Supporting Information

Neuroprotective Tri- and Tetracyclic BChE Inhibitors Releasing Reversible Inhibitors upon Carbamate Transfer

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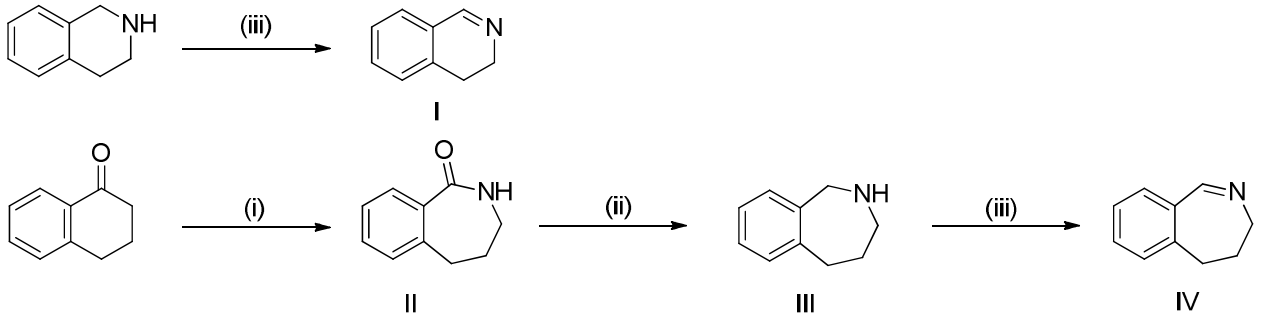
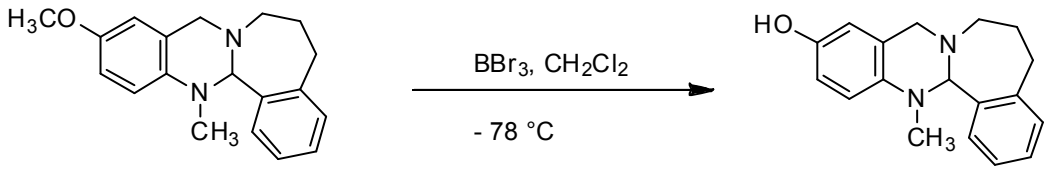
Contents:

Scheme (1): Synthesis of 3,4-dihydroisoquinoline (I) and 4,5-dihydro-3*H*-benzo[*c*]azepine (IV)



Reagents: (i) NaN_3, HCl, 0 °C, rt, 24 hr (ii) $LiAlH_4$, THF, 70 °C, 12 hr (iii) *N*-chlorosuccinimide (*N*-bromosuccinimide for preparation of compound **I**), CH_2Cl_2, rt, 30 min., KOH / EtOH, rt, 24 hr

Scheme (2): 14-Methyl-5,6,7,9,14,14a-hexahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-11-ol (6b)



Synthesis, elemental analysis data, and spectral data of intermediate and target compounds

General methods for synthesis: Melting points are uncorrected and were measured in open capillary tubes, using a Barnstead Electrothermal IA9100 melting point apparatus. ^{1}H and ^{13}C NMR spectral data were obtained from a Bruker Advance spectrometer (300 MHz and 75 MHz, respectively). TLC was performed on silica gel on aluminum foils with fluorescent indicator 254 nm (Merck). For detection iodine vapor, or UV light (254 nm), were used. ESI-MS samples were analyzed using electrospray ionisation ion-trap mass spectrometry in nanospray mode using a Thermo Finnigan LCQ Deca. The CHN analyses were undertaken using Perkin Elmer Elemental Analyser PE2400CHNS. For column chromatography, silica gel 60, 230 - 400 mesh (Merck) was used.

3,4-Dihydroisoquinoline (I)

To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (5.00 g, 37.6 mmol) in 200 mL of CH_2Cl_2, *N*-bromosuccinimide (7.35 g, 41.35 mmol) was added portionwise over 20 min. After the addition was complete, the mixture was stirred until TLC indicated that the starting material was consumed (45 min). Sodium hydroxide (50 mL of a 30% aqueous solution) was added, and stirring was continued for 1 hr at 25 °C. The organic layer was separated and washed with water (100 mL), and the product was extracted with 10% HCl (2 x 100 mL). The combined acidic extracts were washed with CH_2Cl_2 (100 mL) and made basic with concentrated ammonia (pH 9). The liberated oil was extracted with CH_2Cl_2 (3 x 100 mL), dried over Na_2SO_4, and evaporated *in vacuo* to afford

a light yellow oil residue which was purified by column chromatography using ethyl acetate eluent system to afford **1** as a colorless oil (63 g , 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.77 – 2.61 (m, 2H, C$CH_2$$CH_2$), 3.72 (ddt, *J* = 13.7, 9.7, 4.9 Hz, 2H, CH_2CH_2N), 7.16 – 7.07 (m, 1H, arom.), 7.37 – 7.18 (m, 3H, arom.), 8.30 (t, *J* = 2.1 Hz, 1H, N*CH*C) ppm. Spectral data is in accordance with literature data.[1]

