Structure-based design and discovery of new M2 receptor agonists

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SUPPORTING INFORMATION

Table of Content

Table S1. Docking data to the inactive state

compd.	Docking score inactive state	H-bond to $Asn^{6.52}$	compd.	Docking score inactive state	H-bond to $Asn^{6.52}$
1	-40.17	N	**15**	-39.41/ -42.94 [a]	N
2	-42.03	N	**16**	-39.12/ -42.6 [a]	Y/N
3	-44.46	N	**17**	-38.7	N
4	-41.68	N	**18**	-38.05	N
5	-45.13	N	**19**	-43.53/ -43.19 [a]	N
6	-41.13	N	**20**	-48.32	N
7	-41.63/ -44.18/ -41.53/ -32.98 [a]	N	**21**	-41.80	Y
8	-39.62	N	**22**	-44.01	N
9	-39.84	N	**23**	-45.08/ -45.15 [a]	N
10	-42.27/ -42.18 [a]	N	**24**	-47.40	N
11	-40.2/ -39.01 [a]	N	**25**	-44.89	N
12	-39.58/ -41.87 [a]	N	**26**	-42.03	N
13	-37.35/ -40.98 [a]	N	**27**	-43.65	N
14	-39.75/ -38.49 [a]	N	**28**	-36.23	N

[a] Racemic mixture

Table S2. IP-One® screening assay [a]

Compound	pEC_{50} [μM ± SEM][b]	EC_{50} [μM ± SEM]	E_{max} [% ± SEM][c]
1	5.77 ± 0.23	2.8 ± 1.7	99 ± 12
2	-	-	43 ± 18[d]
3	5.78 ± 0.10	1.9 ± 0.5	91 ± 2
4	6.12 ± 0.15	0.90 ± 0.3	81 ± 4
5	-	-	<5
6		-	20[d]
7	-	-	<5
8	-	-	<5
9	-	-	15[d]
10		0.40	-14
11		-	10[d]
12	-	-	<5
13	-	-	<5
14	-	-	<5
15	-	-	<5
16	-	-	<5
17	5.69 ± 0.16	2.9 ± 0.9	33 ± 5
18	5.29 ± 0.07	5.3 ± 0.8	94 ± 7
19	-	-	<5
20	5.69 ± 0.02	2.0 ± 0.1	72 ± 12
21		-	50[c]
22	4.18 ± 1.1	5.8 ± 2.8	84 ± 4
23	6.18 ± 0.07	0.67 ± 0.1	102 ± 5
24		-	<5
25	5.90 ± 0.04	1.3 ± 0.1	99 ± 5
26		-	48 ± 12[d]
27		-	56 ± 0[d]
28	5.72 ± 0.06	2.0 ± 0.2	77 ± 8
iperoxo	10.94 ± 0.13	0.000013 ± 0.000004	99 ± 3
acetylcholine	7.35 ± 0.08	0.050 ± 0.008	92 ± 2
carbachol	6.69 ± 0.08	0.22 ± 0.044	100

[a] Screening on M_2 receptor activation with HEK cells expressing M_2R and the G-protein hybrid $G\alpha_{qi5HA}$ using the IP-One® assay from Cisbio. [b] pEC_{50} and corresponding EC_{50} values ± SEM derived from 3 to 8 individual experiments each done in duplicate. [c] E_{max} values relative to the full effect of carbachol. [d] E_{max} at 10 μM (no complete dose-response curve was available). "/" = not determined.

Table S3. Results of docking screen and their synthesized analogs

compound			K_i [µM][a]			IP accumulation assay[b]		IP accumulation assay[c]	
	Rank	ZINC ID	M_1	M_2	M_3	EC_{50} [µM]	E_{max}[c] [%]	EC_{50} [µM]	E_{max} [%]
29	324	87391701	4.2	6.0	4.1	3.9	85	11	64
30	383	51888450	18	11	36	22	80	22	59
31	406	13483620	64	28	<90	-	<5 [d]	/	/
32	435	12325070	8.3	16	9.7	-	<5 [d]	/	/
33	449	19089243	10	17	9.5	6.8	76	14	56
34	610	36222722	>90	>100	>100	66	24	-	<5
35	624	01442735	39	25	38	-	<10 [d]	/	/
36	776	04384375	47	>55	80	-	<10 [d]	/	/
37	780	11628469	>55	32	30	-	15 [d]	/	/
38	994	15020880	26	>70	27	-	20 [d]	/	/
29a	NA	NA	6.1	10	12	9.6	65	7.4	27
30a	NA	NA	38	39	75	60	66	>100	55
33a	NA	NA	20	46	42	90	61	65	26

[a] Ki values ± SEM derived from 3-6 individual competition binding experiments using the radioligand [^{3}H]*N*-methyl-scopolamine bromide. [b] Screening on M_2 receptor activation with HEK cells expressing M_2R and the G-protein hybrid $G_{\alpha qi5HA}$ using the IP-One® assay from Cisbio. [c] Second, less sensitive IP accumulation assay with COS cells coexpressing M_2R and $G_{\alpha qi5HA}$. [d] E_{max} at 300 µM (no complete dose-response curve was available).

Table S4. 2D structure of the closest known muscarinic ligands

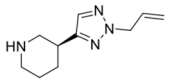
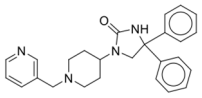
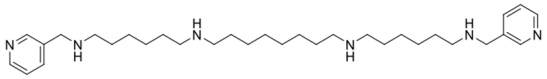
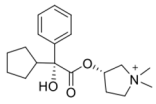
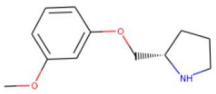
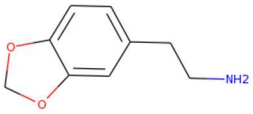
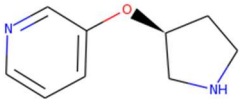
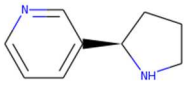
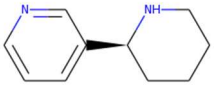
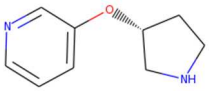
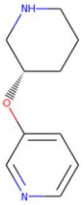
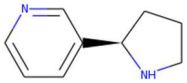
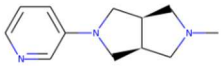
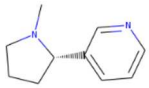
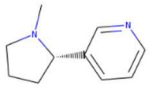
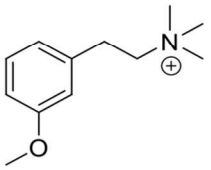
Zinc number	Structure of closest muscarinic ligand
C13739835	
C34802190	
C27984351	
C00000346	

Table S5. 2D structure of the closest known nicotinic ligands

compound	closest target	closest nicotinic ligand		Tc
		zinc id	Structure	
3	CHRNA10	C20221595		0.33
28	Trace amine-associated receptor 1	C259006		0.38
29	α4β2 nAChR	C3932135		0.36
30	NACHRALPHA5	C5898 (Nornicotin)		0.34
		C31165 (Anabasine)		0.34
	α4β2 nAChR	C4638275		0.47
33	α4β2 nAChR	C13704010		0.62
	NACHRALPHA5	C5898 (Nornicotin)		0.40

29a	No close target	NA		NA
30a	α4β2 nAChR	C34017099		0.38
33a	α4β2 nAChR	C391812 (Nicotine)		0.42
	NACHRALPHA5	C391812 (Nicotine)		0.43



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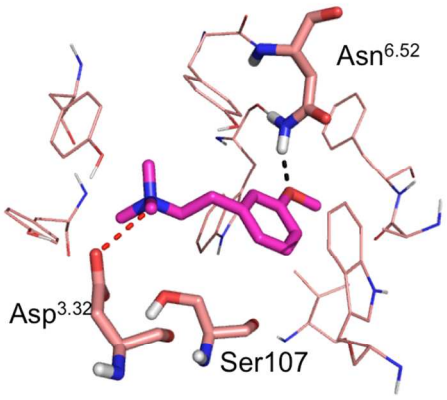
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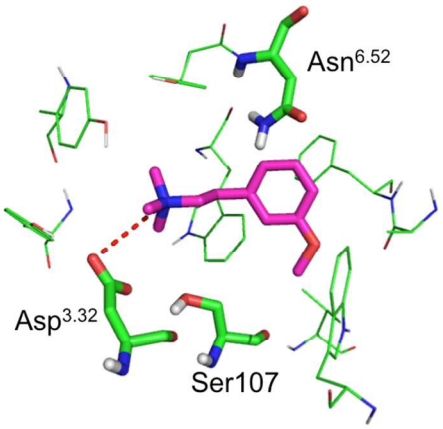
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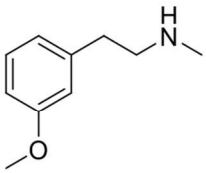

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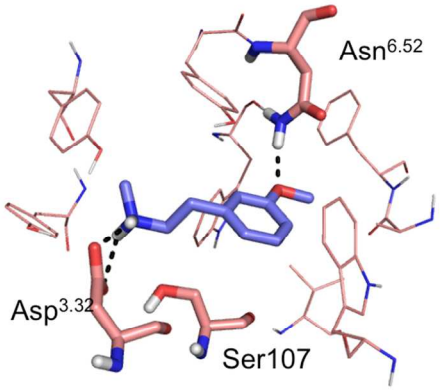
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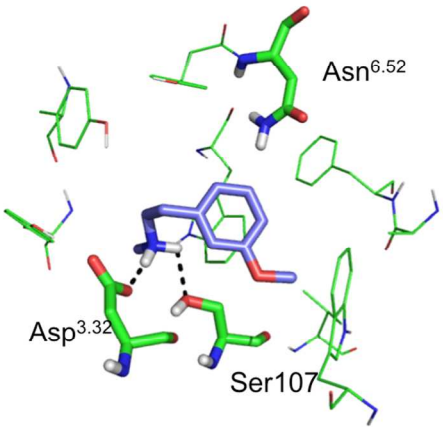
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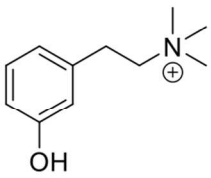

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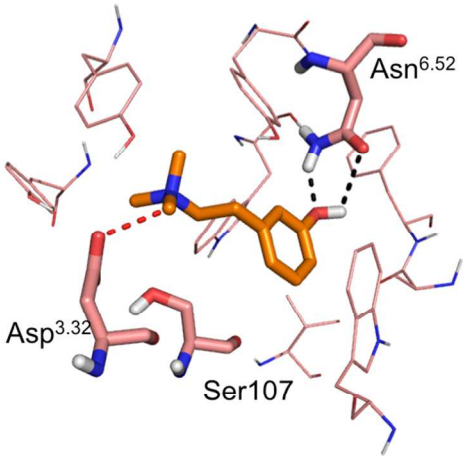
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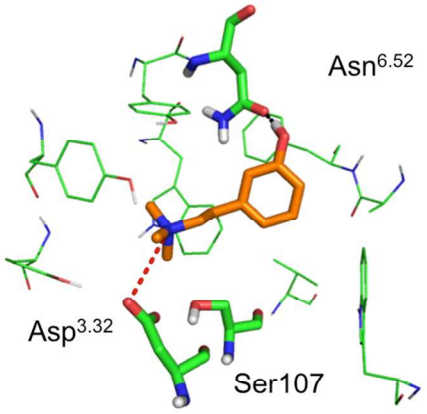
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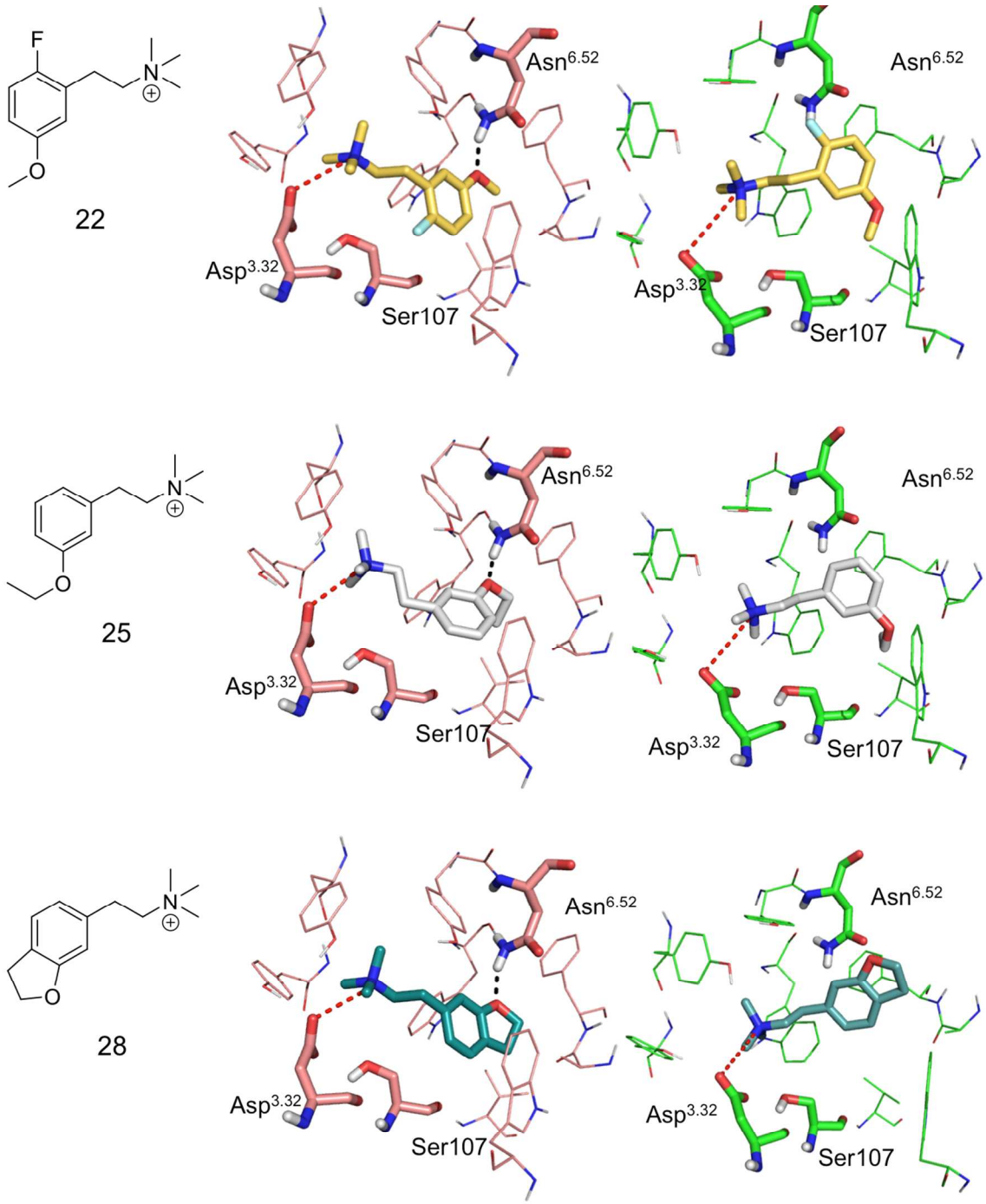


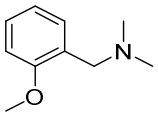
Figure S1. Docking poses of selected compounds in the M_2R active state structure (PDB ID 4MQS) and inactive state (PDB ID 3UON). Hydrogen bonds are represented in black, Ion interactions in red.

