[M+H]^+$. Anal. Calcd for $C_{14}H_{20}N_2O_2$ (248.33): C, 67.72; H, 8.12; N, 11.28. Found: C, 67.34; H, 8.33; N, 10.48.

4.2.14. (3-Fluoro-phenyl)-carbamic acid 1-methyl-piperidin-2-ylmethyl ester (14). The synthesis was done according to the general method with 2-hydroxymethyl-*N*-methylpiperidine **30** (0.25 mL, 1.9 mmol) and *m*-fluorophenylisocyanate (0.21 mL, 1.9 mmol). The final product was obtained as yellowish oil (499.4 mg, 1.8 mmol, 98.7%). IR (film) 2950, 2859, 2803, 2266, 1711, 1614, 1558, 1489, 1447 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.86 (s, 1H), 7.39 (dt, $J = 2.1$Hz, $J = 11.8$ Hz, 1H), 7.28 (dt, $J = 2.1$ Hz, $J = 8.2$ Hz, 1H), 7.22 (dd, $J = 2.1$, $J = 8.2$ Hz, 1H), 6.79 (dt, $J = 6.8$, $J = 8.2$ Hz, 1H), 4.15 (dd, $J = 4.1$ Hz, $J = 11.4$ Hz, 1H), 4.09 (dd, $J = 4.9$ Hz, $J = 11.4$ Hz, 1H), 2.71–2.78 (m, 1H), 2.22 (s, 3H), 2.03–2.09 (m, 1H), 1.99 (dt, $J = 3.2$, $J = 11.6$, 1H), 1.61–1.71 (m, 2H), 1.48–1.55 (m, 1H), 1.39–1.47 (m, 1H), 1.29–1.38 (m, 1H), 1.15–1.26 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.46 (d, $J = 240.9$ Hz), 153.59, 141.23 (d, $J = 11.22$ Hz), 130.46 (d, $J = 9.47$ Hz), 114.11, 108.84 (d, $J = 20.94$), 104.98 (d, $J = 26.43$), 66.04, 62.29, 56.49, 43.22, 28.71, 25.34, 23.67. MS (EI) *m/z* (%) = 267.1 (100) $[M+H]^+$. Anal. Calcd for $C_{14}H_{19}FN_2O_2$ (266.32): C, 63.14; H, 7.19; N, 10.52. Found: C, 63.46; H, 7.22; N, 10.62.

4.2.15. (3-Bromo-phenyl)-carbamic acid 1-methyl-piperidin-2-ylmethyl ester (15). The synthesis was done according to the general method with 2-hydroxymethyl-*N*-methylpiperidine **30** (0.26 mL, 2 mmol) and *m*-bromophenylisocyanate (0.25 mL, 2 mmol). The final product was obtained as yellowish oil (555.2 mg, 1.7 mmol, 84.8%), which crystallized on standing. Mp: 67–68 °C. IR (KBr) 2936, 2856, 2794, 1729, 1705, 1533 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.26 (d, $J = 7.8$ Hz, 1H), 7.12–7.20 (m, 2H), 7.04 (s, 1H), 4.28 (dd, $J = 3.8$ Hz, $J = 11.7$ Hz, 1H), 4.20 (dd, $J = 3.2$ Hz, $J = 11.7$ Hz, 1H), 2.91 (d, $J = 11.7$ Hz, 1H), 2.35 (s, 3H), 2.06–2.12 (m, 2H), 1.76–1.80 (m, 1H), 1.51–1.68 (m, 4H), 1.25–1.35 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.25, 139.26, 130.24, 126.29, 122.73, 121.33, 116.89, 66.27, 62.83, 57.27, 43.02, 29.06, 25.60, 24.10. MS (EI) *m/z* (%) = 326.1 (10) [M^+], 328.0 (9) [M+2]. Anal. Calcd for $C_{14}H_{19}BrN_2O_2$ (327.218): C, 51.39, H, 5.85, N, 8.56. Found: C, 50.81; H, 6.00; N, 8.12.