2,3,4,5-Tetrahydrobenzo[*c*]azepin-1-one (II)

Sodium azide (5.20 g, 8.0 mmol) was added to a stirred solution of α-tetralone (5.80 g, 40.0 mmol) in ice-cooled concentrated HCl (100 mL). The mixture was allowed to warm to room temperature and stirring was continued overnight. After completion of the reaction, the mixture was poured onto ice, basic pH was accomplished by addition of K_2CO_3. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product obtained was purified by column chromatography using CH_2Cl_2 as eluent to afford **2** as light brown crystals, mp 95-98 °C (4.1 g, 64% yield) (lit.[2] mp 97-98 °C). ^{1}H NMR (300 MHz, DMSO) δ: 1.87 (p, *J* = 6.7 Hz, 2H, $CH_2CH_2CH_2$), 2.73 (t, *J* = 7.1 Hz, 2H, C$CH_2$$CH_2$), 2.89 (q, *J* = 6.5 Hz, 2H, CH_2-CH_2-NH), 7.25 (dd, *J* = 7.3, 0.9 Hz, 1H, arom), 7.32 (tt, *J* = 3.5, 1.8 Hz, 1H, arom), 7.56 – 7.45 (m, 1H, arom), 7.45 – 7.37 (m, 1H, arom), 7.99 (bs, 1H, NH) ppm. Spectral data is in accordance with literature data.[2]

2,3,4,5-Tetrahydro-1*H*-benzo[*c*]azepine (III)

A solution of the benzazepinone **II** (2.40 g, 15.0 mmol) in 70 mL of dry THF was added to an ice-cooled, stirred suspension of lithium aluminum hydride (2.00 g, 52.5 mmol) in 70 mL of dry THF. The mixture was stirred at room temperature for 30 min and then heated at reflux for 2 hr. The excess of $LiAlH_4$ was hydrolyzed with water under ice cooling and separated by filtration. The product was extracted with ether and the solvent was evaporated, the crude product was purified by column chromatography using CH_2Cl_2: MeOH: NH_4OH (10:1.0:0.1) eluent system to afford **3** as a brown oil (1.33 g, 60% yield). ^{1}H NMR (300 MHz, DMSO) δ: 1.71 (dd, *J* = 9.8, 3.8 Hz, 2H, $CH_2CH_2CH_2$), 2.95 (m, 2H, C$CH_2$$CH_2$), 3.29 – 3.15 (m, 2H, 2H, CH_2CH_2NH), 3.93 (s, 2H, 2H, CCH_2NH), 7.22 – 7.02 (m, 4H, arom) ppm. Spectral data is in accordance with literature data.[2]

4,5-Dihydro-3*H*-benzo[*c*]azepine (IV)

2,3,4,5-Tetrahydro-1*H*-benzo[*c*]azepine **III** (600 mg, 4.1 mmol) was dissolved in 20 mL of CH_2Cl_2 and *N*-chlorosuccinimide (600 mg, 4.5 mmol) was added portion wise at room temperature. The mixture was stirred at room temperature for 30 min. under N_2. The mixture was then extracted with water (2 × 10 mL), the organic phase dried over Na_2SO_4 and added drop wise to a solution of KOH (240 mg, 4.28 mmol) in 10 mL of ethanol. The resulting mixture was stirred at room temperature overnight and then concentrated *in vacuo*. Water (10 mL) was added to the residue and extracted with CH_2Cl_2 (3 × 10 mL). Organic extracts were dried over Na_2SO_4, the crude product was purified by column chromatography using CH_2Cl_2: petroleum ether (1:1) eluent system to afford **4** as a yellow oil (450 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.25 (td, *J* = 12.7, 6.8 Hz, 2H, 2H,

$CH_2CH_2CH_2$), 2.75 (t, *J* = 6.9 Hz, 2H, CCH_2CH_2), 3.65 – 3.55 (m, 2H, CH_2CH_2N), 7.36 – 7.26 (m, 3H, arom.), 7.25 – 7.17 (m, 1H, arom.), 8.48 (s, 1H, C*CH*N) ppm. Spectral data is in accordance with literature data.[1]

General procedure for the synthesis of compounds 1a-c

A mixture of anthranilic acid or substituted anthranilic acid (1 equiv.) and triphosgene (0.34 equiv.) in dry THF was heated at 40 - 50 °C for 3 hr. the solution was concentrated and *n*-hexane was added. The precipitate was filtered and dried to afford the title compounds **1a-c.**[3]

1*H*-Benzo[*d*][1,3]oxazine-2,4-dione (1a)

The reaction was carried out according to the general procedure, starting from 2-aminobenzoic acid (1.0 g, 6.1 mmol) and triphosgene (610 mg, 2.0 mmol). The title compound was obtained as a beige solid (1.0 g, 82%). mp 234-238 °C (lit.[4] mp 233-234 °C (dec.)). ^{1}H NMR (300 MHz, DMSO) δ: 7.19 – 7.10 (m, 1H, arom.) 7.29 – 7.20 (m, 1H, arom.), 7.78 – 7.69 (m, 1H, arom.), 7.94 – 7.87 (m, 1H, arom.), 11.73 (s, 1H, NH) ppm. Spectral data is in accordance with literature data.[4]

6-Hydroxy-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (1b)

The reaction was carried out according to the general procedure, starting from 2-amino-5-hydroxybenzoic acid (920 mg). The title compound was obtained as a grey solid (950 mg, 89%). mp 275 – 279 °C. ^{1}H NMR (300 MHz, DMSO) δ: 6.90-7.12 (m, 1H, arom.), 7.18-7.22 (m, 2H, arom.), 9.84 (bs, 1H, OH), 11.51 (s, 1H, NH) ppm.