Chemistry

Dry solvents and reagents were of commercial quality and were used as purchased. HR-MS was run on a AB Sciex Triple TOF660 SCiex, source type ESI, or on a Bruker maXis MS in the laboratory of the Chair of Organic Chemistry, Friedrich Alexander University Erlangen-Nuernberg, or on a Bruker maXis MS in the laboratory of the Chair of Bioinorganic Chemistry, Friedrich Alexander University Erlangen-Nuernberg. NMR spectra were obtained on a Bruker Avance 360, a Bruker Avance 400 or a Bruker Avance 600 spectrometer using the solvents indicated. Chemical shifts are reported relative to TMS or acetone to the residual solvent peak. Not detected proton or carbon signals are mentioned. IR spectra were performed on a Jasco FT/IR 410 spectrometer (film on a NaCl pill). Purification by flash chromatography was performed using Silica Gel 60; TLC analyses were performed using Merck 60 F254 aluminum sheets and the spots were visualized under UV light (254 nm) and with reagents such as $KMnO_4$ vapor. Purification by preparative RP-HPLC was performed on Agilent 1100 preparative series, column: VP 250/32 NUCLEODUR C18 HTec 5 mm particles [C18], flow rate: 32 mL/min; eluent system 1: CH_3CN in H_2O + 0.1% HCOOH (0–3 min 10%, 3–15 min 10-45%, 15–8 min 45–100%); eluent system 2: MeOH in H_2O + 0.1% HCOOH (0–3 min 5%, 3–18 min 5–100%); eluent system 3: MeOH in H_2O + 0.1% HCOOH (0–3 min 10%, 3–18 min 10–100%); eluent system 4: CH_3CN in H_2O + 0.1% HCOOH (0–3 min 5%, 3–18 min 5–80%); eluent system 5: MeOH in H_2O + 0.1% HCOOH (0–3 min 5%, 3–16 min 5–55%, 16–18 min 55–100%); eluent system 6: CH_3CN in H_2O + 0.1% HCOOH (0–3 min 5%, 3–10 min 5–30%, 10–13 min 30–100%); eluent system 7: 2% CH_3CN in H_2O + 0.1% HCOOH (isocratic). Analytical HPLC/MS was performed on Agilent 1100 HPLC systems employing a VWL detector (220 nm or 254 nm) connected to a Bruker Esquire 2000. The purity of all test compounds and key intermediates was determined by reverse phase HPLC. HPLC analysis was performed on analytical systems (Agilent 1100 analytical series, VWD detector); System A: Zorbax Eclipse XDB-C8 analytical column, 4.6 mm x 150 mm, 5 µm, flow rate: 0.5 mL/min, eluent: MeOH in H_2O+0.1% HCOOH (0–3 min 10%, 3–18 min 10–100%, 18–24 min 100%); System B: Zorbax Eclipse XDB-C8 analytical column, 4.6 mm x 150 mm, 5 µm, flow rate: 0.5 mL/min, eluent: CH_3CN in

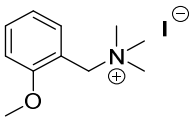
H_2O+0.1% HCOOH (0–3 min 5%, 3–18 min 5–95%, 18–24 min 95%); System C: EC 250/4.6 NUCLEODUR C19 Pyramid, 5 µM, flow rate: 0.5 mL/min, eluent: MeOH in H_2O+0.1% HCOOH (0–6 min 5%, 6–18 min 10–100%, 18–24 min 100%); System D: EC 250/4.6 NUCLEODUR C19 Pyramid, 5 µM, flow rate: 0.5 mL/min, eluent: CH_3CN in H_2O+0.1% HCOOH (0–6 min 5%, 6–18 min 10–95%, 18–24 min 95%). Compound **1–4, 20, 21, 25, 26** were synthesized according to indicated literature.

1-(2-Methoxyphenyl)-*N,N*-dimethylmethanamine (39) [1]



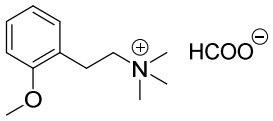
To a solution of 2-methoxybenzaldehyde (150 mg, 1.10 mmol) in dry THF (20 mL) were added dimethylamine (2 M in THF, 2.00 mL, 4.00 mmol), acetic acid (70.0 µL, 1.17 mmol) and sodium triacetoxyborohydride (604 mg, 2.85 mmol). The reaction mixture was stirred at room temperature for 18 h. Subsequently, saturated, aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.01) to give **39** (189 mg, quant.) as brown oil. IR (NaCl): 3413, 2942, 2817, 2769, 1722, 1602, 1493, 1465, 1243, 1109, 1031, 755 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.27 (dd, J = 7.4, 1.6 Hz, 1H), 7.26–7.22 (m, 1H), 6.92 (td, J = 7.4, 1.0 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 3.83 (s, 3H), 3.46 (s, 2H), 2.27 (s, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 158.1, 131.1, 128.4, 126.9, 120.3, 110.6, 58.0, 55.6, 45.6; HPLC (254 nm, system A): t_R= 5.2 min; ESI-MS: 166.3 $[M+H]^+$.

1-(2-Methoxyphenyl)-*N,N,N*-trimethylmethanaminium iodide (1) [2]



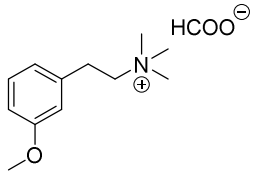
To a solution of compound **39** (12.0 mg, 72.7 µmol) in dry $CHCl_3$ (2.0 mL) was added under Ar-atmosphere methyl iodide (10.0 µL, 161 µmol). The reaction was stirred at room temperature for 16 h. After evaporation, the crude residue was dissolved in $CHCl_3$ and precipitated with diethylether to afforded **1** (15.2 mg, 68%) as white solid. Mp: 162–164 °C; IR (NaCl): 3468, 3003, 1497, 1255, 1023, 889, 763 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 7.58 (ddd, *J* = 8.5, 7.6, 1.7 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.14–7.09 (m, 1H), 4.51 (s, 2H), 3.90 (s, 3H), 3.08 (s, 9H); ^{13}C-NMR (151 MHz, D_2O): δ 159.5, 135.2, 133.6, 121.5, 116.4, 112.7, 64.6, 56.0, 53.1 (t, *J* = 4.5 Hz); HPLC (254 nm, system A): t_R= 12.6 min, purity: 95%, (254 nm, system B): t_R= 12.5 min, purity: 95%, HR-ESIMS: calcd 180.1383, found 180.13801 $[M]^+$.

2-(2-Methoxyphenyl)-*N*,*N*,*N*-trimethylethan-1-aminium formate (2) [3]



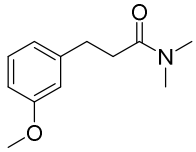
Compound **2** was synthesized according to the protocol of compound **1** using a solution of 2-(2-methoxyphenyl)ethylamine (30.0 µL, 205 µmol) in dry DMF (2 mL), methyl iodide (150 µL, 2.42 mmol) and K_2CO_3 (117 mg, 848 µmol). Purification by preparative HPLC (system 1) afforded **2** (20.0 mg, 40%) as colorless semi solid substance. IR (NaCl): 3258, 2969, 2839, 1590, 1496, 1348, 1249, 1051, 915, 763 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.45 (bs, 1H) 7.40–7.35 (m, 1H), 7.29 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.11–7.07 (m, 1H), 7.03–6.99 (m, 1H), 3.88 (s, 3H), 3.51–3.47 (m, 2H), 3.18 (s, 9H), 3.16–3.10 (m, 2H); ^{13}C-NMR (151 MHz, D_2O): δ 171.6, 157.9, 131.3, 129.8, 124.3, 121.7, 112.1, 66.2, 56.1, 53.5 (t, *J* = 4.5 Hz), 24.8; HPLC (254 nm, system A): t_R= 12.0 min, purity: 99%, (254 nm, system B): t_R= 11.9 min, purity: 99%, ESI-MS: 194.3 $[M]^+$.

2-(3-Methoxyphenyl)-*N*,*N*,*N*-trimethylethan-1-aminium formate (3) [3]



Compound **3** was synthesized according to the protocol of compound **1** using a solution of 2-(3-methoxyphenyl)ethylamine (20.0 µL, 137 µmol) in dry DMF (2 mL), methyl iodide (80.0 µL, 1.29 mmol) and K_2CO_3 (97.8 mg, 714 µmol). Purification by preparative HPLC (system 3) afforded **3** (15.0 mg, 46%) as white solid. Mp: 177.6–180.2 °C; IR (NaCl): 2989, 1591, 1489, 1257, 1170, 1039, 892, 769, 696 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.44 (s, 1H), 7.38–7.35 (m, 1H), 6.99–6.94 (m, 3H), 3.84 (s, 3H), 3.60–3.56 (m, 2H), 3.19 (s, 9H), 3.17–3.13 (m, 2H); ^{13}C-NMR (151 MHz, D_2O): δ 188.1, 159.9, 138.2, 131.0, 122.3, 115.3, 113.5, 67.6, 56.0, 53.7 (t, J = 4.5 Hz), 29.5; HPLC (220 nm, system A): t_R= 10.0 min, purity: > 99%, (220 nm, system B): t_R= 11.4 min, purity: > 99%; HR-ESIMS: calcd 194.1539, found 194.1539 $[M]^+$.

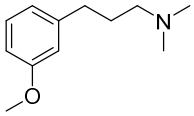
3-(3-Methoxyphenyl)-*N,N*-dimethylpropanamide (40) [4]



To a solution of 3-(3-methoxyphenyl)propanoic acid (420 mg, 2.33 mmol) in dry CH_2Cl_2 (8 mL) was added dimethylamine (2 M in THF, 2.20 mL, 4.40 mmol), triethylamine, (310 µL, 2.24 mmol) and *N,N*-dimethylaminopyridine (30.1 mg, 246 µmol) under N_2-atmosphere at room temperature. The reaction mixture was cooled to 0 °C, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (477 mg, 2.49 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm to room temperature and stirred for additional 2 h. Subsequently, ethyl acetate was added and the organic phase was washed once with saturated, aqueous citric acid solution, twice with saturated, aqueous $NaHCO_3$ solution and once with water. The organic layer was dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 60:1) to give **40** (158 mg, 33%) as

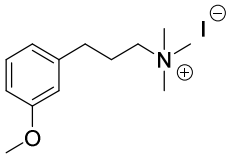
colorless oil. IR (NaCl): 2938, 1642, 1489, 1456, 1399, 1261, 1152, 1050, 872, 783, 697 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.79–6.76 (m, 1H), 6.76–6.73 (m, 1H), 3.79 (s, 3H), 2.97–2.92 (m, 8H), 2.64–2.59 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 172.2, 159.7, 143.2, 129.5, 120.8, 114.2, 111.4, 55.2, 35.5, 35.2, 31.4; HPLC (254 nm, system A): t_R= 17.9 min; ESI-MS: 230.2 $[M+Na]^+$.

3-(3-Methoxyphenyl)-*N,N*-dimethylpropan-1-amine (41) [5]



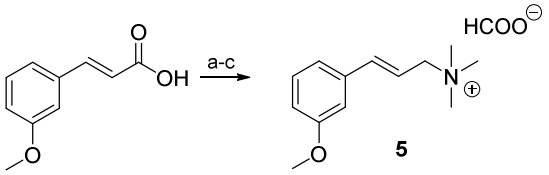
To a solution of $LiAlH_4$ (4 M in THF, 600 µL, 2.40 mmol) in dry THF (5 mL) was added a solution of **40** (150 mg, 725 µmol) in dry THF (2 mL) at 0 °C. The reaction mixture was stirred for 1 h at r.t. and quenched by subsequently adding water. Filtration of the precipitate and evaporation of the solvent afforded **41** (122 mg, 88%) as colorless oil. IR (NaCl): 3420, 2943, 2775, 1602, 1489, 1457, 1260, 1152, 1042, 777, 695 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.23–7.19 (m, 1H), 6.81–6.78 (m, 1H), 6.77–6.73 (m, 2H), 3.81 (s, 3H), 2.66–2.62 (m, 2H), 2.44–2.38 (m, 2H), 2.32 (s, 6H), 1.91–1.82 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 159.7, 143.5, 129.4, 120.8, 114.2, 111.2, 59.0, 55.2, 45.1, 33.6, 28.7; HPLC (254 nm, system A): t_R= 12.5 min; ESI-MS: 194.2 $[M+H]^+$.

3-(3-Methoxyphenyl)-*N,N,N*-trimethylpropan-1-aminium iodide (4) [2]



Compound **4** was synthesized according to the protocol of compound **1**, using a solution of compound **41** (6.0 mg, 31.0 µmol) in dry DMF (2 mL) and methyl iodide (10.0 µL, 161 µmol). The compound was dissolved in $CHCl_3$ and precipitated with diethylether to afford **4** (6.1 mg, 59%) as pale yellow oil. IR (NaCl): 3460, 3010, 2957, 1593, 1486, 1351, 1261, 1155, 1037, 958, 932, 776, 698 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.26–

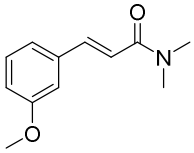
7.19 (m, 1H), 6.85–6.73 (m, 3H), 3.81 (s, 3H), 3.67–3.59 (m, 2H), 3.41 (s, 9H), 2.80–2.70 (m, 2H), 2.19–2.07 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 160.1, 140.9, 130.1, 120.8, 114.3, 112.4, 66.8, 55.6, 54.1, 32.0, 25.0; HPLC (220 nm, system A): t_R= 11.7 min, purity: 98%, (220 nm, system B): t_R= 12.2 min, purity: > 99%; ESI-MS: HR-ESIMS: calcd 208.1696, found 208.1697 $[M]^+$.



Scheme S1. Synthesis of compound **5**. *Reagents and conditions*: a) $HN(CH_3)_2$, Et_3N, DMAP, EDC·HCl, CH_2Cl_2, r.t., 24 h; b) $LiAlH_4$, THF, r.t., 1 h; c) MeI, DMF, r.t., 16 h.

The olefin **5** (scheme 2) was synthesized according to the synthetic strategy of the dihydrobenzofuran **28**, starting from the commercially available 3-methoxy cinnamonic acid.

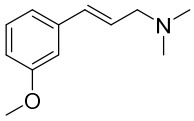
3-(3-Methoxyphenyl)-*N*,*N*-dimethylacrylamide (42) [6]



Compound **42** was synthesized according to the protocol of compound **40** using a solution of 3-methoxy cinnamic acid (414 mg, 2.32 mmol) in dry CH_2Cl_2 (8 mL), dimethylamine (2 M in THF, 2.20 mL, 4.40 mmol), triethylamine (310 µL, 2.24 mmol), *N,N*-dimethylaminopyridine (32.6 mg, 267 µmmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (474 mg, 2.47 mmol). The reaction was stirred at room temperature for 24 h. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 60:1) afforded **42** (368 mg, 77%) as colorless oil. IR (NaCl): 3450, 2962, 1650, 1605, 1493, 1397, 1260, 1159, 1046, 789, 742, 680 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.65 (d, *J* = 15.4 Hz, 1H), 7.34–7.26 (m, 1H), 7.14 (d, *J* = 7.7 Hz,

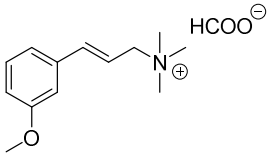
1H), 7.09–7.04 (m, 1H), 6.95–6.84 (m, 2H), 3.85 (s, 3H), 3.14 (s, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 168.1, 161.3, 143.7, 138.3, 131.2, 121.8, 119.3, 116.5, 114.6, 56.8, 32.8, 36.6; HPLC (254 nm, system 1): t_R= 18.5 min; ESI-MS: 206.2 $[M+H]^+$.

3-(3-Methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine (43) [7]



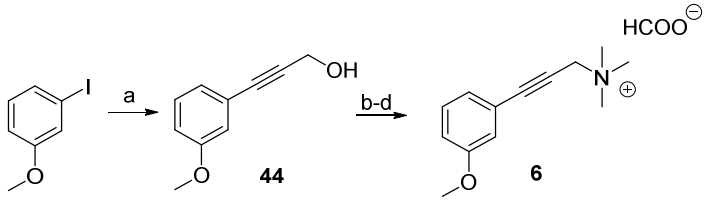
Compound **43** was synthesized according to the protocol of compound **41**, using $LiAlH_4$ (4 M in THF, 400 µL, 1.60 mmol) in dry THF (5 mL) and a solution of compound **42** (107 mg, 522 µmol) in dry THF (2 mL). The reaction time was 1 h. Evaporation of the solvent afforded **43** (74.1 mg, 75%) as colorless oil. IR (NaCl): 2942, 2773, 1599, 1581, 1489, 1465, 1264, 1155, 1043, 973, 774, 688 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.24–7.20 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.94–6.91 (m, 1H), 6.79 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.8, 6.7 Hz, 1H), 3.81 (s, 3H), 3.08 (dd, *J* = 6.7, 1.0 Hz, 2H), 2.28 (s, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 159.8, 138.5, 132.5, 129.5, 127.7, 119.0, 113.2, 111.5, 62.0, 55.2, 45.3; HPLC (254 nm, system A): t_R= 13.1 min; ESI-MS: 192.2 $[M+H]^+$.

3-(3-Methoxyphenyl)-*N*,*N*,*N*-trimethylprop-2-en-1-aminium formate (5)



Compound **5** was synthesized according to the protocol of compound **1**, using a solution of compound **43** (7.4 mg, 38.6 µmol) in dry DMF (2 mL) and methyl iodide (10.0 µL, 161 µmol). Purification by preparative HPLC (system 5) afforded **5** (4.4 mg, 47%) as white solid. IR (NaCl): 2957, 2760, 1597, 1485, 1351, 1259, 1159, 1038, 972, 890, 785, 689 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 7.43–7.38 (m, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.17–7.14 (m, 1H), 7.03 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.97 (d, *J* = 15.7 Hz, 1H), 6.44 (dt, *J* =

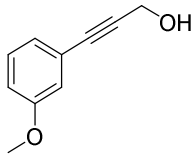
15.5, 7.7 Hz, 1H), 4.08 (d, *J* = 7.7 Hz, 2H), 3.86 (s, 3H), 3.13 (s, 9H) (**H**COO$^-$ was not detected); ^{13}C-NMR (91 MHz, D_2O): δ 160.9, 144.2, 138.3, 131.9, 121.8, 117.3, 116.7, 114.1, 69.8, 57.1, 54.0 (t, J = 4.6 Hz) (H**C**OO$^-$ was not detected); HPLC (254 nm, system A): t_R= 11.9 min, purity: 97%, (254 nm, system B): t_R= 11.9 min, purity: 98%; HR-ESIMS: calcd 206.1539, found 206.1541 $[M]^+$.