4.2.16. (3-Methyl-phenyl)-carbamic acid 1-methyl-piperidin-2-ylmethyl ester (16). The synthesis was done according to the general method with 2-hydroxymethyl-*N*-methylpiperidine **30** (0.26 mL, 2 mmol) and *m*-tolylisocyanate (0.26 mL, 2 mmol). The final product was obtained as yellowish oil (210 mg, 0.6 mmol, 30%), which crystallized on standing. Mp: 73–75 °C. IR (KBr) 2937, 2852, 2803, 1732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.15–7.19 (m, 2H), 6.87 (d, $J = 6.9$ Hz, 1H), 6.81 (s, 1H), 4.25 (dd, $J = 4.1$ Hz, $J = 11.7$ Hz, 1H), 4.23 (dd, $J = 3.2$ Hz, $J = 11.7$ Hz, 1H), 2.88–2.93 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.08–2.13 (m, 2H), 1.75–1.82 (m, 1H), 1.50–1.69 (m, 4H), 1.24–1.34 (m, 1H). ^{13}C

NMR (125 MHz, $CDCl_3$) δ 153.57, 138.98, 137.82, 128.86, 124.20, 119.13, 115.60, 66.25, 62.94, 57.38, 43.22, 29.21, 25.76, 24.18, 21.50. MS (EI) *m/z* (%) = 262.2 (38) [M^+]. Anal. Calcd for $C_{15}H_{22}N_2O_2$ (262.353): C, 68.67; H, 8.45; N, 10.67. Found: C, 68.78; H, 8.47; N, 10.13.

4.2.17. (3-Triflurometh-yl-phenyl)-carbamic acid 1-methyl-piperidin-2-yl-methyl ester (17). The synthesis was done according to the general method with 2-hydroxymethyl-*N*-methylpiperidine **30** (0.20 mL, 1.6 mmol) and *m*-trifluoromethyl-phenylisocyanate (0.22 mL, 1.6 mmol). The final product was obtained as yellowish oil (387.3 mg, 1.2 mmol, 77.5%). IR (film) 2939, 2860, 1713, 1604, 1557, 1489, 1450 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 10.00 (s, 1H), 7.92 (s, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 4.17 (dd, J = 4.1 Hz, J = 11.4 Hz, 1H), 4.12 (dd, J = 4.7 Hz, J = 11.4 Hz, 1H), 2.71–2.78 (m, 1H), 2.21 (s, 3H), 2.04–2.10 (m, 1H), 2.00 (dt, J = 3.1, J = 11.6, 1H), 1.61–1.71 (m, 2H), 1.48–1.55 (m, 1H), 1.40–1.47 (m, 1H), 1.30–1.39 (m, 1H), 1.16–1.27 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.70, 140.21, 129.67 (q, J = 31.6 Hz), 124.27 (q, J = 272.3 Hz), 121.89, 118.77 (q, J = 3.9 Hz), 114. 24, 66.16, 62.27, 56.49, 43.23, 28.71, 25.34, 23.67. MS (EI) *m/z* (%) = 316.0 (100) [M^+]. Anal. Calcd for $C_{15}H_{19}F_3N_2O_2$ (316.33): C, 56.96; H, 6.05; N, 8.86. Found: C, 56.43; H, 6.47; N, 8.37.

4.2.18. Phenyl-carbamic acid 1-methyl-piperidin-3-yl ester (18). The synthesis was done according to the general method with 3-hydroxy-1-methylpiperidine **31** (0.25 mL, 2.1 mmol) and phenylisocyanate (0.23 mL, 2.1 mmol). The final product was obtained as yellowish oil (413.3 mg, 1.8 mmol, 82.6%). IR (film): 2943, 2790, 1730, 1601, 1546, 1444 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.37(d, J = 7.9 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 6.83 (s, 1H), 4.93–4.98 (m, 1H), 2.45–2.65 (m, 3H), 2.29 (s, 3H), 2.21–2.28 (m, 1H), 1.97 (s, 1H), 1.81–1.91 (m, 1H), 1.72 (s, 1H), 1.57–1.64 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$ + TMS) δ 152.97, 138.02, 129.04, 123.29, 118.48, 69.82, 59.29, 55.46, 46.52, 28.43, 21.99. MS (EI) *m/z* (%) = 244.0 [M+H]$^+$. Anal. Calcd for $C_{13}H_{18}N_2O_2$ (243.30): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.41; H 7.74; N, 10.89.