6-Methoxy-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (1c)

The reaction was carried out according to the general procedure, starting from 2-amino-5-methoxybenzoic acid (1.0g). The title compound was obtained as a beige solid (900 mg, 78%). mp 258 – 260 °C (lit. [5] mp 244-256 °C). ^{1}H NMR (300 MHz, DMSO) δ: 3.80 (s, 3H, OCH3), 7.11 (d, *J* = 8.8 Hz, 1H, arom.), 7.52 – 7.28 (m, 2H, arom.), 11.62 (s, 1H, NH) ppm. Spectral data is in accordance with literature data.[5]

General procedure for the synthesis of compounds 2a-c:

To a solution of isatoic anhydride or substituted isatoic anhydride **1a-c** (1 equiv.) in 5 mL DMAc (*N*,*N*-dimethylacetamide), diisopropylethylamine (2 equiv.) was added. The solution was stirred for 10 min prior to addition of methyl iodide (2 equiv.). The solution was heated at 40 °C overnight. The solution was allowed to cool to room temperature and 15 mL of cold water was added. The resulting suspension was stirred vigorously for 30 min, filtered, washed with 20 mL water and 20 mL *n*-hexane, the crude product was purified by column chromatography using (10:1) CH_2Cl_2: MeOH eluent system to afford the title compounds **2a-c.** Synthetic procedure is described in ref. 6.

1-Methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (2a)

The reaction was carried out according to the general procedure, starting from 1*H*-benzo[*d*][1,3] oxazine-2,4-dione **1a** (450 mg). The title compound was obtained as a beige solid (410 mg, 83%). mp 164 - 166 °C (lit.[3] mp 163 - 165 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.59 (s, 3H, N*CH*$_3$), 7.20 (t, *J* = 6.3 Hz, 1H, arom.), 7.35 – 7.28 (m, 1H, arom.), 7.83 – 7.73 (m, 1H, arom.), 8.20 – 8.11 (m, 1H, arom.) ppm. Spectral data is in accordance with literature data.[3]

6-Hydroxy-1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (2b)

The reaction was carried out according to the general procedure, starting from 6-hydroxy-1*H*-benzo[*d*] [1,3]oxazine-2,4-dione **1b** (500 mg), the title compound was obtained as a beige solid (220 mg, 41%). mp 248 – 251 °C. ^{1}H NMR (300 MHz, $CDCl_3$ + MeOD) δ: 3.30 (s, 3H, N*CH*$_3$), 6.90 (d, *J* = 9.0 Hz, 1H, arom.), 7.05 (dd, *J* = 9.0, 2.9 Hz, 1H, arom.), 7.24 (d, *J* = 2.9 Hz, 1H, arom.) ppm. ^{13}C NMR (300 MHz, $CDCl_3$ + MeOD) δ: 35.51 (NCH_3), 116.18 (arom.), 118.36 (arom.), 119.55 (arom.), 129.72 (arom.), 138.8 (arom.), 145.69 (CO), 152.37 (CO), 158.01 (COH) ppm.

6-Methoxy-1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (2c)

The reaction was carried out according to the general procedure, starting from 6-methoxy-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **1c** (538 mg), the title compound was obtained as a beige solid (490 mg, 85%). mp 214 – 217 °C (lit.[6] mp 216-218 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.57 (s, 3H, N*CH*$_3$), 3.88 (s, 3H, O*CH*$_3$), 7.12 (d, *J* = 9.1 Hz, 1H, arom.), 7.35 (dd, *J* = 9.1, 3.0 Hz, 1H, arom.), 7.58 (d, *J* = 3.0 Hz, 1H, arom.) ppm. Spectral data is in accordance with literature data.[6]

General procedure for the synthesis of compounds 3a-c and 4a,c:

A suspension of *N*-methylisatoic anhydride or substituted *N*-methylisatoic anhydride **2a-c** (1.0 equiv.) and 3,4-dihydroisoquinoline **I** or 4,5-dihydro-3*H*-benzo[*c*]azepine **IV** (1.2 equiv.) respectively, in dry toluene was refluxed for 24 hr. After cooling, the solvent was removed under reduced pressure and the residue was purified by column chromatography using petroleum ether: ethyl acetate as an eluent system to afford the title compounds **3a-c** and **4a,c.** Synthetic procedure is described in ref. 7b of the main article.