Scheme S2. Synthesis of compound **6**. *Reagents and conditions*: a) propargyl alkohol, $Pd(PPh_3)_4$, CuI, Et_3N, THF, r.t., 16 h; b) MsCl, Et_3N, CH_2Cl_2, r.t., 3 h; c) $HN(CH_3)_2$, DMF, r.t., 3 h, then 50 °C, 16 h; d) MeI, DMF, r.t., 16 h.

For the synthesis of the alkyne **6** (scheme 3), 3-iodoanisole was first reacted in a palladium catalyzed Sonogashira coupling with propargyl alcohol and CuI to the phenyl acetylene [8]. In situ activation of the alcohol to the corresponding chloride [9] was followed by a nucleophilic substitution with *N,N*-dimethylamine to afford the tertiary amine [10] which was methylated to compound **6**.

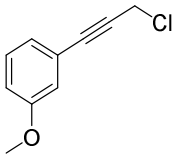
3-(3-Methoxyphenyl)prop-2-yn-1-ol (44) [8]



To a solution of tetrakis(triphenylphosphin)palladium(0) (94.2 mg, 81.6 µmol) and CuI (36.7 mg, 193 µmol) in dry THF (10 mL) were added under N_2-atmosphere triethylamine (0.5 ml) and 3-iodoanisole (200 µL, 1.68 mmol). Subsequently, propargylalcohol (300 µL, 5.19 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. After evaporation, the crude residue was dissolved in $CHCl_3$ and

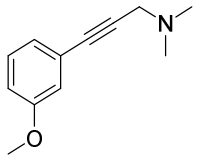
the organic layer was washed once with saturated, aqueous NH_4Cl solution, once with saturated, aqueous $NaHCO_3$ solution and once with saturated aqueous NaCl solution. The organic layer was dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **44** (280 mg, quant.) as pale yellow oil. IR (NaCl): 3365, 2939, 1604, 1576, 1481, 1420, 1319, 1290, 1206, 1165, 1043, 973, 855, 782, 687 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.23–7.20 (m, 1H), 7.05–7.02 (m, 1H), 6.97 (dd, *J* = 2.5, 1.4 Hz, 1H), 6.88 (ddd, *J* = 8.4, 2.6, 0.8 Hz, 1H), 4.49 (s, 2H), 3.79 (s, 3H), 1.71 (s, 1H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 159.3, 129.4, 124.2, 123.5, 116.6, 115.1, 87.0, 85.6, 55.3, 51.7; HPLC (254 nm, system A): t_R= 18.0 min; ESI-MS: 163.2 $[M+H]^+$.

1-(3-Chloroprop-1-yn-1-yl)-3-methoxybenzene (45) [9]



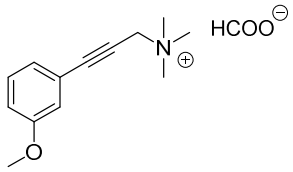
To a solution of compound **44** (110 mg, 679 µmol) and triethylamine (100 µL, 723 µmol) in dry CH_2Cl_2 (4 mL) was added methanesulfonyl chloride (60.0 µL, 775 µmol) under N_2-atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, subsequently, additional methanesulfonyl chloride (50.0 µL, 646 µmol) and triethylamine (100 µL, 723 µmol) were added and the reaction was stirred at room temperature for 2 h. Saturated, aqueous NH_4Cl solution was added and the mixture was stirred for 10 min. The organic layer was washed twice with saturated, aqueous NH_4Cl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:1) to give **45** (16.8 mg, 15%) as colorless oil. IR (NaCl): 2962, 2923, 1259, 1088, 1041, 1022, 865, 798, 686 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.18–7.11 (m, 1H), 7.00–6.95 (m, 1H), 6.93–6.88 (m, 1H), 6.83 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.31 (s, 2H), 3.73 (s, 3H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 158.3, 128.4, 123.4, 122.0, 115.6, 114.5, 85.2, 82.5, 54.3, 30.1; HPLC (254 nm, system A): t_R= 20.5 min; ESI-MS: 181.3 $[M+H]^+$.

3-(3-Methoxyphenyl)-*N*,*N*-dimethylprop-2-yn-1-amine (46) [10]

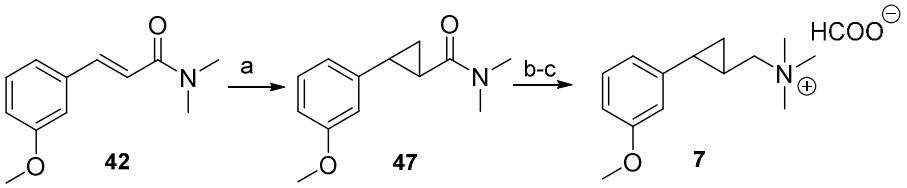


To a solution of compound **45** (12.0 mg, 66.4 µmol) in dry DMF (2 mL) was added dimethylamine (2 M in THF, 400 µL, 800 mmol) under Ar-atmosphere. The reaction was stirred at room temperature for 3 h and then at 50 °C for 16 h. After cooling to room temperature, evaporation afforded **46** (12.4 mg, quant.) as pale, yellow oil. IR (NaCl): 3419, 2963, 1668, 1605, 1471, 1292, 1261, 1044, 913, 792, 736 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.22–7.18 (m, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.94–6.92 (m, 1H), 6.91–6.87 (m, 1H), 4.02 (s, 2H), 3.75 (s, 3H), 2.81 (s, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 158.5, 128.7, 123.5, 120.8, 116.0, 115.1, 89.6, 75.1, 54.4, 46.7, 41.1; HPLC (254 nm, system A): t_R= 14.2 min; ESI-MS: 190.2 $[M+H]^+$.

3-(3-Methoxyphenyl)-*N*,*N*,*N*-trimethylprop-2-yn-1-aminium formate (6)



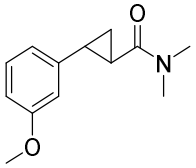
Compound **6** was synthesized according to the protocol of compound **1**, using a solution of compound **46** (8.6 mg, 45.4 µmol) in dry DMF (2 mL) and methyl iodide (20.0 µL, 322 µmol). Purification by preparative HPLC (column 1, system 5) afforded **6** (3.4 mg, 28%) as white solid. IR (NaCl): 2989, 2901, 1394, 1066, 669 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.47 (s, 1H), 7.42–7.37 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 7.11 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.47 (s, 2H), 3.84 (s, 3H), 3.27 (s, 9H); ^{13}C-NMR (151 MHz, D_2O): δ 171.5, 159.4, 130.7, 125.6, 122.1, 117.8, 117.0, 91.6, 76.9, 57.8, 56.1, 53.4 HPLC: (254 nm, system A): t_R= 12.5 min, purity: 97%, (254 nm, system B): t_R= 12.8 min, purity 98%, HR-ESIMS: calcd 204.1383, found 204.1382 $[M]^+$.



Scheme S3. Synthesis of compound **7**. *Reagents and conditions*: a) $(CH_3)_3SOI$, NaH, DMSO, r.t., 16 h; b) $LiAlH_4$, THF, r.t., 1 h; c) MeI, DMF, r.t., 16 h.

For the synthesis of the cyclopropyl based target compound, the amide **42** [6] was treated with trimethylsulfoxonium iodide and NaH in DMSO to give the cyclopropyl derivative **47** in 30% yield. The reduction of the amide with $LiAlH_4$ was followed by methylation of the tertiary amine to the quarternary ammonium derivative **7**. Selective NOE experiments of the amide **47** proofed the trans conformation of the cyclopropane linker.

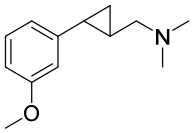
2-(3-Methoxyphenyl)-*N*,*N*-dimethylcyclopropane-1-carboxamide (47)



A mixture of NaH (60% suspension, 101 mg, 2.50 mmol) and trimethylsulfoxonium iodide (600 mg, 2.72 mmol) in dry DMSO (2 mL) was stirred under N_2-atmosphere at room temperature until a clear solution was obtained. Subsequently, a solution of compound **42** (150 mg, 731 µmol) in dry DMSO (2 mL) was added dropwise and the reaction was stirred at room temperature for 16 h. Water and $CHCl_3$ were added and the aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 2:1 → 1:1) to give **47** (47.5 mg, 30%) as colorless oil. IR (NaCl): 2917, 1633, 1492, 1418, 1255, 1157, 1047, 913, 783, 695 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.21–7.17 (m, 1H), 6.76–6.72 (m, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.69–6.65 (m, 1H), 3.80 (s, 3H), 3.13 (s, 3H), 2.99 (s, 3H), 2.45 (ddd, *J* = 9.1, 6.2, 4.3 Hz, 1H), 1.98 (ddd, *J* = 8.3, 5.3, 4.3 Hz, 1H), 1.63 (ddd, *J* = 9.6, 8.5, 5.9 Hz, 1H), 1.25 (ddd, *J* = 8.3, 6.2, 4.3 Hz, 1H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 171.9,

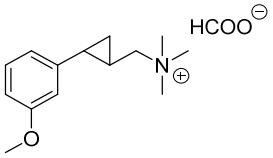
159.8, 143.0, 129.4, 118.4, 112.2, 111.4, 55.2, 37.3, 35.9, 25.5, 23.2, 16.3; HPLC (254 nm, system A): t_R= 18.0 min; ESI-MS: 220.3 $[M+H]^+$.

1-(2-(3-Methoxyphenyl)cyclopropyl)-*N*,*N*-dimethylmethanamine (48)



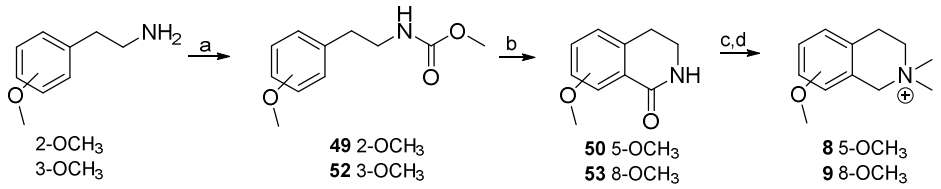
Compound **48** was synthesized according to the protocol of compound **41** using $LiAlH_4$ (4 M in THF, 150 µL, 600 µmol) in dry THF (3 mL) and a solution of compound **47** (40.0 mg, 183 µmol) in dry THF (1 mL). The reaction time was 1 h. Evaporation of the solvent afforded **48** (35.1 mg, 95%) as colorless oil. IR (NaCl): 2771, 1604, 1458, 1263, 1156, 1043, 739, 694 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.19–7.12 (m, 1H), 6.72–6.64 (m, 2H), 6.63–6.59 (m, 1H), 3.78 (s, 3H), 2.41 (dd, *J* = 12.5, 6.3 Hz, 1H), 2.33–2.25 (m, 7H), 1.72–1.63 (m, 1H), 1.29–1.18 (m, 1H), 1.02–0.93 (m, 1H), 0.87–0.79 (m, 1H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 159.7, 144.7, 129.3, 118.2, 111.6, 110.7, 63.9, 55.2, 45.4, 22.7, 21.5, 15.1; HPLC (254 nm, system A): t_R= 4.9 min; ESI-MS: 206.2 $[M+H]^+$.

1-(2-(3-Methoxyphenyl)cyclopropyl)-*N*,*N*,*N*-trimethylmethanaminium formate (7)



Compound **7** was synthesized according to the protocol of compound **1**, using a solution of compound **48** (11.0 mg, 53.6 µmol) in dry DMF (2 mL) and methyl iodide (10.0 µL, 161 µmol). Purification by preparative HPLC (system 2) afforded **7** (6.5 mg, 47%) as white solid. IR (NaCl): 3389, 2989, 2900, 1603, 1394, 1256, 1066, 1051, 879 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.76 (s, 1H), 7.34–7.29 (m, 1H), 6.91–6.87 (m, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.81–6.77 (m, 1H), 3.83 (s, 3H), 3.48 (dd, *J* = 13.4, 6.6 Hz, 1H), 3.36 (dd, *J* = 13.6, 7.9 Hz, 1H), 3.16 (s, 9H), 2.11–2.05 (m, 1H), 1.54–1.47 (m, 1H), 1.34 (dt, *J* = 8.7, 5.6 Hz, 1H), 1.15 (dt, *J* = 9.1, 5.5 Hz, 1H); ^{13}C-NMR (151 MHz, D_2O): δ 171.1,

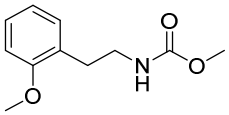
159.9, 143.4, 130.8, 119.1, 112.5, 112.3, 70.7, 56.0, 53.5 (t, J = 4.5 Hz), 23.0, 17.1, 14.5; HPLC (220 nm, system A): t_R= 15.3 min, purity: 97%, (220 nm, system B): t_R= 14.1 min, purity: 96%; ESI-MS: 220.4 $[M]^+$.



Scheme S4. Synthesis of compound **8** and **9**. *Reagents and conditions*: a) methyl chloroformate, Et_3N, THF, r.t., 5–24 h; b) PPA, 145 °C, 10 min; c) $LiAlH_4$, THF, reflux, 3 h; d) MeI, K_2CO_3, DMF, r.t., 16 h.

The tetrahydroisoquinoline derivatives and **8** [11] and **9** (scheme 5) were synthesized starting from 3- and 2-methoxy phenethylamine, respectively. The synthesis of the carbamates **49** [12] and **52** [13] was followed by cyclisation in polyphosphoric acid at 145 °C to give the lactames **50** [14] and **53** [13]. After reduction with $LiAlH_4$, the quarternary tetrahydroisoquinolines **8** and **9** were obtained by alkylation with methyl iodide and K_2CO_3 as base.

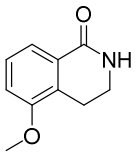
Methyl (2-methoxyphenethyl)carbamate (49) [12]



Compound **49** was synthesized according to the protocol of compound **52** using a solution of 2-(2-methoxyphenyl)-ethylamine (500 µL, 3.31 mmol) and triethylamine (550 µL, 4.00 mmol) in dry THF (15 mL) and methylchloroformiate (1.30 mL, 16.7 mmol). The reaction time was 5 h. Evaporation of the solvent gave **49** (680 mg, 98%) as pale yellow oil. IR (NaCl): 3336, 2958, 2837, 1705, 1602, 1533, 1495, 1465, 1244, 1121, 1029, 755 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.15 (td, *J* = 8.0, 1.6 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.85–6.81 (m, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 4.72 (bs, 1H), 3.76 (s, 3H), 3.57 (s, *J* = 16.9 Hz, 3H), 3.38–3.31 (m, 2H), 2.78–2.72 (m, 2H); ^{13}C-NMR

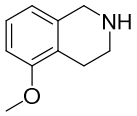
(151 MHz, $CDCl_3$): δ 157.6, 157.0, 130.6, 127.9, 127.3, 120.6, 110.4, 55.3, 51.9, 41.2, 30.7; HPLC (254 nm, system A): t_R= 19.0 min; ESI-MS: 232.3 $[M+Na]^+$.

5-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (50) [14]



Compound **50** was synthesized according to the protocol of compound **53** using polyphosphoric acid (4.0 g) and compound **49** (247 mg, 1.18 mmol). Purification by column chromatography on silica gel (ethyl acetate/MeOH, 19:1) afforded **50** (40.0 mg, 22%) as colorless oil. IR (NaCl): 3389, 3194, 2967, 1676, 1583, 1489, 1414, 1347, 1267, 1222, 1053, 753 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.36–7.27 (m, 1H), 7.01 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.06 (bs, 1H), 3.86 (s, 3H), 3.53 (td, *J* = 6.7, 2.9 Hz, 2H), 2.97 (t, *J* = 6.7 Hz, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 166.4, 155.8, 130.1, 127.8, 127.4, 120.1, 113.8, 55.8, 40.1, 21.7; HPLC (254 nm, system A): t_R= 16.2 min; ESI-MS: 200.2 $[M+Na]^+$.