4.2.19. (3-Fluoro-phenyl)-carbamic acid 1-methyl-piperidin-3-yl ester (19). The synthesis was done according to the general method with 3-hydroxy-1-methylpiperidine **31** (0.24 mL, 2 mmol) and *m*-fluoro-phenylisocyanate (0.23 mL, 2 mmol). The final product was obtained as yellowish oil (384.9 mg, 1.5 mmol, 76.3%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 11.0 Hz, 1H), 7.19 (dt, J = 6.5 Hz, J = 8.2 Hz, 1H), 6.97 (d, J = 1.3, J = 8.2 Hz, 1H), 6.94 (s, 1H), 6.71 (ddt, J = 0.88 Hz, J = 2.48 Hz, J = 8.35 Hz, 1H), 4.91–4.95 (m, 1H), 2.42–2.63 (m, 3H), 2.26 (s, 3H), 2.15–2.24 (m, 2H), 1.78–1.87 (m, 1H), 1.68 (s, 1H), 1.55–1.63 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.17 (d, J = 244.3 Hz), 152.66, 139.66 (d, J = 11.0 Hz), 130.06 (d, J = 9.47 Hz), 113.64, 109.87 (d, J = 21.19 Hz), 105.81 (d, 26.68 Hz), 70.00, 59.14, 55.38, 46.43, 28.29, 21.88. MS (EI) *m/z* (%) = 253.1 (100) [M+H]$^+$. Anal. Calcd for $C_{13}H_{18}FN_2O_2$ (252.29): C, 61.89; H, 6.79; N, 11.10. Found: C, 60.97; H, 6.81; N, 10.93.

4.2.20. (3-Trifluoromethyl-phenyl)-carbamic acid 1-methyl-piperidin-3-yl ester (20). The synthesis was done according to the general method with 3-hydroxy-1-methylpiperidine **31** (0.2 mL, 1.7 mmol) and *m*-trifluoromethyl-phenylisocyanate (0.23 mL, 1.7 mmol). The final product was obtained as yellowish oil (421.5 mg, 1.4 mmol, 84.5%). Mp: 112–114 °C. IR (KBr) 2949, 2862, 2796, 1725, 1601, 1551, 1445 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 7. 9 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 4.92–4.97 (m, 1H), 2.43–2.64 (m, 3H), 2.26 (s, 3H), 2.19–2.25 (m, 1H), 1.89 (s, 1H), 1.78–1.88 (m, 1H), 1.66–1.75 (s, 1H), 1.55–1.64 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.76, 138.60, 131.49 (q, J = 32.4 Hz), 129.51, 123.86 (q, J = 272.5 Hz), 119.83 (q, J = 3.82 Hz), 115.11, 70.26, 59.13, 55.39, 46.45, 28.32, 21.88. MS (EI) *m/z* (%) = 303.5 (100) [M^+]. Anal. Calcd for $C_{13}H_{18}F_3N_2O_2$ (302.30): C, 55.63; H, 5.67; N, 9.27. Found: C, 55.09; H, 5.68; N, 9.23.