5,6,13,13a-Tetrahydro-13-methylisoquinolino[1,2-*b*]quinazolin-8-one (3a)

The reaction was carried out according to the general procedure, starting from 1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **2a** (400 mg, 2.26 mmol) and 3,4-dihydroisoquinoline **I** (355 mg, 2.71 mmol). The title compound was obtained as a colorless viscous oil (380 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3H, NCH_3), 2.93 – 2.80 (m, 1H, C*CH*$_2$CH$_2$), 3.10 – 2.96 (m, 1H, C*CH*$_2$CH$_2$), 3.36 – 3.16 (m, 1H, N*CH*$_2$CH$_2$), 4.77 – 4.56 (m, 1H, N*CH*$_2$CH$_2$), 5.75 (s, 1H, NCHN), 7.13 – 7.04 (m, 2H, arom.), 7.25 – 7.20 (m, 1H, arom.), 7.34 – 7.27 (m, 2H, arom.), 7.41 – 7.35 (m, 1H, arom.), 7.50 – 7.42 (m, 1H, arom.), 8.09 – 8.02 (m, 1H, arom.)

ppm. Spectral data is in accordance with literature data with the synthetic procedure described in ref. 7b of the main article.

5,6,13,13a-Tetrahydro-10-hydroxy-13-methylisoquinolino[1,2-*b*]quinazolin-8-one (3b)

The reaction was carried out according to the general procedure, starting from 6-hydroxy-1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **2b** (500 mg, 2.60 mmol) and 3,4-dihydroisoquinoline **I** (400 mg, 3.10 mmol). The title compound was obtained as yellow viscous oil (170 mg, 23%). ESI-MS: 281.0 *m/z* $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H, NCH_3). 2.86 (m, 1H, C*CH*$_2$CH$_2$), 2.99 (m, 1H, C*CH*$_2$CH$_2$), 3.37 – 3.23 (m, 1H, N*CH*$_2$CH$_2$), 4.66 (m, 1H, N*CH*$_2$CH$_2$), 5.75 (s, 1H, NCHN), 7.13 – 7.02 (m, 2H, arom.), 7.25 – 7.19 (m, 1H, arom.), 7.39 – 7.27 (m, 2H, arom.), 7.55 – 7.41 (m, 1H, arom.), 7.97 (s, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.69 (C*CH*$_2$CH$_2$), 36.31 (NCH_3), 38.99 (N*CH*$_2$CH$_2$), 71.98 (NCHN), 114.37 (arom.), 121.72 (arom.), 123.85 (arom.), 123.88 (arom.), 127.19 (arom.), 128.27 (arom.), 128.51 (arom.), 128.51 (arom.), 131.78 (arom.), 136.75 (arom.), 144.44 (arom.), 153.43(COH), 164.63 (CO) ppm.

10-Methoxy-13-methyl-13,13a-dihydro-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (3c)

The reaction was carried out according to the general procedure, starting from 6-methoxy-1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **2c** (300 mg, 1.45 mmol) and 3,4-dihydroisoquinoline **I** (228 mg, 1.74 mmol). The title compound was obtained as yellow viscous oil (150 mg, 35%). ESI-MS: 294.2 *m/z*$[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, NCH_3), 3.05 – 2.78 (m, 2H, C*CH*$_2$CH$_2$), 3.35 – 3.14 (m, 1H, N*CH*$_2$CH$_2$), 3.84 (s, 3H, OCH_3), 4.65 (m, 1H, N*CH*$_2$CH$_2$), 5.71 (s, 1H, NCHN), 7.13 – 6.99 (m, 2H, arom.), 7.37 – 7.17 (m, 3H, arom.), 7.46 (d, *J* = 6.7 Hz, 1H, arom.), 7.56 (d, *J* = 2.6 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.71(C*CH*$_2$CH$_2$), 36.28 (NCH_3), 38.82 (N*CH*$_2$CH$_2$), 55.75 (OCH_3), 71.81 (NCHN), 110.53 (arom.), 121.39 (arom.), 123.67 (arom.), 124.13 (arom.), 127.10 (arom.), 128.21 (arom.), 128.38 (arom.), 128.53 (arom.), 132.03 (arom.), 136.90 (arom.), 145.10 (arom.), 155.92 (*C*OCH_3), 164.15 (CO) ppm.

14-Methyl-6,7,14,14a-tetrahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (4a)

The reaction was carried out according to the general procedure, starting from 1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **2a** (610 mg, 3.45 mmol) and 4,5-dihydro-3*H*-benzo[*c*]azepine **IV** (600 mg, 4.14 mmol). The title compound was obtained as light brown viscous oil (360 mg, 38%). ESI-MS: 278.2 m/z $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.87 – 1.69 (m, 2H, CH_2*CH*$_2$CH$_2$), 2.05 – 1.92 (m, 1H, N*CH*$_2$CH$_2$), 3.04 (m, 2H, C*CH*$_2$CH$_2$), 3.13 (s, 3H, NCH_3), 4.99 (dt, *J* = 13.6, 3.1 Hz, 1H, N*CH*$_2$CH$_2$), 5.78 (s, 1H, N*CH*N), 6.69 (t, *J* = 7.3 Hz, 1H, arom.), 6.81 (ddd, *J* = 13.3, 6.5, 3.4 Hz, 2H, arom.), 6.96 (td, *J* = 7.5, 1.7 Hz, 1H, arom.), 7.17 – 7.08 (m, 2H, arom.), 7.50 – 7.41 (m, 1H, arom.), 7.90 – 7.82 (m, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.50 (CH_2*CH*$_2$CH$_2$), 35.21(C*CH*$_2$CH$_2$), 37.11 (NCH_3), 48.06 (N*CH*$_2$CH$_2$), 76.85 (NCHN), 110.70, 116.35 (arom.), 117.80 (arom.), 125.33 (arom.), 126.02 (arom.), 128.15 (arom.), 129.23 (arom.), 130.74 (arom.), 133.93 (arom.), 138.05 (arom.), 140.85 (arom.), 147.22 (arom.), 161.92 (CO) ppm.