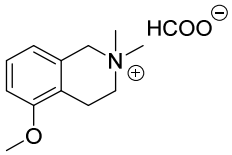
5-Methoxy-1,2,3,4-tetrahydroisoquinoline (51) [15]



Compound **51** was synthesized according to the protocol of compound **41** using $LiAlH_4$ (4 M in THF, 100 µL, 400 µmol) in dry THF (5 mL) and a solution of compound **50** (18.0 mg, 102 µmol) in dry THF (4 mL). The reaction time was 3 h. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.01) afforded **51** (11.8 mg, 70%) as pale yellow oil. IR (NaCl): 2920, 2849, 2360, 1590, 1469, 1259, 1098, 1013, 773 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.13–7.06 (m, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 4.00 (s, 2H), 3.82 (s, 3H), 3.15 (t, *J* = 6.1 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H) (NH was not detected); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 157.4, 136.7,

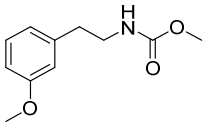
126.2, 123.5, 118.4, 107.4, 55.3, 48.1, 43.6, 23.2; HPLC (254 nm system A): t_R= 7.5 min; ESI-MS: 164.3 $[M+H]^+$.

5-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-2-ium formate (8) [11]



Compound **8** was synthesized according to the protocol of compound **1** using a solution of compound **51** (9.0 mg, 55.2 µmol) in dry DMF (2 mL), methyl iodide (30.0 µL, 483 µmol) and K_2CO_3 (30.0 mg, 217 µmol). Purification by preparative HPLC (system 2) afforded **8** (10.4 mg, 80%) as white solid. IR (NaCl): 3396, 2935, 1682, 1595, 1474, 1353, 1267, 1200, 1098, 1005, 914, 775 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 9.26 (bs, 1H), 7.41–7.32 (m, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 4.56 (s, 2H), 3.89 (s, 3H), 3.71 (t, *J* = 6.5 Hz, 2H), 3.20 (s, 6H), 3.09 (t, *J* = 6.3 Hz, 2H); ^{13}C-NMR (91 MHz, D_2O): δ 171.1, 157.4, 129.2, 128.2 119.7, 118.6, 111.2, 63.8, 60.2, 56.3, 51.8, 19.7; HPLC (220 nm, system A): t_R= 10.4 min, purity: > 99%, (220 nm, system B): t_R= 10.8 min, purity: > 99%; HR-ESIMS: calcd 192.1383, found 192.1385 $[M]^+$.

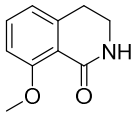
Methyl (3-methoxyphenethyl)carbamate (52) [13]



A solution of 2-(3-methoxyphenyl)-ethylamine (500 µL, 3.31 mmol) and triethylamine (550 µL, 4.00 mmol) in dry THF (15 mL) was cooled under Ar-atmosphere to 0 °C. Subsequently, methylchloroformiate (1.30 mL, 16.7 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. Subsequently, water was added and the aqueous phase was extracted three times with $CHCl_3$. The combined organic layers were washed with saturated, aqueous NaCl solution, dried (Na_2SO_4) and the solvent was evaporated to give **52** (700 mg, quant.) as yellow oil. IR (NaCl): 3337,

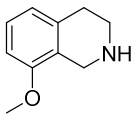
2948, 2837, 1706, 1602, 1527, 1495, 1244, 1121, 1049, 1029, 754 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.24–7.20 (m, 1H), 6.80–6.76 (m, 2H), 6.75–6.71 (m, 1H), 4.68 (bs, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.48–3.39 (m, 2H), 2.83–2.74 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 159.9, 157.0, 140.4, 129.6, 121.1, 114.5, 111.9, 55.2, 52.1, 42.1, 36.2; HPLC (254 nm, system A): t_R= 13.3 min; ESI-MS: 323.2 $[M+Na]^+$.

8-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (53) [13]



Polyphosphoric acid (5.0 g) was heated to 145°C. Subsequently, compound **52** (400 mg, 1.90 mmol) was added and the reaction mixture was stirred at 145 °C for 10 minutes. Iced cooled water was added and the aqueous phase was extracted three times with $CHCl_3$. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (ethyl acetate/MeOH, 19:1) to give **53** (45.0 mg, 13%) as pale yellow solid. Mp: 144–146 °C; IR (NaCl): 3192, 2938, 1655, 1603, 1478, 1319, 1275, 1252, 1158, 1026, 844, 782 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.40–7.34 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.45 (bs, 1H), 3.94 (s, 3H), 3.46 (td, *J* = 6.3, 3.6 Hz, 2H), 2.96–2.90 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 165.1, 160.1, 142.0, 132.7, 119.5, 117.7, 110.9, 56.2, 39.8, 30.2; HPLC (254 nm, system A): t_R= 15.3 min; ESI-MS: 178.3 $[M+H]^+$.

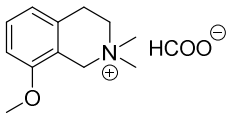
8-Methoxy-1,2,3,4-tetrahydroisoquinoline (54) [13]



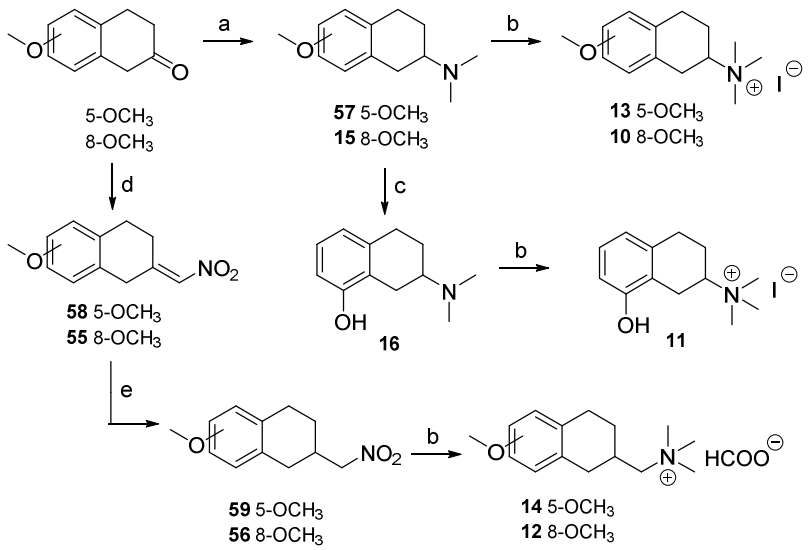
Compound **54** was synthesized according to the protocol of compound **41** using $LiAlH_4$ (4 M in THF, 100 µL, 400 µmol) in dry THF (5 mL) and a solution of compound **53** (45.0 mg, 254 µmol) in dry THF (4 mL). The reaction time was 3 h. Purification by

column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 20:1:0.02) afforded **54** (25.0 mg, 61%) as pale yellow oil. IR (NaCl): 2920, 2849, 2723, 2468, 2361, 1589, 1469, 1258, 1098, 1013, 773 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.14–7.09 (m, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 3.98 (s, 2H), 3.80 (s, 3H), 3.12 (t, *J* = 5.9 Hz, 2H), 2.81 (t, *J* = 5.8 Hz, 2H), 2.25 (bs, 1H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 156.0, 135.8, 126.5, 124.0, 121.4, 107.1, 55.2, 43.1, 43.1, 28.9; HPLC (254 nm, system A): t_R= 10.9 min; ESI-MS: 164.3 $[M+H]^+$.

8-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-2-ium formate (9)



Compound **9** was synthesized according to the protocol of compound **1** using a solution of compound **54** (12.0 mg, 73.6 µmol) in dry DMF (2 mL), methyl iodide (30.0 µL, 483 µmol) and K_2CO_3 (30.2 mg, 218 µmol). Purification by preparative HPLC (system 3) afforded **9** (10.0 mg, 58%) as white solid. IR (NaCl): 3000, 1593, 1473, 1267, 1096, 941, 779 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.44 (s, 1H,), 7.43–7.31 (m, 1H), 7.02–6.91 (m, 2H), 4.50 (s, 2H), 3.86 (s, 3H), 3.67 (t, *J* = 6.5 Hz, 2H), 3.24 (t, *J* = 6.2 Hz, 2H), 3.21 (s, 6H); ^{13}C-NMR (91 MHz, D_2O): δ 171.5, 156.6, 130.9, 129.9, 121.2, 115.7, 109.7, 59.7, 56.2, 52.2, 30.5, 23.9; HPLC (220 nm, system A): t_R= 11.3 min, purity: > 99%, (220 nm system B): t_R= 11.3 min, purity: > 99%; HR-ESIMS: calcd 192.1383, found 192.1383 $[M]^+$.

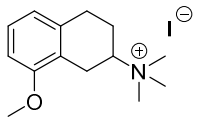


Scheme S5. Synthesis of compound **10** - **16**. *Reagents and conditions*: a) $HN(CH_3)_2$, AcOH, sodium triacetoxyborohydride, THF, r.t., 16–18 h; b) MeI, $CHCl_3$, r.t., 16 h; c) HBr (48% aqueous solution), reflux, 2 h; d) AcOH, NH_4OAc, CH_3NO_2, reflux, 4–5 h; e) $LiAlH_4$, THF, r.t., 4-8 h.

The quarternary aminotetralin ions **10** - **15** were synthesized starting from 8-methoxy-2-tetralone and 5-methoxy-2-tetralone, respectively (scheme 6). For compound **10**, **11** and **13** the first step was a reductive amination of these ketones with *N,N*-dimethylamine and sodium triacetoxyborohydride in THF, giving the tertiary amines **15** [16] and **57** [17]. Subsequently, these tertiary amines were alkylated with methyl iodide at room temperature to give the salts **10** and 1**3**. For the synthesis of the hydroxy derivative **11**, the methoxy group was cleaved under reflux conditions in aqueous HBr and subsequently, the tertiary amine **16** [18] was methylated to give the phenol **11** with an overall yield of 60%.

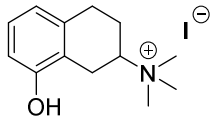
The synthesis of the homolog quarternary ammonium derivative **12** and **14** started with an Henry reaction of the corresponding tetralone in nitromethane with acetic acid and ammonium acetate to give the nitro olefins **55** und **58** [19]**.** Reduction with $LiAlH_4$ to primary amines **56** and **59** was followed by alkylation with methyl iodide in DMF at room temperature. Purification with preparative HPLC gave the quarternary ammonium derivatives **12** and **14** with a yield of 41% and 90%, respectively.

8-Methoxy-*N,N,N*-trimethyl-1,2,3,4-tetrahydronaphthalen-2-aminium iodide (10)



Compound **10** was prepared according to the protocol of compound **1**, using a solution of compound **15** (15.0 mg, 73.1 mmol) in dry $CHCl_3$ (2 mL) and methyl iodide (10.0 µL, 161 µmol). The compound was dissolved in MeOH and precipitated with diethyl ether to afford **10** (12.8 mg, 51%) as pale yellow solid. Mp: 230–234 °C; IR (NaCl): 2900, 1559, 1472, 1340, 1259, 1066, 780, 669 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO): δ 7.18–7.13 (m, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 3.80 (s, 3H), 3.76–3.69 (m, 1H), 3.19–3.14 (m, 2H), 3.12 (s, 9H), 2.99–2.93 (m, 1H), 2.88–2.80 (m, 1H), 2.76 (dd, *J* = 15.3, 12.3 Hz, 1H), 2.44–2.37 (m, 1H), 1.72 (qd, *J* = 12.3, 4.9 Hz, 1H); ^{13}C-NMR (151 MHz, DMSO): δ 156.8, 135.7, 127.0, 121.0, 120.2, 107.6, 70.3, 55.2, 50.3 (t, *J* = 3.0 Hz), 28.4, 23.2, 22.4; HPLC (220 nm, system A): t_R= 11.6 min, purity: 98%, (220 nm, system B): t_R= 12.4 min, purity: > 99%; HR-ESIMS: calcd 220.1696, found 220.1700 $[M]^+$.

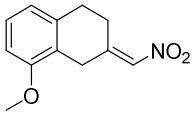
8-Hydroxy-*N,N,N*-trimethyl-1,2,3,4-tetrahydronaphthalen-2-aminium iodide (11)



Compound **11** was prepared according to the protocol of compound **1**, using a solution of compound **16** (16.1 mg, 84.2 mmol) in dry $CHCl_3$ (2 mL) and methyl iodide (10.0 µL, 161 µmol). The compound was dissolved in MeOH and precipitated with diethyl ether to afford **10** (10.0 mg, 38%) as white solid. IR (NaCl): 3234, 2971, 1588, 1465, 1394, 1242, 1066, 669 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 7.15–7.10 (m, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 3.77–3.70 (m, 1H), 3.34–3.29 (m, 1H), 3.19 (s, 9H), 3.08–3.02 (m, 1H), 2.95–2.87 (m, 1H), 2.85–2.78 (m, 1H), 2.49–2.43 (m, 1H), 1.84 (qd, *J* = 12.3, 4.9 Hz, 1H); ^{13}C-NMR (151 MHz, D_2O): δ 154.6, 137.4, 128.2, 120.6, 120.5, 113.1, 72.3, 51.4 (t, *J* = 3.0 Hz), 29.0, 24.1, 23.5; HPLC (220 nm, system A): t_R= 9.8 min,

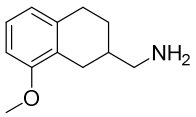
purity: 97%, (220 nm, system B): t_R= 10.4 min, purity: 97%; HR-ESIMS: calcd 206.1539, found 206.1540 $[M]^+$.

8-Methoxy-2-(nitromethylene)-1,2,3,4-tetrahydronaphthalene (55) [19]



To a solution of 8-methoxy-2-tetralone (200 mg, 1.14 mmol) in nitromethane (5 mL) were added acetic acid (50.0 µL, 874 µmol) and ammonium acetate (90.0 mg, 1.18 mmol). The reaction mixture was stirred under reflux conditions for 5 h and was then allowed to cool to room temperature. Subsequently, water was added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:1) to give **55** (216 mg, 87%) as yellow oil. IR (NaCl): 2939, 2837, 1668, 1551, 1473, 1368, 1266, 1156, 1082, 773 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.18–7.14 (m, 1H), 7.04–7.02 (m, 1H), 6.77–6.72 (m, 2H), 5.06 (s, 2H), 3.83 (s, 3H), 2.89–2.85 (m, 2H), 2.40 (t, *J* = 8.2 Hz, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 156.7, 155.4, 136.8, 129.2, 127.8, 126.3, 120.1, 109.1, 55.5, 28.0, 27.4, 25.1; HPLC (254 nm, system A): t_R= 20.4 min; ESI-MS: 173.3 $[M\text{-}NO_2]^+$.

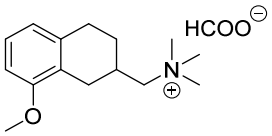
(8-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)methanamine (56) [19]



$LiAlH_4$ (2.8 M in THF, 1.16 mL, 3.25 mmol) was dissolved under Ar-atmosphere in dry THF (5 mL) and cooled to 0 °C. A solution of compound **55** (106 mg, 484 mmol) in dry THF (2 mL) was added dropwise and the mixture was stirred at room temperature for 18 h. Subsequently, the reaction was quenched with aqueous NaOH solution (1 M) and the precipitate was removed by filtration. After evaporation, the crude residue was

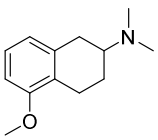
purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.01) to give **56** (24.0 mg, 28%) as pale yellow oil. IR (NaCl): 3441, 2927, 2837, 1585, 1470, 1325, 1254, 1072, 768 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.10–7.06 (m, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 2.98–2.91 (m, 1H), 2.87–2.69 (m, 4H), 2.19–2.11 (m, 1H), 2.01–1.92 (m, 1H), 1.76–1.67 (m, 1H), 1.39–1.30 (m, 1H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 157.4, 138.2, 125.9, 121.7, 121.1, 106.8, 55.4, 55.2, 29.7, 29.2, 27.6, 26.7; HPLC (254 nm, system A): t_R= 14.7 min; ESI-MS: 192.2 $[M+H]^+$.

1-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N,N,N*-trimethylmethanaminium formate (12)



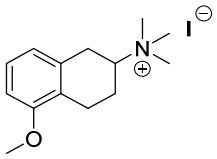
Compound **12** was prepared according to the protocol of compound **1** using a solution of compound **56** (10.0 mg, 52.3 mmol) in dry DMF (2 mL) and methyl iodide (40.0 µL, 644 µmol) and K_2CO_3 (33.9 mg, 246 µmol). Purification by preparative HPLC (system 1) afforded **12** (6.0 mg, 41%) as pale yellow semi solid substance. IR (NaCl): 2989, 2900, 1559, 1507, 1394, 1250, 1066, 892 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.44 (s, 1H), 7.24–7.20 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 3.49–3.37 (m, 2H), 3.20 (s, 9H), 3.08–3.02 (m, 1H), 2.94–2.82 (m, 2H), 2.45–2.31 (m, 2H), 2.08–2.02 (m, 1H), 1.66–1.56 (m, 1H); ^{13}C-NMR (151 MHz, D_2O): δ 171.6, 157.4, 138.1, 127.5, 123.9, 121.9, 108.7, 73.0, 56.1, 53.9 (t, *J* = 4.5 Hz), 29.7, 29.6, 28.9, 28.4; HPLC (220 nm, system A): t_R= 15.0 min, purity: 98%, (220 nm system B): t_R= 13.5 min, purity: 97%; HR-ESIMS: calcd 234.1852, found 234.1851 $[M]^+$.