4.2.21. Phenyl-carbamic acid 1-aza-bicyclo[2.2.2.]oct-3-yl ester (21). The synthesis was done according to the general method with 3-quinuclidinole **32** (258 mg, 2 mmol) and phenylisocyanate (0.19 mL, 2 mmol). The solid was crystallized from diethyl ether. The final product was obtained as white crystals (228.3 mg, 0.9 mmol, 46%). Mp: 120 °C. IR (KBr) 2947, 2870, 1725, 1600, 1548 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.9 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 6.87 (s, 1H), 4.80–4.85 (m, 1H), 3.27 (ddd, J = 2.2 Hz, J = 6.3 Hz, J = 14.5 Hz, 1H), 2.70–2.99 (m, 5H), 2.08–2.12 (m, 1H), 1.82–1.93 (m, 1H), 1.67–1.75 (m, 1H), 1.54–1.62 (m, 1H), 1.38–1.47 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$ + TMS) δ 153.22, 137.86, 129.05, 123.44, 118.64, 71.78, 55.28, 47.27, 46.38, 25.32, 24.29, 19.35. MS (70 eV, 25 °C) *m/z* (%) = 247.3 (100) [M+H]$^+$. Anal. Calcd for $C_{14}H_{18}N_2O_2$ (246.31): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.74; H, 7.28; N, 10.38.

4.2.22. (3-Fluoro-phenyl)-carbamic acid 1-aza-bicyclo[2.2.2.]oct-3-yl ester (22). The synthesis was done according to the general method with 3-quinuclidinole **32** (241 mg, 1.9 mmol) and *m*-fluoro-phenylisocyanate (0.22 mL, 1.9 mmol). The oily residue was crystallized from diethyl ether to yield **22** as white crystalline powder (437.3 mg, 1.7 mmol, 88%). Mp: 127–129 °C. IR (KBr) 2947, 2869, 1727, 1606, 1568, 1495 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 10.7 Hz, 1H), 7.21 (dt, J = 6,3 Hz, J = 8.2 Hz, 1H), 7.07 (s, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.72 (dt, J = 2.4 Hz, J = 8.3 Hz, 1H), 4.79–4.85 (m, 1H), 3.26 (ddd, J = 2.1 Hz, J = 8.5 Hz, J = 14.6 Hz, 1H), 2.69–2,95 (m, 5H), 2.06–2.11 (m, 1H), 1.79–1.87 (m, 1H), 1.66–1.74 (m, 1H), 1.53–1.62 (m, 1H), 1.37–1.46 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.16 (d, J = 244.6 Hz), 153.03, 139.62 (d, J = 11.0 Hz), 130.10 (d, J = 9.47 Hz), 113.83, 110.01 (d, J = 21.44 Hz), 106.01 (d, J = 28.67), 72.29, 55.29, 47.29,

46.45, 25.36, 24.43, 19.41. MS (70 eV, 25 °C) *m/z* (%) = 265.4 (100) $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}FN_2O_2$ (264.30): C, 63.62; H, 6.48; N, 10.60. Found: C, 64.09, H, 6.65, N, 11.02.

4.2.23. (3-Bromo-phenyl)-carbamic acid 1-aza-bicyclo-[2.2.2]oct-3-yl ester (23). The synthesis was done according the general method with 3-quinuclidinole **32** (254 mg, 2 mmol) and 3-bromo-phenylisocyanate (0.25 mL, 2 mmol). The oily residue was crystallized from diethyl ether to yield **23** as white crystalline powder (488 mg, 1.5 mmol, 75%). Mp: 162 °C. IR (KBr) 3163, 2943, 2866, 1722, 1595 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + TMS) δ 7.65 (s, 1H), 7.26 (s, 1H), 7.13–7.20 (m, 2H), 7.08 (s, 1H), 4.80–4.91 (m, 1H), 3.27 (ddd, J = 1.9 Hz, J = 8.4 Hz, J = 14.5 Hz, 1H), 2.73–2.96 (m, 5H), 2.09–2.18 (m, 1H), 1.81–1.87 (m, 1H), 1.68–1.75 (m, 1H), 1.55–1.61 (m, 1H), 1.40–1.46 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$ + TMS) δ 153.08, 139.38, 130.30, 126.33, 122.76, 121.57, 117.05, 72.47, 55.37, 47.34, 46.50, 25.38, 24.53, 19.49. MS (70 eV, 25 °C) *m/z* (%) = 324.1 (40) $[M^+]$, 326.0 (39) [M+2]. Anal. Calcd for $C_{14}H_{17}BrN_2O_2$ (325.21): C, 51.7; H, 5.27; N, 8.61. Found: C, 51.05; H, 5.22; N, 8.60.