11-Methoxy-14-methyl-6,7,14,14a-tetrahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (4c)

The reaction was carried out according to the general procedure, starting from 6-methoxy-1-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **2c** (300 mg, 1.45 mmol) and 4,5-dihydro-3*H*-benzo[*c*]azepine **IV** (253 mg, 1.74 mmol). The title compound was obtained as yellow viscous oil (190 mg, 43%). ESI-MS: 308 m/z $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.85 – 1.72 (m,1H, $CH_2CH_2CH_2$), 2.02 – 1.90 (m, 1H, $CH_2CH_2CH_2$), 3.07 – 2.98 (m,2H, CCH_2CH_2), 3.09 (s, 3H, NCH_3), 3.71 – 3.61 (m,1H, NCH_2CH_2), 3.77 (s,3H, OCH_3), 5.05 – 4.92 (m, 1H, NCH_2CH_2), 5.73 (s, 1H, NCHN), 6.81 – 6.72 (m, 2H, arom.), 6.99 – 6.93 (m, 1H, arom.), 7.20 – 7.05 (m, 3H, arom.), 7.42 (d, J = 3.0 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.45 ($CH_2CH_2CH_2$), 35.19 (CCH_2CH_2), 37.72 (NCH_3), 47.98 (NCH_2CH_2), 55.74 (OCH_3), 77.03 (NCHN), 111.76 (arom.), 113.04 (arom.), 117.25 (arom.), 122.07 (arom.), 125.82 (arom.), 128.07 (arom.), 130.68 (arom.), 138.20 (arom.), 140.78 (arom.), 141.92 ($COCH_3$ 152.26 (arom.), 161.77 (CO) ppm.

General procedure to synthesize compounds 5a-c and 6a,c:

A solution of **3a-c** or **4a,c** (1 equiv.) respectively, in dry THF was added drop wise to a suspension of lithium aluminum hydride (3 equiv.) in dry THF under nitrogen atmosphere. The mixture was heated to reflux for 3 hr, and then the reaction mixture was poured into ice water, basified with 20% aq NaOH, and extracted with ethyl acetate. The combined extracts were washed with saturated aq. NaCl solution and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a crude product, which was column chromatographed on a silica gel using petroleum ether: ethyl acetate (2:1) as an eluent system to afford **5a-c** or **6a,c** respectively. Synthetic procedure is described in ref. 7b of the main article.

6,8,13,13a-Tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazoline (5a)

The reaction was carried out according to the general procedure, starting from 5,6,13,13a-tetrahydro-13-methylisoquinolino[1,2-*b*]quinazolin-8-one **3a** (160 mg, 0.6 mmol), and lithium aluminum hydride (70 mg, 1.8 mmol), the title compound was obtained as a yellow viscous oil (120 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.62 (s, 3H, NCH_3), 2.95 – 2.68 (m, 2H, CCH_2CH_2), 3.18 – 3.03 (m, 1H NCH_2CH_2), 3.30 (dt, J = 10.9, 5.3 Hz, 1H, NCH_2CH_2), 4.01 (dd, J = 53.9, 15.5 Hz, 2H, CCH_2N), 4.90 (s, 1H, NCHN), 6.85 (td, J = 7.4, 1.1 Hz, 1H, arom.), 6.97 – 6.90 (m, 1H, arom.), 7.03 – 6.97 (m, 1H, arom.), 7.25 – 7.13 (m, 4H, arom.), 7.42 – 7.34 (m, 1H, arom.) ppm. Spectral data is in accordance with literature data with the synthetic procedure described in ref. 7b of the main article.