5-Methoxy-*N,N*-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (57) [17]



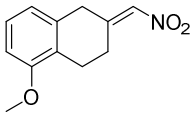
Compound **57** was prepared according to the protocol of compound **39** using a solution of 5-methoxy-2-tetralone (222 mg, 1.26 mmol) in dry THF (5 mL), dimethylamine (2 M in THF, 2.00 mL, 4.00 mmol), acetic acid (80.0 µL, 1.33 mmol) and sodium triacetoxyborohydride (600 mg, 2.83 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.01) afforded **57** (188 mg, 72%) as pale yellow oil. IR (NaCl): 2937, 2835, 1587, 1469, 1262, 1094, 767 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.12–7.05 (m, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 3.81 (s, 3H), 3.03–2.90 (m, 2H), 2.82–2.71 (m, 1H), 2.65–2.47 (m, 2H), 2.39 (s, 6H), 2.21–2.11 (m, 1H), 1.64–1.50 (m, 1H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 157.2, 136.2, 126.4, 124.7, 121.5, 107.3, 60.9, 55.3, 41.2, 31.7, 25.2, 23.0; HPLC (254 nm, system A): t_R= 12.0 min; ESI-MS: 206.2 $[M+H]^+$.

5-Methoxy-*N*,*N*,*N*-trimethyl-1,2,3,4-tetrahydronaphthalen-2-aminium iodide (13)



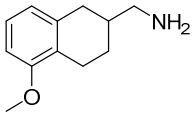
Compound **13** was prepared according to the protocol of compound **1**, using a solution of compound **57** (37.0 mg, 180 mmol) in dry $CHCl_3$ (2 mL) and methyl iodide (30.0 µL, 483 µmol). The compound was dissolved in $CHCl_3$ and precipitated with diethyl ether to afford **13** (38.3 mg, 61%) as pale yellow solid. Mp: 233–235 °C; IR (NaCl): 3424, 2971, 1589, 1470, 1259, 1066, 887, 779 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 7.29–7.21 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 3.76–3.66 (m, 1H), 3.37–3.30 (m, 1H), 3.17 (s, 9H), 3.15–3.08 (m, 2H), 2.63 (ddd, *J* = 17.6, 12.2, 5.6 Hz, 1H), 2.56–2.46 (m, 1H), 1.82 (qd, *J* = 12.2, 5.4 Hz, 1H); ^{13}C-NMR (91 MHz, D_2O): δ 157.2, 134.6, 128.1, 124.1, 122.5, 109.6, 71.8, 56.3, 51.4 (t, *J* = 4.6 Hz), 29.6, 23.4, 23.4. HPLC (254 nm, system A): t_R= 12.2 min, purity: 98%, (254 nm, system B): t_R= 11.7 min, purity: 99%; HR-ESIMS: calcd 220.1696, found 220.1699 $[M]^+$.

5-Methoxy-2-(nitromethylene)-1,2,3,4-tetrahydronaphthalene (58)



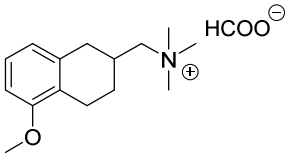
Compound **58** was synthesized according to the protocol of compound **55** using a solution 5-methoxy-2-tetralone (346 mg, 1.97 mmol) in nitromethane (5 mL), acetic acid (80.0 µL, 1.32 mmol) and ammonium acetate (140 mg, 1.82 mmol). Purification by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:1) afforded **58** (268 mg, 69%) as yellow oil. IR: (NaCl): 2938, 3838, 1670, 1553, 1471, 1368, 1267, 1092, 910, 775, 732, 650 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 8.2, 7.6 Hz, 1H), 6.83–6.80 (m, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.59–6.56 (m, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 2.92–2.87 (m, 2H), 2.44–2.39 (m, 2H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 156.2, 133.6, 131.8, 129.0, 127.0, 122.8, 119.8, 111.0, 100.0, 55.5, 24.9, 20.0; HPLC (254 nm system A): t_R= 19.8 min; ESI-MS: 173.3 $[M\text{-}NO_2]^+$.

(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)methanamine (59) [20]



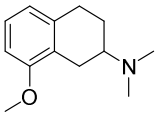
Compound **59** was synthesized according to the protocol of compound **56** using $LiAlH_4$ (4 M in THF, 700 µl, 2.80 mmol) in dry THF (4 mL) and a solution of compound **58** (98.2 mg, 448 µmol) in dry THF (1 mL). The reaction time was 3 h. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 30:2:0.03) afforded **59** (24.7 mg, 28%) as pale yellow oil. IR (NaCl): 3419, 2927, 2835, 1635, 1585, 1468, 1308, 1253, 1099, 765 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.10–7.05 (m, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.81 (s, 3H), 2.92–2.85 (m, 2H), 2.72 (d, *J* = 5.3 Hz, 2H), 2.53 (ddd, *J* = 17.6, 11.2, 6.2 Hz, 1H), 2.48–2.42 (m, 1H), 2.02 (ddt, *J* = 15.5, 5.6, 2.8 Hz, 1H), 1.79–1.71 (m, 1H), 1.35 (ddd, *J* = 24.0, 11.3, 5.7 Hz, 1H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 157.4, 137.7, 126.1, 125.8, 121.6, 107.1, 55.4, 47.9, 37.4, 34.0, 26.8, 22.9; HPLC (254 nm, system A): t_R= 14.3 min; ESI-MS: 192.2 $[M+H]^+$.

1-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N,N,N*-trimethylmethanaminium formate (14)



Compound **14** was synthesized according to the protocol of compound **1** using a solution of compound **59** (9.4 mg, 49.3 µmol) in dry DMF (2 mL), methyl iodide (30.0 µL, 483 µmol) and K_2CO_3 (27.6 mg, 200 µmol). Purification by preparative HPLC (system 2) afforded **14** (12.5 mg, 90%) as white solid. IR (NaCl): 2989, 2900, 1735, 1394, 1255, 1057, 892 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.49 (s, 1H), 7.23–7.19 (m, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 3.43 (dd, *J* = 13.6, 4.6 Hz, 1H), 3.37–3.32 (m, 1H), 3.19 (s, 9H), 3.05 (dd, *J* = 16.2, 4.1 Hz, 1H), 2.87–2.80 (m, 1H), 2.73–2.59 (m, 2H), 2.39–2.31 (m, 1H), 2.14–2.08 (m, 1H), 1.64 (dtd, *J* = 13.2, 10.5, 5.8 Hz, 1H); ^{13}C-NMR (151 MHz, D_2O): δ 157.4, 137.0, 127.4, 125.2, 122.4, 109.2, 72.5, 56.2, 54.1 (t, J = 4.5 Hz), 35.7, 29.4, 28.9, 22.4 (H**C**OO^- was not detected); HPLC (220 nm, system A): t_R= 13.8 min, purity: > 99%, (220 nm, system B): t_R= 13.4 min, purity: 97%; HR-ESIMS: calcd 234.1852, found 234.1855 $[M]^+$.

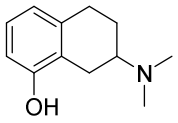
8-Methoxy-*N,N*-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (15) [16]



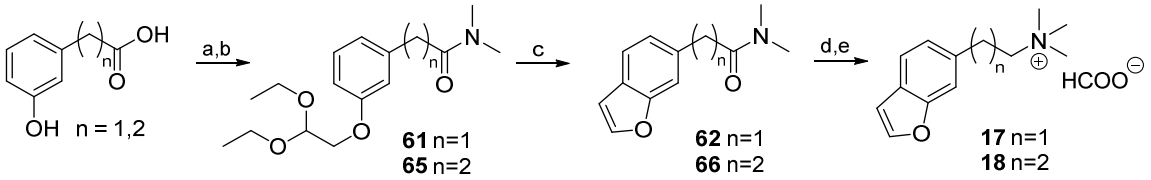
Compound **15** was prepared according to the protocol of compound **39** using a solution of 5-methoxy-2-tetralone (1.09 g, 6.17 mmol) in dry THF (20 mL), dimethylamine (2 M in THF, 11.0 mL, 22.0 mmol), acetic acid (380 µL, 6.70 mmol) and sodium triacetoxyborohydride (3.27 g, 15.4 mmol). Reaction time was 18 h at room temperature. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.01) to give **15** (1.09 g, 83%) as pale brown solid. Mp: 45–48.5 °C; IR (NaCl): 2931, 2771, 1587, 1469, 1332, 1096, 1036, 764 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.11–7.06 (m, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.02

(dd, *J* = 16.8, 4.5 Hz, 1H), 2.93–2.86 (m, 1H), 2.86–2.78 (m, 1H), 2.67–2.59 (m, 1H), 2.47 (dd, *J* = 16.8, 11.0 Hz, 1H), 2.42 (s, 6H), 2.16–2.08 (m, 1H), 1.60 (qd, *J* = 12.0, 5.2 Hz, 1H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 157.5, 137.5, 126.1, 124.2, 120.7, 106.9, 60.9, 55.3, 41.6, 29.4, 26.1, 25.3; HPLC (254 nm, system A): t_R= 11.8 min, purity: 98%, (254 nm, system B): t_R= 11.5 min, purity: 98%; ESI-MS: 206.3 $[M+H]^+$.

7-(Dimethylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (16) [18]



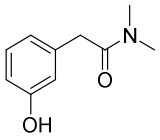
A suspension of compound **15** (295 mg, 1.44 mmol) in aqueous HBr (48%, 15 mL) was stirred under Ar-atmosphere and reflux conditions for 2 h and was then allowed to cool to room temperature. The aqueous phase was adjusted to pH 9 with saturated, aqueous $NaHCO_3$ solution before the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.01) to give **16** (295 mg, 82%) as brown solid. Mp: 158–161 °C; IR (NaCl): 3197, 2944, 1584, 1465, 1337, 1275, 1083, 1036, 881, 761 cm^{-1}; ^{1}H-NMR (360 MHz, DMSO): δ 9.16 (s, 1H), 6.92–6.81 (m, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 2.87–2.59 (m, 3H), 2.48–2.40 (m, 1H), 2.32 (dd, *J* = 16.5, 10.3 Hz, 1H), 2.25 (s, 6H), 2.03–1.88 (m, 1H), 1.44 (qd, *J* = 11.3, 5.4 Hz, 1H); ^{13}C-NMR (91 MHz, DMSO): δ 155.0, 137.2, 125.6, 122.3, 118.8, 111.4, 60.0, 41.4, 28.7, 25.4, 25.4; HPLC: (220 nm, system A): t_R= 10.4 min, purity: 97%, (220 nm, system B): t_R= 10.7 min, purity: 96%; ESI-MS: 192.3 $[M+H]^+$.



Scheme S6. Synthesis of compounds **17** and **18**. *Reagents and conditions*: a) $HN(CH_3)_2$, PyBOP, DIPEA, DMF, r.t., 18 h; b) 1. NaH, DMF, r.t., 1 h, 2. bromoacetaldehyde diethylacetal, DMF, r.t. to 40 °C, 16 h; c) 1. AcOH, 2. BF_3 etherate, CH_2Cl_2, r.t., 24 h; d) $LiAlH_4$, THF, r.t., 1 h; e) MeI, K_2CO_3, DMF, r.t., 16 h.

For the synthesis of the bicyclic benzofurans **17** and **18** (scheme 7), 3-hydroxy phenylacetic acid and 3-hydroxy phenylpropionic acid were converted to the *N,N*-dimethylamide analogs followd by alkylation of the phenol moiety with protected bromoacetaldehyde (**61** and **65**). Under acidic conditions the acetales were cleaved and BF_3 etherate catalyzed cyclization resulted in the benzofurans **62** and **66**. Reduction of the amides and methylation of the obtained tertiary amines resulted in the products **17** and **18**. For both derivatives (**62** and **66**) the cyclisation reaction led to two regioisomers. Whilst those of the propionic amide **56** could be separated by flash chromatography, the separation of the isomers of the acetamide derivative **62** was only successful using preparative HPLC.

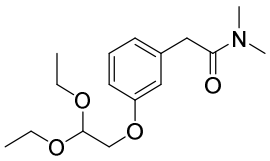
2-(3-Hydroxyphenyl)-*N,N*-dimethylacetamide (60) [21]



To a solution of 3-hydroxyphenyle acetic acid (498 mg, 3.29 mmol) and benzotriazol-1-yl-oxytripyrrolidinophosphonium-hexafluorophosphate (1.99 g, 3.83 mmol) in dry DMF (20 mL) was added diisopropyleethylamine (1.00 mL, 5.88 mmol) and the mixture was stirred at room temperature for 10 min. Subsequently, dimethylamine (2 M in THF, 4.00 mL, 8.00 mmol) was added and the reaction was stirred at room temperature for 18 h. After evaporation, the crude residue was dissolved in ethyl acetate and the organic layer was washed twice with saturated, aqueous $NaHCO_3$ solution, once with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 60:1) to give **60** (182 mg, 31%) as pale brown oil. IR: 3234, 2961, 1626, 1587, 1486, 1457, 1404, 1260, 1148, 845, 776, 693 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.19–7.12 (m, 1H), 7.10 (s,

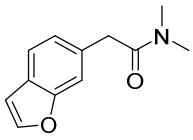
1H), 6.91–6.87 (m, 1H), 6.76–6.69 (m, 2H), 3.68 (s, 2H), 3.00 (s, 3H), 2.98 (s, 3H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 171.6, 157.0, 136.0, 129.8, 120.6, 115.3, 114.3, 41.0, 37.9, 35.9; HPLC (254 nm, system A): t_R= 14.6 min; ESI-MS: 180.2 $[M+H]^+$.

2-(3-(2,2-Diethoxyethoxy)phenyl)-*N,N*-dimethylacetamide (61)



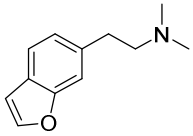
To a solution of compound **60** (221 mg, 1.24 mmol) in dry DMF (20 mL) was added NaH (60% suspension, 58.2 mg, 1.46 mmol) under Ar-atmosphere at 0 °C. The suspension was stirred at room temperature for 1 h. Subsequently, bromoacetaldehyde diethylacetal (300 µL, 1.98 µmol) was added dropwise and the reaction was stirred at 40 °C for 16 h. After cooling to room temperature, water was added and the mixture was stirred for additional 20 min. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 60:1) to give **61** (152 mg, 42%) as colorless oil. IR (NaCl): 3483, 2976, 2932, 1647, 1490, 1447, 1396, 1262, 1134, 1072, 775 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.24–7.19 (m, 1H), 6.86–6.82 (m, 2H), 6.82–6.78 (m, 1H), 4.82 (t, *J* = 5.2 Hz, 1H), 3.99 (d, *J* = 5.2 Hz, 2H), 3.76 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.68 (s, 2H), 3.63 (dq, *J* = 9.4, 7.0 Hz, 2H), 2.98 (s, 3H), 2.96 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.9, 158.9, 136.6, 129.6, 121.4, 115.2, 112.9, 100.5, 68.5, 62.6, 41.2, 37.8, 35.6, 15.3; HPLC (254 nm, system A): t_R= 19.0 min; ESI-MS: 318.4 $[M+H]^+$.

2-(Benzofuran-6-yl)-*N,N*-dimethylacetamide (62)



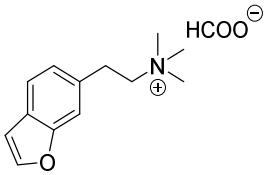
Compound **61** (150 mg, 507 µmol) was dissolved in acetic acid (5 mL) and the solvent was subsequently evaporated. The crude residue was dissolved in CH_2Cl_2 (10 mL) under Ar-atmosphere and BF_3 etherate (250 µL, 2.03 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. Subsequently, an aqueous NaOH solution (1 M) was added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) afforded **62** (16.0 mg, 15%) as pale yellow oil. Subsequently, seperation of the regioisomers was carried out by preparative HPLC (eluent: 35% CH_3CN in H_2O + 0.1% HCOOH, 20 min isocratic). IR (NaCl): 3478, 2986, 2091, 1629, 1431, 1392, 1269, 1244, 1136, 1043, 762 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 2.2 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.15 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.74 (dd, *J* = 2.2, 0.9 Hz, 1H), 3.83 (s, 2H), 3.02 (s, 3H), 2.98 (s, 3H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 171.1, 155.3, 145.0, 131.5, 126.2, 123.7, 121.1, 111.6, 106.4, 41.1, 37.8, 35.7; HPLC (254 nm, system A): t_R= 17.6 min; ESI-MS: 204.2 $[M+H]^+$.