4.2.24. *m*-Tolyl-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester (24). The synthesis was done according to the general method with 3-quinuclidinole **32** (254 mg, 2 mmol) and *m*-tolylisocyanate (0.26 mL, 2 mmol). The resulting oily residue was purified by column chromatography eluting with CH_2Cl_2/MeOH (90:10 → 90:50) and crystallized from diethyl ether. The final product was obtained as white crystalline powder (150 mg, 0.57 mmol, 28%). Mp: 150 °C. IR (KBr) 2938, 2866, 2780, 1710, 1598, 1559 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 4.84–4.85 (m, 1H), 3.34 (qui, J = 1.7 Hz, 1H), 3.25 (ddd, J = 2.4 Hz, J = 8.4 Hz, J = 14.7 Hz, 1H), 2.77–2.95 (m, 5H), 2.34 (s, 3H), 2.10–2.14 (m, 1H), 1.98–2.06 (m, 1H), 1.78–1.85 (m, 1H), 1.66–1.72 (m, 1H), 1.52–1.58 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.94, 140.34, 140.03, 129.96, 125.10, 120.75, 117.33, 72.54, 56.36, 48.28, 47.33, 26.82, 25.13, 21.86, 20.37. MS (70 eV, 25 °C) *m/z* (%) = 260.2 (25) $[M^+]$. Anal. Calcd for $C_{15}H_{20}N_2O_2$ (260.34): C, 68.20; H, 7.74; N, 10.76. Found: C, 68.37; H, 7.72; N, 10.98.

4.2.25. (3-Trifluoromethyl-phenyl)-carbamic acid 1-aza-bicyclo[2.2.2.]oct-3-yl ester (25). The synthesis was done according to the general method with 3-quinuclidinole **32** (202 mg, 1.6 mmol) and *m*-trifluoromethyl-phenylisocyanate (0.22 mL, 1.6 mmol). The final product was obtained as white crystalline powder (398.7 mg, 1.3 mmol, 80%). Mp: 147–149 °C. IR (KBr) 2953, 2873, 1721, 1607, 1570 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.54 (d, J = 7.3 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 7.9 Hz, 2H), 7.09 (s, 1H), 4.79–4.86 (m, 1H), 3.26 (ddd, J = 2.1 Hz, J = 8.4 Hz, J = 14.5 Hz, 1H), 2.70–2.90 (m, 5H), 2.07–2.12 (m, 1H), 1.79–1.87 (m, 1H), 1.66–1.74 (m, 1H), 1.53–1.62 (m, 1H), 1.38–1.46 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.11, 138.57, 131.48 (q, J = 32.3 Hz), 129.57, 123.85 (q, J = 272.4 Hz), 121.53, 119.91 (q, J = 3.57 Hz), 115.34, 72.56, 55.33, 47.31, 46.47, 25.36, 24.47, 19.43. MS (70 eV, 25 °C) *m/z* (%) = 315.5 (100) $[M+H]^+$. Anal. Calcd for $C_{15}H_{17}F_3N_2O_2$ (314.31): C, 57.32; H, 5.45; N, 8.91. Found: C, 56.29; H, 5.41; N, 8.51.