6,8,13,13a-Tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-ol (5b)

The reaction was carried out according to the general procedure, starting from 5,6,13,13a-tetrahydro-10-hydroxy-13-methylisoquinolino[1,2-*b*]quinazolin-8-one **3b** (160 mg, 0.6 mmol), and lithium aluminum hydride (70 mg, 1.8 mmol). The title compound was obtained as a light yellow solid (100 mg, 65%). mp 161-167°C. ESI-MS: 266.9 *m/z* $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.51 (s, 3H, NCH_3), 2.87 – 2.62 (m, 2H, CCH_2CH_2), 3.36 –

3.05 (m, 2H, N$CH_2$$CH_2$), 3.96 – 3.66 (m, 2H, CCH_2N), 4.75 (s, 1H, NCHN), 5.30 (s, 1H, OH), 6.33 (t, *J* = 11.6 Hz, 1H, arom.), 6.63 (dd, *J* = 8.6, 2.2 Hz, 1H, arom.), 6.82 (dd, *J* = 28.3, 8.7 Hz, 1H, arom.), 7.15 (dd, *J* = 8.3, 3.6 Hz, 1H, arom.), 7.28 – 7.18 (m, 2H, arom.), 7.56 – 7.38 (m, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.55 (C$CH_2$$CH_2$), 38.80 ($NCH_3$), 48.81 (N$CH_2$$CH_2$), 56.55 ($CCH_2$N), 77.36 (NCHN), 113.11 (arom.), 114.83 (arom.), 122.50 (arom.), 126.09 (arom.), 126.49 (arom.), 127.31 (arom.), 128.43 (arom.), 128.70 (arom.), 133.98 (arom.), 136.10 (arom.), 142.16 (arom.), 150.27(COH) ppm. Elem. Anal. ($C_{17}H_{18}N_2O$ + 0.1CH_3OH) Calc.: C, 76.20; H, 6.88; N, 10.39; O, 6.53 Found: C 75.89, H 6.72, N 10.04.

6,8,13,13a-Tetrahydro-10-methoxy-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazoline (5c)

The reaction was carried out according to the general procedure, starting from 10-methoxy-13-methyl-13,13a-dihydro-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **3c** (180 mg, 0.61 mmol) and lithium aluminum hydride (70 mg, 1.8 mmol). The title compound was obtained as a white solid (100 mg, 59%). mp 147-152 ºC. ESI-MS: 280.2 *m/z* $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.51 (s, 3H, NCH_3), 2.85 – 2.61 (m, 2H, C$CH_2$$CH_2$), 3.34 – 3.05 (m, 2H, N$CH_2$$CH_2$), 3.79 (s, 3H, OCH_3), 4.04 – 3.83 (m, 2H, CCH_2N), 4.74 (s, 1H, NCHN), 6.58 (d, *J* = 2.9 Hz, 1H, arom.), 6.77 (dd, *J* = 8.8, 2.9 Hz, 1H, arom.), 7.01 – 6.91 (m, 1H, arom.), 7.32 – 7.08 (m, 3H, arom.), 7.50 (m, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.90 (C$CH_2$$CH_2$), 38.77 ($NCH_3$), 48.89 (N$CH_2$$CH_2$), 55.58 ($OCH_3$), 57.02 ($CCH_2$N), 77.41 (NCHN), 111.27 (arom.), 113.39 (arom.), 122.76 (arom.), 126.02 (arom.), 126.87 (arom.), 127.16 (arom.), 128.47 (arom.), 128.62 (arom.), 134.22 (arom.), 136.29 (arom.), 142.84 (arom.), 154.17 (arom.) ppm. Elem. Anal. ($C_{18}H_{20}N_2O$) Calc.: C, 77.11; H, 7.19; N, 9.99; O, 5.71 Found: C 76.78, H 7.14, N 9.66.

14-Methyl-5,6,7,9,14,14a-hexahydrobenzo[3,4]azepino[2,1-*b*]quinazoline (6a)

The reaction was carried out according to the general procedure, starting from 14-methyl-6,7,14,14a-tetrahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **4a** (180 mg, 0.65 mmol) and lithium aluminum hydride (76 mg, 2.0 mmol). The title compound was obtained as a white solid (100 mg, 59%). mp 136-141ºC. ESI-MS: 264.3 *m/z* $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.96 – 1.60 (m, 2H, $CH_2$$CH_2$$CH_2$), 2.98 – 2.84 (m, 1H, N$CH_2$$CH_2$), 3.14 – 2.98 (m, 1H, N$CH_2$$CH_2$), 3.05 (s, 3H, NCH_3), 3.55 – 3.39 (m, 2H, C$CH_2$$CH_2$), 3.74 – 3.57 (m, 2H, CCH_2N), 5.44 (s, 1H, NCHN), 6.67 (td, *J* = 7.3, 0.7 Hz, 1H, arom.), 6.74 (d, *J* = 8.1 Hz, 1H, arom.), 6.83 (t, *J* = 6.0 Hz, 2H, arom.), 7.02 (td, *J* = 7.4, 1.8 Hz, 1H, arom.), 7.24 – 7.10 (m, 3H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.81 ($CH_2$$CH_2$$CH_2$), 35.83 (N$CH_2$$CH_2$), 37.42 (C$CH_2$$CH_2$), 37.42 ($NCH_3$), 49.17 (C$CH_2$N) 56.80 (C$CH_2$N), 78.25 (NCHN), 110.55 (arom.), 116.41 (arom.), 120.58 (arom.), 125.74 (arom.), 126.46 (arom.), 127.58 (arom.), 127.58 (arom.), 127.83 (arom.), 129.89 (arom.), 138.13 (arom.), 141.54 (arom.), 144.39 (arom.) ppm. Elem. Anal. ($C_{18}H_{20}N_2$ + 0.1 CH_3OH) Calc.: C, 81.25; H, 7.68; N, 10.47; O, 0.60 Found: C 80.93, H 7.65, N 10.34.