2-(Benzofuran-6-yl)-*N*,*N*-dimethylethan-1-amine (63)



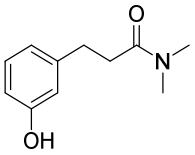
Compound **63** was synthesized according to the protocol of compound **41** using $LiAlH_4$ (4 M in THF, 15 µL, 60.0 µmol) in dry THF (1 mL) and a solution of compound **62** (3.0 mg, 15.0 µmol) in dry THF (1 mL). The reaction time was 1 h. Evaporation of the solvent afforded **63** (2.5 mg, 88%) as colorless oil. IR (NaCl): 3349, 2917, 2849, 1463, 1433, 1053, 910, 733, 647 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 7.7, 3.7 Hz, 1H), 7.35 (s, 1H), 7.09 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.72 (dd, *J* = 2.2, 0.9 Hz, 1H), 2.93–2.88 (m, 2H), 2.63–2.57 (m, 2H), 2.32 (s, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 155.3, 144.6, 135.8, 125.5, 123.7, 120.9, 111.3, 106.4, 59.6, 45.3, 30.4; HPLC (254 nm, system A): t_R= 11.8 min; ESI-MS: 190.3 $[M+H]^+$.

2-(Benzofuran-6-yl)-*N,N,N*-trimethylethan-1-aminium formate (17)



Compound **17** was synthesized according to the protocol of compound **1** using a solution of compound **63** (5.1 mg, 26.9 µmol) in dry DMF (2 mL) and methyl iodide (20.0 µL, 322 µmol). Purification by preparative HPLC (system 4) afforded **17** (3.0 mg, 46%) as white solid. IR (NaCl): 3439, 2972, 2814, 1685, 1584, 1437, 1368, 1206, 1181, 1130, 802, 724 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.46 (s, 1H), 7.77 (d, *J* = 2.2 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.24 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.90 (dd, *J* = 2.2, 0.9 Hz, 1H), 3.66–3.60 (m, 2H), 3.29 (dd, *J* = 10.3, 6.9 Hz, 2H), 3.20 (s, 9H); ^{13}C-NMR (151 MHz, D_2O): δ 171.7, 147.3, 146.7, 129.9, 124.5, 122.4, 117.3, 112.3, 107.1, 57.0, 53.7 (t, *J* = 4.5 Hz), 29.6; HPLC: (220 nm, system A): t_R= 12.7 min, purity: > 99%, (220 nm, system B): t_R= 12.6 min, purity: > 99%; HR-ESIMS: calcd 204.1383, found 204.1385 $[M]^+$.

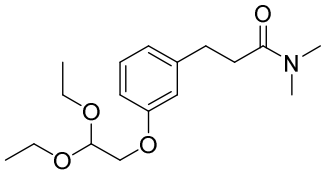
3-(3-Hydroxyphenyl)-*N,N*-dimethylpropanamide (64) [4]



Compound **64** was synthesized according to the protocol of compound **60** using a solution of 3-hydroxyphenyle propionic acid (500 mg, 3.01 mmol) and benzotriazol-1-yl-oxytripyrrolidinophosphonium-hexafluorophosphat (1.18 g, 3.48 mmol) in dry DMF (20 mL), diisopropylamine (1.00 mL, 5.88 mmol) and a dimethylamine (2 M in THF, 4.0 mL, 8.00 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 60:1) afforded **64** (575 mg, quant.) as colorless oil. IR (NaCl): 3242, 2938, 1623, 1489, 1456, 1404, 1261, 1157, 785, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$):

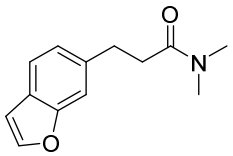
δ 7.17–7.11 (m, 1H), 6.81–6.77 (m, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.71 (dd, *J* = 8.1, 2.4 Hz, 1H), 2.96 (s, *J* = 6.5 Hz, 3H), 2.95–2.88 (m, 5H), 2.66–2.57 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 172.7, 156.5, 142.9, 129.6, 120.1, 115.6, 113.4, 37.4, 35.7, 35.1, 31.7; HPLC (254 nm, system A): t_R= 16.2 min; ESI-MS: 194.3 $[M+H]^+$.

3-(3-(2,2-Diethoxyethoxy)phenyl)-*N,N*-dimethylpropanamide (65)



Compound **65** was synthesized according to the protocol of compound **61** using a solution of compound **64** (383 mg, 1.98 mmol) in dry DMF (20 mL), NaH (60%, 161 mg, 4.03 mmol) and bromoacetaldehyde diethylacetale (500 µL, 3.30 mmol). The mixture was stirred at room temperature. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 60:1) afforded **65** (188 mg, 31%) as pale yellow oil. IR (NaCl): 2975, 2931, 1648, 1488, 1448, 1398, 1264, 1135, 1073, 784, 698 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.21–7.17 (m, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.81–6.78 (m, 1H), 6.76 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.83 (t, *J* = 5.2 Hz, 1H), 3.99 (d, *J* = 5.2 Hz, 2H), 3.76 (dq, *J* = 9.3, 7.1 Hz, 2H), 3.64 (dq, *J* = 9.4, 7.1 Hz, 2H), 2.97–2.91 (m, 8H), 2.62–2.57 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 172.1, 158.8, 143.1, 129.4, 121.1, 115.0, 112.1, 100.5, 68.5, 62.6, 37.2, 35.5, 35.2, 31.4; HPLC (254 nm, system A): t_R= 19.6 min; ESI-MS: 332.4 $[M+Na]^+$.

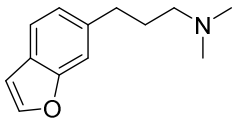
3-(Benzofuran-6-yl)-*N,N*-dimethylpropanamide (66)



Compound **66** was synthesized according to the protocol of compound **62** first using a solution of compound **65** (100 mg, 324 µmol) in acetic acid (3 mL). Subsequently, the

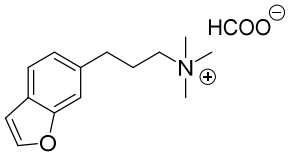
crude residue was dissolved in CH_2Cl_2 (5.0 mL) and BF_3 etherate (150 µL, 1.22 mmol) was added. Seperation of the regioisomers and purification by column chromatography on silica gel (*n*-hexane/ethyl acetate, 2:1) afforded **66** (9.3 mg, 13%) as colorless oil. IR (NaCl): 2926, 1641, 1489, 1398, 1261, 1144, 1026, 814 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 2.2 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.37 (s, 1H), 7.12 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.72 (dd, *J* = 2.1, 0.9 Hz, 1H), 3.11–3.06 (m, 2H), 2.96 (s, 3H), 2.93 (s, 3H), 2.70–2.64 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 172.3, 155.5, 144.8, 138.3, 125.7, 123.7, 121.1, 111.2, 106.5, 37.3, 35.8, 35.6, 31.7; HPLC (254 nm, system A): t_R= 18.8 min; ESI-MS: 218.2 $[M+H]^+$.

3-(Benzofuran-6-yl)-*N,N*-dimethylpropan-1-amine (67)

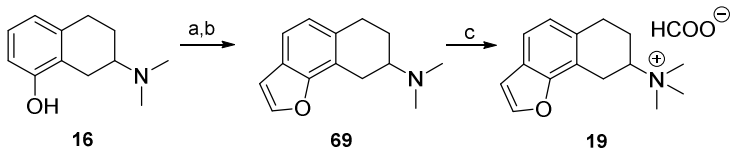


Compound **67** was synthesized according to the protocol of compound **63** using a $LiAlH_4$ (4 M in THF, 60.0 µL, 120.0 µmol) in dry THF (1 mL) and a solution of compound **66** (6.0 mg, 27.6 µmol) in dry THF (1 mL). The reaction time was 1 h. Evaporation of the solvent afforded **67** (3.3 mg, 54%) as colorless oil. IR (NaCl): 3434, 2155, 2062, 1652, 1635, 1146, 1092 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.60 (d, *J* = 2.2 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.32 (s, 1H), 7.07 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.74 (dd, *J* = 2.2, 0.9 Hz, 1H), 2.99–2.93 (m, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.76 (s, 6H), 2.28–2.21 (m, 2H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 155.3, 145.1, 135.8, 126.1, 123.2, 121.4, 111.0, 106.4, 57.4, 43.0, 32.8, 26.0; HPLC (254 nm, system A): t_R= 14.2 min; ESI-MS: 204.2 $[M+H]^+$.

3-(Benzofuran-6-yl)-*N,N,N*-trimethylpropan-1-aminium formate (18)



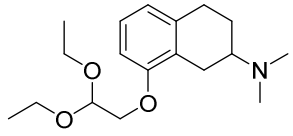
Compound **18** was synthesized according to the protocol of compound **1** using a solution of compound **67** (1.5 mg, 7.39 µmol) in dry DMF (2 mL) and methyl iodide (10.0 µL, 161 µmol). Purification by preparative HPLC (system 2) afforded **18** (2.0 mg, quant.) as white solid. IR (NaCl): 2937, 2809, 1685, 1584, 1560, 1369, 1205, 1181, 1131 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 7.75 (d, *J* = 2.2 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.49 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 1.3 Hz, 1H), 3.35–3.27 (m, 2H), 3.07 (s, 9H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.20–2.15 (m, 2H) ($HCOO^-$ was not detected); ^{13}C-NMR (151 MHz, D_2O): δ 151.0, 146.3, 137.5, 124.2, 122.1, 121.9, 111.7, 107.1, 66.6, 53.5, 32.2, 24.9 ($HCOO^-$ was not detected); HPLC (254 nm, system A): t_R= 14.1 min, purity: 96%, (254 nm, system B): t_R= 13.2 min, purity: 97%; HR-ESIMS: calcd 218.1539, found 218.1539 $[M]^+$.



Scheme S7. Synthesis of compound **19**. *Reagents and conditions*: a) 1. NaH, DMF, r.t., 1 h, 2. bromoacetaldehyde diethylacetal, DMF, 70 °C, 4 h; b) 1. AcOH, 2. BF_3 etherate, CH_2Cl_2, r.t., 24 h; c) MeI, $CHCl_3$, r.t., 16 h.

For the synthesis [22] of the tricyclic benzofuran **19** (scheme 8), compound **16** was alkylated with protected bromoacetaldehyde and cyclized analog to compounds **17** and **18**. Finally, the quarternary ammonium salt **10** was obtained by methylation of the tertiary amine **69**.

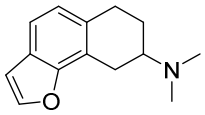
8-(2,2-Diethoxyethoxy)-*N,N*-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (68)



Compound **68** was synthesized according to the protocol of compound **61** using a solution of compound **16** (70.0 mg, 366 µmol l) in dry DMF (4 mL), NaH (60%,

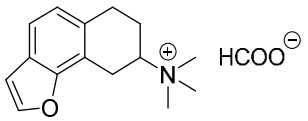
41.2 mg, 1.70 mmol) and bromoacetaldehyde diethylacetale (80.0 µL, 532 µmol). The mixture was stirred at at 70 °C for 4 h. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) afforded **68** (76.6 mg, 69%) as pale brown semi solid substance. IR (NaCl): 2975, 2931, 2771, 1587, 1456, 1374, 1346, 1257, 1135, 1101, 1077, 763 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.08–7.03 (m, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 4.85 (t, *J* = 5.2 Hz, 1H), 4.03–3.96 (m, 2H), 3.82–3.75 (m, 2H), 3.70–3.62 (m, 2H), 3.07–3.02 (m, 1H), 2.89 (ddd, *J* = 8.1, 5.1, 3.4 Hz, 1H), 2.81 (ddd, *J* = 16.8, 12.1, 5.0 Hz, 1H), 2.64–2.56 (m, 1H), 2.53–2.45 (m, 1H), 2.40 (s, 6H), 2.14–2.08 (m, 1H), 1.58 (qd, *J* = 12.0, 5.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 156.5, 137.7, 126.1, 124.7, 121.1, 108.1, 100.9, 69.0, 62.9, 62.9, 60.9, 41.7, 29.4, 25.9, 25.7, 15.4, 15.4; HPLC (220 nm, system A): t_R= 15.3 min; ESI-MS: 308.5 $[M+H]^+$.

_N,N_-Dimethyl-6,7,8,9-tetrahydronaphtho[1,2-_b_]furan-8-amine (69)



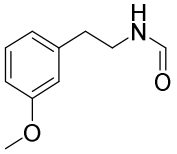
Compound **69** was synthesized according to the protocol of compound **62** first using a solution of compound **68** (60.0 mg, 195 µmol) in acetic acid (2 mL). Subsequently, the crude residue was dissolved in CH_2Cl_2 (4.0 mL) and BF_3 etherate (100 µL, 810 µmol) was added. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.01) afforded **69** (15.4 mg, 36%) as pale brown oil. IR (NaCl): 2928, 2772, 1494, 1456, 1321, 1263, 1151, 1129, 1026, 878, 815, 798, 734 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.50 (d, *J* = 2.2 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 3.30–3.20 (m, 1H), 3.02–2.85 (m, 2H), 2.85–2.73 (m, 1H), 2.67 (tdd, *J* = 10.8, 4.7, 2.6 Hz, 1H), 2.39 (s, 6H), 2.19–2.07 (m, 1H), 1.64 (qd, *J* = 11.4, 5.5 Hz, 1H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 152.8, 143.1, 131.5, 123.4, 122.5, 118.6, 117.3, 105.7, 59.5, 40.7, 28.1, 25.6, 24.1; HPLC (254 nm, system A): t_R= 14.2 min; APCI-MS: 216.2 $[M+H]^+$.

***N,N,N*-Trimethyl-6,7,8,9-tetrahydronaphtho[1,2-b]furan-8-aminium formate (19)**



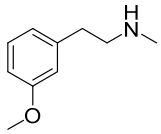
Compound **19** was synthesized according to the protocol of compound **1** using a solution of compound **69** (7.0 mg, 33.0 µmol) in dry $CHCl_3$ (2 mL) and methyl iodide (10.0 µL, 161 µmol). Purification by preparative HPLC (system 3) afforded **19** (7.0 mg, 77%) as white solid. IR (NaCl): 2989, 1590, 1490, 1394, 1049, 879, 669 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 7.77 (d, *J* = 2.1 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 3.87–3.80 (m, 1H), 3.66 (ddd, *J* = 15.4, 5.5, 2.3 Hz, 1H), 3.23 (s, 9H) 3.22–3.16 (m, 2H), 3.08–3.01 (m, 1H), 2.57–2.52 (m, 1H), 1.95 (qd, *J* = 12.4, 5.1 Hz, 1H) ($HCOO^-$ was not detected); ^{13}C-NMR (151 MHz, D_2O): δ 187.1, 153.6, 146.0, 131.9, 125.5, 123.9, 120.2, 117.0, 107.4, 71.8, 51.5 (t, *J* = 3.0 Hz), 28.8, 24.0, 23.8; HPLC (254 nm, system A): t_R= 13.9 min, purity: 98%, (254 nm, system B): t_R= 13.2 min, purity: 98%; HR-ESIMS: calcd 230.1539, found 230.1543 $[M]^+$.

***N*-(3-Methoxyphenethyl)formamide (70)** [23]



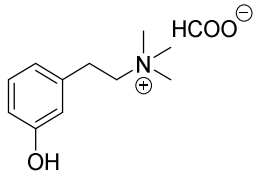
A solution of 2-(3-methoxyphenyl)ethylamine (63.2 mg, 418 µmol) in formic acid (1 mL) was stirred under reflux conditions for 24 h. After cooling to room temperature, water was added and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). Evaporation afforded **70** (17.1 mg, 23%) as colorless oil. IR (NaCl): 3286, 3051, 2940, 1665, 1602, 1585, 1489, 1456, 1260, 1153, 1039, 783 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.26–7.21 (m, 1H), 6.80–6.77 (m, 2H), 6.76–6.73 (m, 1H), 5.50 (s, 1H), 3.80 (d, *J* = 1.6 Hz, 3H), 3.63–3.54 (m, 2H), 2.86–2.81 (m, 2H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 161.2, 160.1, 140.2, 129.9, 121.2, 114.7, 112.1, 55.4, 39.2, 35.7; HPLC (254 nm, system A): t_R= 16.3 min; ESI-MS: 180.4 $[M+H]^+$.