4.2.26. Biphenyl-3-yl-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester (26). In a 10-mL microwave glass tube were placed 3-bromo-carbamic acid 1-aza-bicyclo-[2.2.2]oct-3-yl ester **23** (325 mg, 1 mmol), phenylboronic acid (244 mg, 2 mmol), tetrakis-(triphenylphosphin)-palladium(0) (58 mg, 0.05 mmol), Na_2CO_3 (233 mg, 2.2 mmol), toluene (5 mL) and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Enhanced microwave irradiation of 100 W was used, the temperature being ramped from room temperature to 120 °C. Once 120 °C was reached, the reaction mixture was held for 20 min. Then, the mixture was allowed to cool to room temperature, the reaction vessel was opened and the solvent was evaporated under pressure. The oily residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (80:20). The final product was crystallized from the mixture of diethyl ether/petroleum ether and obtained as a yellow crystalline powder (37.7 mg, 0.11 mmol, 22.7%). Mp: 201–202 °C. IR (KBr) 3189, 2934, 2868, 1716 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.79 (s, 1H), 7.58 (d, J = 7.1 Hz, 2H), 7.43–7.47 (m, 3H), 7.33–7.37 (m, 2H), 7.25 (d, J = 8.2 Hz, 1H), 4.68–4.71 (m, 1H), 3.15 (ddd, J = 1.8 Hz, J = 7.9 Hz, J = 14.5 Hz, 1H), 2.57–2.72 (m, 5H), 1.98 (sx, J = 3.2 Hz, 1H), 1.78–1.83 (m, 1H), 1.59–1.65 (m, 1H), 1.47–1.54 (m, 1H), 1.33–1.39 (m, 1H). ^{13}C NMR (125 MHz, DMSO) δ 153.6, 140.9, 140.4, 139.9, 129.4, 129.1, 127.6, 126.7, 120.9, 117.4, 116.6, 71.4, 55.3, 47.1, 46.1, 25.4, 24.4, 19.3. MS (70 eV, 25 °C) *m/z* (%) = 322.2 (10) $[M^+]$. Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322.41): C, 74.5; H, 6.88; N, 8.69. Found: C, 74.28; H, 6.48; N, 8.15.

4.2.27. [3-(Styryl)-phenyl]carbamic acid 1-aza-bicyclo-[2.2.2]oct-3-yl ester (27). In a 10-mL microwave glass tube were placed 3-bromo-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester **23** (325 mg, 1 mmol), styrylboronic acid (300 mg, 2 mmol), tetrakis-(triphenylphosphin)-palladium(0) (115.5 mg, 0.1 mmol), Na_2CO_3 (233 mg, 2.2 mmol), toluene (5 mL) and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 60 W was used, the temperature being ramped from room temperature to 120 °C. Once 120 °C was reached, the reaction mixture was held for 10 min. Then the mixture was allowed to cool to room temperature, the reaction vessel was opened and the solvent was evaporated under pressure. The oily residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH (90:10). The final product was crystallized from the mixture of diethyl ether/petroleum ether and obtained as a yellow crystalline powder (101.1 mg, 0.2 mmol, 39%). Mp: 174–175 °C. IR (KBr): 3021, 2945, 2771, 2661, 2589, 1728, 1589, 1547, 1224, 960 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.70 (s, 1H), 7.59 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.4 Hz, 3H), 7.26–7.29

(m, 2H), 7.20 (d, $J = 16.6$ Hz, 1H), 7.13 (d, $J = 16.6$Hz, 1H), 4.93–5.00 (m, 1H), 3.68 (ddd, $J = 2.1$ Hz, $J = 8.4$ Hz, $J = 13.7$ Hz, 1H), 3.15–3.25 (m, 5H), 2.28 (sx, $J = 2.9$ Hz, 1H), 2.03–2.12 (m, 1H), 1.73–1.91 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.0, 139.3, 137.7, 136.9, 129.2, 128.8, 128.7, 128.5, 127.9, 126.7, 121.2, 118.03, 116.5, 67.6, 53.1, 45.9, 45.1, 24.0, 20.2, 16.9. MS (70 eV, 25 °C) *m/z* (%) = 348.2 (100) [M^+]. Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.45): C, 75.83; H, 6.94; N, 8.04. Found: C, 75.68; H, 6.96; N, 8.23.

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