11-Methoxy-14-methyl-5,6,7,9,14,14a-hexahydrobenzo[3,4]azepino[2,1-*b*]quinazoline (6c)

The reaction was carried out according to the general procedure, starting from 11-methoxy-14-methyl-6,7,14,14a-tetrahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **4c** (200 mg, 0.65 mmol) and lithium aluminum hydride (76 mg, 2.0 mmol). The title compound was obtained as a white solid (145 mg, 76%). mp 149-153 °C. ESI-MS: 294.3 *m/z* $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.73 – 1.56 (m, 1H, $CH_2CH_2CH_2$), 1.95 – 1.75 (m, 1H, $CH_2CH_2CH_2$), 2.93 (m, 2H, NCH_2CH_2), 3.00 (s, 3H, NCH_3), 3.48 (m, 2H, CCH_2CH_2), 3.69 – 3.58 (m, 2H, CCH_2N), 3.73 (s, 3H, OCH_3), 5.33 (s, 1H, NCHN), 6.45 (d, J = 2.7 Hz, 1H, arom.), 6.76 (dt, J = 18.1, 5.8 Hz, 2H, arom.), 6.84 (dd, J = 10.9, 5.3 Hz, 1H, arom.), 7.05 – 6.94 (m, 1H, arom.), 7.22 – 7.08 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.86 ($CH_2CH_2CH_2$), 29.73 (NCH_3), 35.86 (CCH_2CH_2), 38.48 (NCH_2CH_2), 55.67 (OCH_3), 56.61 (CCH_2N), 78.54 (NCHN), 112.54 (arom.), 112.92 (arom.), 112.99 (arom.), 122.44 (arom.), 125.64 (arom.), 127.49 (arom.), 128.45 (arom.), 129.77 (arom.), 138.33 (arom.), 139.22 (arom.), 141.55 (arom.), 151.52 (arom.) ppm. Elem. Anal. ($C_{19}H_{24}N_2Cl_2O$ + 0.7 CH_3OH) Calc.: C, 60.71; H, 6.93;Cl, 18.19; N, 7.19; O, 6.98 Found: C 60.83, H 7.02, N 6.90.

14-Methyl-5,6,7,9,14,14a-hexahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-11-ol (6b)

11-Methoxy-14-methyl-5,6,7,9,14,14a-hexahydrobenzo[3,4]azepino[2,1-*b*]quinazoline **6c** (300 mg, 1.07 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C. After addition of a 1 M BBr_3 solution in CH_2Cl_2 (2.2 mL corresponding to 2.2 mmol) at this temperature, the reaction mixture was allowed to come to room temperature and stirred for 16 hr, aq 2 N NaOH was added until the excess of BBr_3 had been completely hydrolyzed. After addition of ethyl acetate (10 mL), the solution was neutralized using 6 N HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography using ethyl acetate: petroleum (2:1) as an eluent system to afford the title compound as a pale brown solid (110 mg, 39% yield). mp 209-211°C ESI-MS: 280.2 *m/z* $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.79 – 1.42 (m, 2H, $CH_2CH_2CH_2$), 2.74 (m, 2H, NCH_2CH_2), 3.19 (s, 3H, NCH_3), 3.23 (m, 2H, CCH_2CH_2), 3.54 – 3.30 (m, 2H, CCH_2N), 5.10 (s, 1H, NCHN), 6.22 (m, 1H, arom.), 6.57 – 6.45 (m, 2H, arom.), 6.72 (m, 1H, arom.), 6.84 (m, 1H, arom.), 7.02 – 6.93 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.76 ($CH_2CH_2CH_2$), 30.52 (NCH_3), 34.92 (CCH_2CH_2), 38.77 (NCH_2CH_2), 56.81 (CCH_2N), 78.63 (NCHN), 112.90 (arom.), 112.98 (arom.), 114.10 (arom.), 114.51 (arom.), 123.04 (arom.), 124.90 (arom.), 127.03 (arom.), 128.45 (arom.), 129.43 (arom.), , 139.22 (arom.), 141.55 (arom.), 148.45 (arom.) ppm. ($C_{19}H_{24}N_2Cl_2O$ + 0.6 CH_3OH) Calc.: C, 74.57; H, 7.54; N, 9.35; O, 8.54 Found: C, 74.42; H, 7.15; N, 9.17.