2-(3-Methoxyphenyl)-*N*-methylethan-1-amine (20) [24]



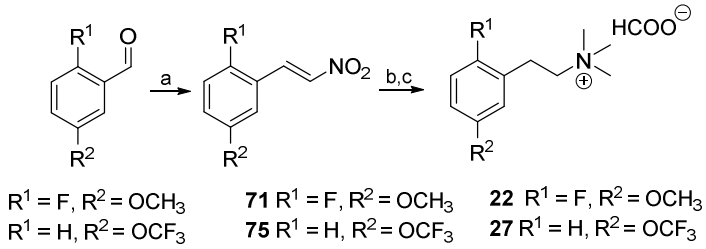
Compound **20** was synthesized according to the protocol of compound **41** using $LiAlH_4$ (4 M in THF, 60.0 µL, 240 µmol) in dry THF (2 mL) and a solution of compound **70** (10.0 mg, 55.8 µmol) in dry THF (1 mL). The reaction time was 1 h. After evaporation, purification by preparative HPLC (system 4) afforded **20** (4.1 mg, 35%) as white solid (formate salt). IR (NaCl): 2924, 2853, 1597, 1356, 1210, 1052, 974, 802, 772 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.46 (s, 1H), 7.39–7.34 (m, 1H), 6.98–6.91 (m, 3H), 3.84 (s, 3H), 3.34–3.29 (m, 2H), 3.04–2.98 (m, 2H), 2.70 (s, 3H); ^{13}C-NMR (151 MHz, D_2O): δ 171.6, 164.3, 131.0, 122.2, 115.2, 103.5, 56.0, 50.6, 33.5, 32.3 ($HCOO^-$ was not detected); HPLC (220 nm, system A): t_R= 8.9 min, purity > 99%, (220 nm, system B): t_R= 11.2 min, purity > 99%; ESI-MS: 166.3 $[M+H]^+$.

2-(3-Hydroxyphenyl)-*N,N,N*-trimethylethan-1-aminium formate (21) [2]



Compound **21** was synthesized according to the protocol of compound **16** using a solution of compound **3** (18.4 mg, 76.9 µmol) in aqueous HBr (48%, 2 mL). After evaporation of the solvent by lyophilisation, purification of the crude residue by preparative HPLC (system 5) afforded **21** (8.3 mg, 48%) as white solid. IR (NaCl): 3167, 29258, 1613, 1588, 1483, 1353, 1281, 1160, 772, 699 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 7.31–7.27 (m, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.86–6.82 (m, 2H), 3.59–3.53 (m, 2H), 3.18 (s, 9H), 3.13–3.08 (m, 2H); ^{13}C-NMR (151 MHz, D_2O): δ 182.4, 156.5, 138.3, 131.1, 121.6, 116.4, 114.9, 67.6, 53.7 (t, *J* = 4.5 Hz), 29.4; HPLC (220 nm, system A): t_R=

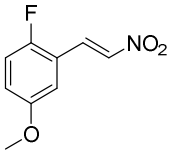
4.9 min, purity: > 99%, (220 nm, system B): t_R= 5.9 min, purity: 99%; HR-ESIMS: calcd 180.13829, found 180.13840 $[M]^+$.



Scheme S8. Synthesis of the target compounds **22** and **27**. *Reagents and conditions*: a) AcOH, NH_4OAc, CH_3NO_2, reflux, 1.5 - 3 h; b) $LiAlH_4$, THF, r.t., 4 - 5 h; c) MeI, K_2CO_3, $CHCl_3$, r.t., 16 h.

A fluoro substituent in para position to the methoxy group (**22**) as well as a trifluoromethoxy substituent at the aromatic moiety (**27**) could be incorporated starting with the corresponding benzaldehydes. A Henry reaction gave the nitroolefines **71**[25] and **75**[26], which were treated with $LiAlH_4$ to give the primary amines. Methylation of these amines resulted in the quarternary ammonium derivatives **22** and **27**.

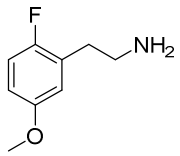
1-Fluoro-4-methoxy-2-(2-nitrovinyl)benzene (71) [25]



Compound **71** was synthesized according to the protocol of compound **55** using a solution of 2-fluoro-5-methoxybenzaldehyde (800 mg, 3.19 mmol), acetic acid (320 µL, 5.33 mmol) and ammonium acetate (506 mg, 6.56 mmol) in nitromethane (10 mL). The reaction time was 1.5 h. Purification by column chromatography on silica gel (*n*-hexane/ethyl acetate, 9:1) gave **71** (266 mg, 26%) as yellow solid. Mp: 81.7–86 °C; IR (NaCl): 3139, 1631, 1590, 1502, 1348, 1285, 1225, 1040, 970, 845, 762, 715 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 8.01 (d, *J* = 13.8 Hz, 1H), 7.70 (d, *J* = 13.8 Hz, 1H), 7.14–7.06 (m, 1H), 7.03–6.98 (m, 1H), 6.98–6.91 (m, 1H), 3.83 (s, 3H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 156.5 (d, *J* = 249 Hz), 156.2 (d, *J* = 2.3 Hz), 139.7 (d, *J* = 11.4Hz), 132.7 (d, *J*

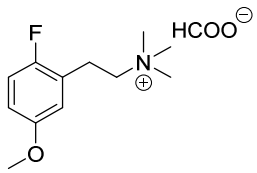
= 0.9 Hz), 119.4 (d, *J* = 8.9 Hz), 118.8 (d, *J* = 13.9 Hz), 117.4 (d, *J* = 24.0 Hz), 115.0 (d, *J* = 2.7 Hz), 56.1; HPLC (254 nm, system A): t_R= 24.1 min; ESI-MS: 152.3 $[(M+H)-NO_2]^+$.

2-(2-Fluoro-5-methoxyphenyl)ethan-1-amine (72) [25]



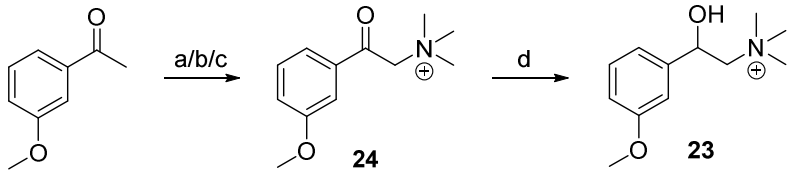
Compound **72** was synthesized according to the protocol of compound **56** using $LiAlH_4$ (1 M in THF, 3.00 mL, 3.00 mmol) in dry THF (10 mL) and a solution of compound **71** (104 mg, 528 µmol) in dry THF (2 mL). The reaction time was 5 h. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 30:1:0.03) afforded **72** (45.4 mg, 50%) as pale, yellow oil. IR (NaCl): 3364, 3292, 2939, 1594, 1500, 1279, 1209, 1152, 1038, 810, 726 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.98–6.93 (m, 1H), 6.74 (dd, *J* = 5.9, 3.1 Hz, 1H), 6.73–6.68 (m, 1H), 3.78 (s, 3H), 3.71–3.68 (m, 1H), 3.12–2.94 (m, 2H), 2.79 (t, *J* = 6.3 Hz, 2H), 1.72–1.66 (m, 1H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 155.8 (d, *J* = 237 Hz), 155.7 (d, *J* = 1.5 Hz), 127.0 (d, *J* = 18.2 Hz), 116.3 (d, *J* = 4.9 Hz), 115.8 (d, *J* = 24.0 Hz), 112.7 (d, *J* = 8.2 Hz), 55.8, 42.0, 33.0; HPLC (254 nm, system A): t_R= 5.1 min; ESI-MS: 170.3 $[M+H]^+$.

2-(2-Fluoro-5-methoxyphenyl)-*N*,*N*,*N*-trimethylethan-1-aminium formate (22)



Compound **22** was synthesized according to the protocol of compound **1** using a solution of compound **72** (10.0 mg, 59.1 µmol) in dry $CHCl_3$ (2 mL), methyl iodide (20.0 µL, 322 µmol) and K_2CO_3 (26.1 mg, 191 µmol). Purification by preparative HPLC (system 1) afforded **22** (8.4 mg, 67%) as white solid. IR (NaCl): 3413, 2957, 2815, 1689, 1613,

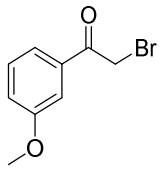
1505, 1352, 1213, 1121, 1043, 819, 718 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.50 (s, 1H), 7.19–7.12 (m, 1H), 6.98–6.93 (m, 2H), 3.84 (s, 3H), 3.61–3.56 (m, 2H), 3.27–3.17 (m, 11H); ^{13}C-NMR (91 MHz, D_2O): δ 155.8 (d, *J* = 2.3 Hz), 154.4 (d, *J* = 243 Hz), 127.1 (d, *J* = 17.8 Hz), 117.0 (d, *J* = 20.0 Hz), 116.9 (d, *J* = 2.6 Hz), 115.0 (d, *J* = 9.0 Hz), 66.1, 56.6, 53.6 (t, *J* = 4.1 Hz), 23.6 ($HCOO^-$ was not detected); HPLC (220 nm, system A): t_R= 12.2 min, purity: > 99%, (220 nm, system B): t_R= 12.1 min, purity: > 99%; HR-ESIMS: calcd 212.14452, found 212.14480 $[M]^+$.



Scheme S9. Synthesis of the target compounds **23** and **24**. *Reagents and conditions*: a) Br_2, $CHCl_3$, r.t., 24 h; b) $HN(CH_3)_2$, $CHCl_3$, r.t., 8 h; c) MeI, DMF, r.t., 16 h; d) PS-BH_3, THF/MeOH, r.t., 6 h.

Bromination of 3-methoxy acetophenone, followed by a nucleophilic substitution with *N,N*-dimethylamine and methylation of the tertiary amine resulted in the ketone **24**. Reduction of the carbonyl group with polymer supported BH_3 gave the desired benzylic alcohol **23**.

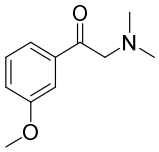
2-Bromo-1-(3-methoxyphenyl)ethan-1-one (73) [27]



To a solution of 3-methoxy acetophenone (120 mg, 800 µmol) in $CHCl_3$ (4 mL) was added Br_2 (15.0 µL, 293 µmol) dropwise. The reaction was stirred at room temperature for 24 h and additional Br_2 (15.0 µL, 293 µmol each time) was added after 2 h, 5 h and 11 h. Subsequently, saturated, aqueous $Na_2S_2O_3$ solution was added and the mixture was

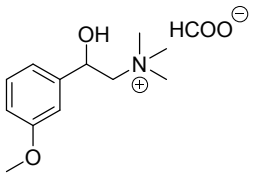
stirred for 15 min. CH_2Cl_2 was added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers where washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/*n*-hexane, 2:1) to give **73** (181 mg, quant.) as white solid. Mp: 62–64 °C; IR (NaCl): 2943, 1683, 1597, 1488, 1433, 1281, 1163, 1023, 861, 788, 682 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.56 (ddd, *J* = 7.7, 1.5, 0.9 Hz, 1H), 7.51 (dd, *J* = 2.5, 1.7 Hz, 1H), 7.42–7.38 (m, 1H), 7.16 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 1H), 4.45 (s, 2H), 3.87 (s, 3H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 191.1, 160.0, 135.3, 129.8, 121.5, 120.5, 113.2, 55.5, 30.9; HPLC (254 nm, system A): t_R= 16.0 min; ESI-MS: 231.2 $[M+H]^+$.

2-(Dimethylamino)-1-(3-methoxyphenyl)ethan-1-one (74) [28]



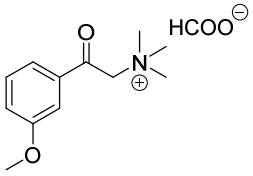
To a solution of compound **73** (102 mg, 445 µmol) in dry $CHCl_3$ (5 mL) was added dimethylamine (2 M in THF, 2.20 mL, 4.40 mmol) dropwise. The reaction was stirred at room temperature for 8 h. After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 1:1:0.015) to give **64** (37.8 mg, 43%) as orange oil. IR (NaCl): 2941, 2836, 1676, 1584, 1466, 1263, 1043, 763 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.58–7.54 (m, 1H), 7.52 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.39–7.33 (m, 1H), 7.11 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 2H), 2.44 (s, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 171.0, 159.7, 133.6, 129.3, 122.4, 119.2, 114.3, 55.6, 45.1, 34.9; HPLC (254 nm, system A): t_R= 10.7 min; ESI-MS: 194.4 $[M+H]^+$.

2-Hydroxy-2-(3-methoxyphenyl)-*N,N,N*-trimethylethan-1-aminium formate (23)



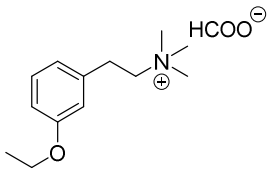
A suspension of BH_3 resin (20-50 mesh, 2.0 mmol/g, 200 mg, 400 µmol) in dry THF (2 mL) and dry MeOH (2 mL) was stirred under Ar-atmosphere at room temperature for 30 min. Subsequently, a solution of compound **24** (25.0 mg, 98.8 µmol) in dry MeOH (1 mL) was added droppwise and the reaction was stirred at room temperature for 6 h. The resin was filtered off. After evaporation, the crude residue was purified by preparative HPLC (system 6) to give **23** (20.4 mg, 80%) as colorless semi solid substance. IR (NaCl): 3365, 3220, 2917, 2844, 1652, 1601, 1488, 1436, 1325, 1281, 1035, 961, 777, 699 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO): δ 8.83 (s, 1H), 7.34–7.27 (m, 1H), 7.04–6.97 (m, 2H), 6.88 (d, *J* = 7.5 Hz, 1H), 5.22 (d, *J* = 9.2 Hz, 1H), 3.77 (s, 3H), 3.61–3.47 (m, 1H), 3.47–3.38 (m, 1H), 3.22 (s, 9H); ^{13}C-NMR (151 MHz, DMSO): δ 172.7, 159.3, 143.4, 129.6, 118.2, 113.3, 111.9, 67.5, 60.7, 55.1, 53.5; HPLC (220 nm, system A): t_R= 8.5 min, purity: 95%, (220 nm, system B): t_R= 10.2 min, purity: > 99%; HR-ESIMS: calcd 210.14886, found 210.14890 $[M]^+$.

2-(3-Methoxyphenyl)-*N*,*N*,*N*-trimethyl-2-oxoethan-1-aminium formate (24)



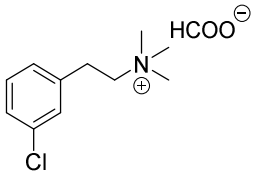
Compound **24** was synthesized according to the protocol of compound **1** using a solution of compound **74** (125 mg, 648 µmol) in dry DMF (2 mL) and methyl iodide (70.0 µL, 1.13 mmol). Purification by preparative HPLC (system 4) afforded **24** (45.5 mg, 28%) as white solid. IR (NaCl): 3464, 2917, 1696, 1581, 1457, 1431, 1268, 1043, 920, 859, 771, 682 cm^{-1}; ^{1}H-NMR (600 MHz, DMSO): δ 8.58 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.56–7.51 (m, 1H), 7.49 (s, 1H), 7.33 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.37 (s, 2H), 3.85 (s, 3H), 3.32 (s, 9H); ^{13}C-NMR (91 MHz, DMSO): δ 191.1, 167.0, 159.4, 135.6, 130.2, 120.5, 120.3, 112.6, 67.2, 55.5, 53.4; HPLC (220 nm, system A): t_R= 11.7 min, purity: > 99%; (220 nm, system B): t_R= 11.7 min; purity: > 99%; HR-ESIMS: calcd 208.1332, found 208.1331 $[M]^+$.

2-(3-Ethoxyphenyl)-*N,N,N*-trimethylethan-1-aminium formate (25) [3]



Compound **25** was synthesized according to the protocol of compound **1** using a solution of compound **21** (4.1 mg, 18.2 µmol) in dry DMF (2 mL), ethyliodide (20.0 µL, 250 µmol) and K_2CO_3 (7.6 mg, 55.5 µmol). After stirring at room temperature for 16 h, additional ethyliodide (10.0 µL, 125 µmol) and K_2CO_3 (10.0 mg, 73.0 µmol) were added and the reaction was stirred at room temperature for additional 24 h. Purification by preparative HPLC (system 4) afforded **25** (3.2 mg, 69%) as white solid. IR (NaCl): 3446, 2934, 1599, 1475, 1394, 1257, 1172, 1047, 944, 766, 698 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.45 (bs, 1H), 7.39–7.33 (m, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.96–6.93 (m, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.62–3.53 (m, 2H), 3.18 (s, 9H), 3.17–3.12 (m, 2H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (151 MHz, D_2O): δ 180.2, 159.1, 138.2, 131.0, 122.4, 116.0, 114.2, 67.6, 65.1, 53.7 (t, J = 4.5 Hz), 29.5, 14.6; HPLC (220 nm, system A): t_R= 12.6 min, purity: 98%, (220 nm, system B): t_R= 12.4 min, purity: 98%, HR-ESIMS: calcd 208.16959, found 208.16975 $[M]^+$.

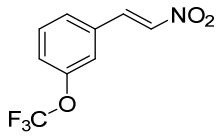
2-(3-Chlorophenyl)-*N,N,N*-trimethylethan-1-aminium formate (26) [29]



Compound **26** was synthesized according to the protocol of compound **1** using a solution of 2-(3-chlorophenyl)ethylamine (20.0 µL, 144 µmol) in dry DMF (2 mL), methyl iodide (80.0 µL, 1.28 mmol) and K_2CO_3 (56.5 mg, 412 µmol). Purification by preparative HPLC (system 1) afforded **26** (24.6 mg, 72%) as white semi solid substance. IR (NaCl): 3392, 3015 2829, 1597, 1480, 1256, 1081, 973, 921, 772, 695 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.59 (s, 1H), 7.40–7.34 (m, 3H), 7.28–7.24 (m, *J* = 6.4, 2.0 Hz, 1H), 3.60–3.53

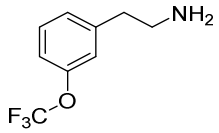
(m, 2H), 3.19 (s, 9H), 3.18–3.11 (m, 2H); ^{13}C-NMR (91 MHz, D_2O): δ 138.3, 134.5, 131.0, 129.3, 127.9, 127.8, 67.2 (t, J = 2.7 Hz), 53.6 (t, J = 3.6 Hz), 29.0 ($HCOO^-$ was not detected); HPLC (220 nm, system A): t_R= 11.1 min, purity: 99%, (220 nm, system B): t_R= 12.4 min, purity > 99%; HR-ESIMS: calcd 198.10440, found 198.10496 $[M]^+$.

1-(2-Nitrovinyl)-3-(trifluoromethoxy)benzene (75) [26]



Compound **75** was synthesized according to the protocol of compound **55** using a solution of 3-(trifluoromethoxy)-benzaldehyde (80.0 mg, 560 µmol), acetic acid (40.0 µL, 700 µmol) and ammonium acetate (50.7 mg, 658 µmol) in nitromethane (3 mL). The reaction time was 3 h. Purification by column chromatography on silica gel (*n*-hexane/ethyl acetate, 9:1) gave **75** (125 mg, 96%) as yellow oil. IR (NaCl): 3113, 1642, 1584, 1524, 1349, 1257, 1213, 1163, 964, 788, 699 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.98 (d, *J* = 13.7 Hz, 1H), 7.58 (d, *J* = 13.7 Hz, 1H), 7.54–7.46 (m, 2H), 7.42–7.32 (m, 2H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 150.0 (q, J = 1.8 Hz), 138.6, 137.4, 132.3, 131.1, 127.5, 124.3, 121.2, 120.5 (q, *J* = 259 Hz); HPLC (254 nm, system A): t_R= 20.5 min; ESI-MS: 234.4 $[M+H]^+$.

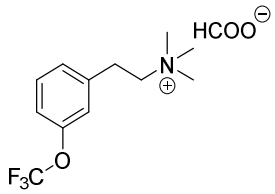
2-(3-(Trifluoromethoxy)phenyl)ethan-1-amine (76) [26]



Compound **76** was synthesized according to the protocol of compound **56** using $LiAlH_4$ (1 M in THF, 2.50 mL, 2.50 mmol) in dry THF (10 mL) and a solution of compound **75** (105 mg, 451 µmol) in dry THF (2 mL). The reaction time was 4 h. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 30:1:0.03) afforded **76** (38.8 mg, 42%) as pale, yellow oil. IR (NaCl): 3358, 2934, 1589, 1489, 1262, 1217,

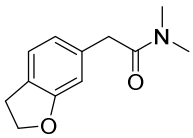
1163, 795, 701 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.35–7.29 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.11–7.04 (m, 2H), 3.05–2.96 (m, 2H), 2.85–2.76 (m, 2H), 2.00 (s, 2H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 149.6 (q, *J* = 1.5 Hz), 142.0, 129.9, 127.4, 121.4, 120.6 (q, *J* = 266 Hz), 118.9, 43.2, 39.3; HPLC (254 nm, system A): t_R= 15.5 min; ESI-MS: 206.3 $[M+H]^+$.

_N,N,N_-Trimethyl-2-(3-(trifluoromethoxy)phenyl)ethan-1-aminium formate (27)



Compound **27** was synthesized according to the protocol of compound **1** using a solution of compound **76** (22.0 mg, 107 µmol) in dry DMF (2 mL), methyl iodide (80.0 µL, 1.29 mmol) and K_2CO_3 (47.1 mg, 343 µmol). Purification by preparative HPLC (system 3) afforded **27** (23.6 mg, 73%) as white solid. IR (NaCl): 3392, 3012, 2829, 1615, 1489, 1356, 1249, 1217, 1167, 773 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.47 (s, 1H), 7.50–7.45 (m, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.31–7.26 (m, 2H), 3.63–3.56 (m, 2H), 3.24–3.16 (m, 11H); ^{13}C-NMR (91 MHz, D_2O): δ 171.5, 149.8 (q, J = 1.8 Hz), 138.6, 131.2, 128.3, 122.1, 120.9 (q, 258 Hz), 120.6, 67.3 (t, J = 2.7 Hz), 53.7 (t, J = 3.6 Hz), 29.2; HPLC (254 nm, system A): t_R= 14.3 min, purity: 98%, (254 nm, system B): t_R= 13.3 min, purity: 97%; HR-ESIMS: calcd 248.12568, found 248.12638 $[M]^+$.

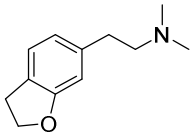
2-(2,3-Dihydrobenzofuran-6-yl)-_N,N_-dimethylacetamide (77) [30]



Compound **77** was synthesized according to the protocol of compound **64** using a solution of 2-(2,3-dihydrobenzofuran-6-yl) acetic acid (50.0 mg, 281 µmol) and [O-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium-hexafluorophosphate] (120 mg,

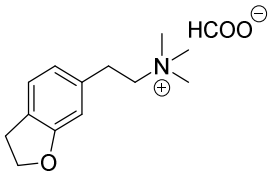
316 µmol) in dry DMF (3 mL), diisopropylamine (90.0 µL, 526 µmol) and dimethylamine (2 M in THF, 1.50 mL, 3.00 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH, 60:1) afforded **77** (40.5 mg, 70%) as colorless oil. IR (NaCl): 2925, 2855, 1643, 1497, 1434, 1395, 1244, 1134, 990, 791 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.12 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.69 (s, 1H), 4.55 (t, *J* = 8.7 Hz, 2H), 3.66 (s, 2H), 3.17 (t, *J* = 8.7 Hz, 2H), 2.98 (s, 3H), 2.95 (s 3H); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 171.2, 160.7, 135.3, 125.6, 125.0, 120.9, 109.9, 71.5, 41.2, 37.9, 35.8, 29.6; HPLC (254 nm, system A): t_R= 13.0 min; ESI-MS: 228.4 $[M+Na]^+$.

2-(2,3-Dihydrobenzofuran-6-yl)-*N*,*N*-dimethylethan-1-amine (78)



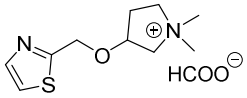
Compound **78** was synthesized according to the protocol of compound **41** using $LiAlH_4$ (1 M in THF, 280 µL, 280 µmol) in dry THF (4 mL) and a solution of compound **77** (8.0 mg, 39.0 µmol) in dry THF (1 mL). The reaction time was 1 h. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 30:1:0.03) afforded **78** (4.0 mg, 54%) as pale yellow oil. IR (NaCl): 3408, 2943, 2858, 2779, 1624, 1591, 1498, 1433, 1427, 1101, 986, 808, 764 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.5 Hz, 1H), 6.69 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.64 (s, 1H), 4.55 (t, *J* = 8.7 Hz, 2H), 3.16 (t, *J* = 8.6 Hz, 2H), 2.81–2.75 (m, 2H), 2.66–2.58 (m, 2H), 2.38 (s, 6H); ^{13}C-NMR (91 MHz, $CDCl_3$): δ 160.5, 140.2, 124.9, 124.8, 120.8, 109.7, 71.4, 61.5, 45.3, 34.0, 29.6; HPLC (254 nm, system A): t_R= 11.5 min; ESI-MS: 192.0 $[M+H]^+$.

2-(2,3-Dihydrobenzofuran-6-yl)-*N*,*N*,*N*-trimethylethan-1-aminium formate (28)



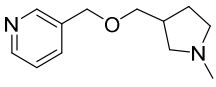
Compound **28** was synthesized according to the protocol of compound **1** using a solution of compound **78** (4.0 mg, 20.9 µmol) in dry DMF (2 mL) and methyl iodide (10.0 µL, 161 µmol). Purification by preparative HPLC (system 2) afforded **28** (3.0 mg, 57%) as white solid. IR (NaCl): 3020, 2982, 2772, 1663, 1460, 1435, 1246, 1017, 985 cm^{-1}; ^{1}H-NMR (600 MHz, D_2O): δ 8.47 (s, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.79 (s, 1H), 4.60 (t, *J* = 8.7 Hz, 2H), 3.60–3.51 (m, 2H), 3.24–3.19 (m, 2H), 3.17 (s, 9H), 3.13–3.08 (m, 2H); ^{13}C-NMR (151 MHz, D_2O): δ 171.6, 160.0, 146.0, 127.5, 126.3, 122.2, 110.2, 72.6, 67.7, 53.7 (t, *J* = 4.5 Hz), 29.4, 29.3; HPLC (220 nm, system A): t_R= 11.3 min, purity: 95%, (220 nm, system B): t_R= 11.7 min, purity: > 99%; HR-ESIMS: calcd 206.15394, found 206.15406 $[M]^+$.

1,1-Dimethyl-3-(thiazol-2-ylmethoxy)pyrrolidin-1-ium 29a



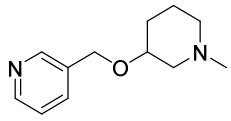
Compound **29a** was synthesized according to the protocol of compound **1** using a solution of 2-((pyrrolidin-3-yloxy)methyl)thiazole (7.00 mg, 38 µmol) in dry DMF (1 mL), methyl iodide (21 µL, 340 µmol) and K_2CO_3 (15.0 mg, 114 µmol). Purification by preparative HPLC (system 7) afforded **29a** (7.70 mg, 78%) as colorless oil. ^{1}H-NMR (400 MHz, D_2O): δ 7.84 (br s, 1H), 7.65 (br d, *J* = 2.2 Hz, 1H), 4.96–4.85 (m, 2H), 4.68 (br s, *J* = 1.4 Hz, 1H), 3.88–3.78 (m, 2H), 3.74 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.63 (ddd, *J* = 12.1, 8.5, 7.2 Hz, 1H), 3.30 (s, 3H), 3.22 (s, 3H), 2.75–2.58 (m, 1H), 2.52–2.33 (m, 1H); ^{13}C-NMR (1501 MHz, D_2O) δ 171.5, 142.7, 121.9, 78.4, 71.1(t, *J* = 3.7 Hz), 67.6, 65.7(t, *J* = 3.3 Hz), 54.1(q, *J* = 4.4 Hz), 30.7; HPLC (254 nm, system C): t_R= 4.5 min, purity: 99%, (254 nm, system D): t_R= 3.8 min, purity: 99%; HR-ESIMS: calcd 213.1056, found 213.1052 $[M]^+$.

3-(((1-Methylpyrrolidin-3-yl)methoxy)methyl)pyridine 30a



To obtain the free base of the 3-((pyrrolidin-3-ylmethoxy)methyl)pyridine hydrochloric acid, the compound was dissolved in water and basified to pH 10, three times with CH_2Cl_2 and the solvent was removed under reduced pressure. To a solution of 3-((pyrrolidin-3-ylmethoxy)methyl)pyridine (80 mg, 0.42 mmol) in dry 1,2-dichloroethane/methanol (11 mL, 10:1) was added formaldehyde (aqu. solution stabilized with MeOH, 37 wt%,156 µL, 2.10 mmol), and sodium triacetoxyborohydride (356 mg, 1.68 mmol). The reaction mixture was stirred for 2 h at room temperature and subsequently, saturated, aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated, aqueous NaCl solution and dried (Na_2SO_4). After evaporation, the crude residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 7:1:0.01) to give **30a** (46.0 mg, 53%) as light brown oil. ^{1}H-NMR (400 MHz, D_2O) δ 8.52 (d, *J* = 1.7 Hz, 1H), 8.50 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.88 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.48 (ddd, *J* = 7.9, 5.0, 0.7 Hz, 1H), 4.61 (s, 2H), 3.60 – 3.41 (m, 2H), 2.85 – 2.67 (m, 1H), 2.64 – 2.45 (m, 3H), 2.34 (dd, *J* = 10.0, 6.3 Hz, 1H), 2.31 (s, 3H), 2.05 – 1.87 (m, 1H), 1.47 (td, *J* = 13.3, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 148.7, 148.6, 137.8, 133.8, 124.6, 74.1, 70.3, 58.5, 55.1, 40.9, 37.2, 27.6; HPLC (254 nm, system C): t_R= 3.1 min, purity: 95%, (254 nm, system D): t_R= 2.6 min, purity: 95%; HR-ESIMS: calcd 207.1492, found 207.1493 $[M+H]^+$.

3-(((1-Methylpiperidin-3-yl)oxy)methyl)pyridine 33a



Compound **33a** was prepared according to the protocol of compound **30a** using a solution of 3-((piperidin-3-yloxy)methyl)pyridine (43.0 mg, 0.22 mmol) in dry 1,2-dichloroethane/methanol (5 mL, 10:1), formaldehyde (aqu. solution stabilized with MeOH, 37 wt%, 65.0 µL, 110 µmol), and sodium triacetoxyborohydride (187 mg, 880 µmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 aqu. 25%, 10:1:0.1) afforded **33a** (8.80 mg, 19%) as a colorless oil. ^{1}H-NMR (400 MHz, D_2O) δ: 8.89–8.30 (m, 2H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.49 (dd, *J* = 7.5, 5.0 Hz, 1H), 4.70

(s, 2H), 3.99 (br s, 1H), 3.57–3.18 (m, 2H), 3.16–2.96 (m, 1H), 2.82 (s, 3H), 2.12–1.95 (m, 2H), 1.86–1.53 (m, 2H); ^{13}C-NMR (100 MHz, D_2O) δ 148.9, 148.8, 137.9, 134.2, 124.8, 70.5, 68.3, 57.1, 55.0, 44.1, 30.5, 30.3; HPLC (254 nm, system C): t_R= 2.9 min, purity: 95%, (254 nm, system D): t_R= 2.5 min, purity: 95%; HR-ESIMS: calcd 207.1492, found 207.1491 $[M+H]^+$.

Biological experiments:

IP-One® screening assay on M_2R activation: Receptor activation properties for all compounds at M_2R were performed applying the IP accumulation assay IP-One® (Cisbio, Codolet, France) according to the manufactorer's protocol. In brief, HEK-293T cells were grown to a confluence of approx. 70% and transiently cotransfected with the human M_2R and the hybrid G-protein $G\alpha_{qi5\text{-}HA}$ ($G\alpha_q$ protein with the last five amino acids at the C-terminus replaced by the corresponding sequence of $G\alpha_i$; greatful gift from The J. David Gladstone Institutes, San Francisco, CA), using the transfection method with the TransIT-293 Mirus transfection reagent (MoBiTec, Goettingen, Germany). After one day cells were detached from the culture dish with Versene (Life Technologies GmbH, Darmstadt, Germany), seeded into black 384-well plates (10000 cells/well) and maintained for 24 h at 37 °C. After incubation with the test compounds dissolved in stimulation buffer (ten different concentrations for each compound, total range from 0.01 pM up to 300 µM) for 2 h at 37 °C the detection reagents were added (IP1-d2 conjugate and Anti-IP1cryptate TB conjugate each dissolved in lysis buffer) and incubation was continued for 1 h at room temperature. Time resolved fluorescence resonance energy transfer (HTRF) was determined using the Clariostar plate reader (BMG, Ortenberg, Germany). Dose-response measurements were performed as duplicates. Resulting activation curves were normalized to the maximum effect of carbachol (100%) and buffer (0%) and analyzed using the algorithms for nonlinear regression in PRISM 6.0 (GraphPad, San Diego, CA). For all compounds 3-8 individual dose-response curves were measured, the corresponding EC_{50} and E_{max} values of each mean curve were calculated and summarized to get the average EC_{50} and E_{max} values ± SEM.

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