14-Methyl-5,6,7,9,14,14a-hexahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-11-yl heptylcarbamate (7)

1-Isocyanatoheptane (70 mg , 0.50 mmol) was added to a stirred mixture of 14-methyl-5,6,7,9,14,14a-hexahydrobenzo[3,4]azepino[2,1-*b*]quinazolin-11-ol **6b** (100 mg, 0.36 mmol) and sodium hydride (8 mg, 0.32 mmol) in dry THF (10 mL). Stirring was continued for 20 hr at room temperature, and removal of the solvent gave a residue that was purified by column chromatography using (15:1) ethyl acetate: MeOH as eluent system to afford the title compound as a yellow viscous oil (110 mg, 73% yield). ESI-MS: 422.1 m/z $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.7 Hz, 3H, CH_2CH_3), 1.29 (m, 8H, $CH_3(CH_2)_4CH_2$), 1.61 – 1.45 (m, 2H,

CONHCH$_2$*CH$_2$*CH$_2$), 1.90 – 1.61 (m, 2H, CH$_2$*CH$_2$*CH$_2$), 3.13 – 2.78 (m, 5H, NCH$_3$, N*CH$_2$*CH$_2$), 3.33 – 3.11 (m, 2H, C*CH$_2$*CH$_2$), 3.74 – 3.33 (m, 4H, CCH$_2$N+CONH*CH$_2$*), 4.97 (dd, *J* = 19.8, 14.2 Hz, 1H, NH), 5.39 (s, 1H, NCHN), 6.71 – 6.56 (m, 2H, arom.), 6.81 (d, *J* = 7.5 Hz, 1H, arom.), 6.92 (dd, *J* = 8.8, 2.6 Hz, 1H, arom.), 7.04 – 6.96 (m, 1H, arom.), 7.20 – 7.08 (m, 2H, arom.) ppm. ^{13}C NMR (75 MHz, CDCl3) δ: 14.10 (CH$_2$*CH$_3$*), 22.61 (hept.CH$_2$), 26.73 (hept.CH$_2$), 28.96 (CH$_2$*CH$_2$*CH$_2$), 29.88 (hept.CH$_2$), 31.75 (hept.CH$_2$), 35.73 (C*CH$_2$*CH$_2$), 37.70 (NCH$_3$), 41.27 (hept.CH$_2$), 56.60 (C*CH$_2$*N), 77.26 (NCHN), 111.06 (arom.), 119.65 (arom.), 120.44 (arom.), 121.17 (arom.), 125.84 (arom.), 127.67 (arom.), 129.86 (arom.), 129.86 (arom.), 137.82 (arom.), 141.43 (arom.), 141.84 (arom.), 155.35 (arom.) ppm. Elem. Anal. (C$_{26}$H$_{35}$N$_3$O$_2$ + 0.1 CH$_2$Cl$_2$) Calc.: C, 72.89; H, 8.25; Cl, 1.65; N, 9.77; O, 7.44 Found: C, 72.73; H, 8.14; N, 9.53.

13-Methyl-6,8,13,13a-tetrahydro-5*H*-isoquinolino[1,2-*b*]quinazolin-10-yl ethyl(methyl)carbamate (8a)

To a suspension of sodium hydride (18 mg, 0.75 mmol) in dry THF (15 mL), 6,8,13,13a-tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-ol **5b** (100 mg, 0.376 mmol) solution in dry THF (5 mL) was added. The suspension was stirred for 30 min at room temperature. A solution of ethyl(methyl)carbamic chloride (22 μL, 91 mg, 0.75 mmol) in dry THF (5 mL) was added dropwise and the mixture was stirred overnight. H$_2$O (15 mL) was added followed by 15 mL of saturated K$_2$CO$_3$ solution until basic pH (pH = 9-10). The mixture was extracted with ethyl acetate (4 x 25 mL). The combined organic phase was washed with NaOH solution (0.1 M, 2 x 5 mL), dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography using (30:1) CH$_2$Cl$_2$: MeOH as an eluent system to afford the title compound as a pale yellow oil (80 mg, 61% yield). ESI-MS: 352.0 *m/z* [M+H]$^+$. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.22 (m, 3H, CONCH$_2$*CH$_3$*), 2.57 (s, 3H, N-CH$_3$), 2.78 (m, 2H, N*CH$_2$*CH$_2$), 2.98 (s, 1.5H, CON*CH$_3$*), 3.05 (s, 1.5H, CON*CH$_3$*), 3.10 (m, 1H, C*CH$_2$*CH$_2$), 3.32 – 3.22 (m, 1H, C*CH$_2$*CH$_2$), 3.43 (m, 2H, CON*CH$_2$*CH$_3$), 4.13 – 3.79 (m, 2H,CCH$_2$N), 4.83 (s, 1H, NCHN), 6.77 (s, 1H, arom.), 6.94 – 6.85 (m, 2H, arom.), 7.15 (m, 1H, arom.), 7.25 – 7.18 (m, 2H, arom.), 7.43 – 7.34 (m, 1H, arom.) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ: 12.51 (CONCH$_2$*CH$_3$,* rotamer), 13.22 (CONCH$_2$*CH$_3$,* rotamer), 28.63 (C*CH$_2$*CH$_2$), 33.59 (CON*CH$_3$,* rotamer), 33.77 (CON*CH$_3$,* rotamer), 37.87 (NCH3), 44.04 (CON*CH$_2$*CH$_3$), 47.84 (N*CH$_2$*CH$_2$), 56.26 (C*CH$_2$*N), 76.37 (NCHN), 119.67 (arom.), 120.07 (arom.), 120.40 (arom.), 125.28 (arom.), 125.79 (arom.), 127.45 (arom.), 128.76 (arom.), 128.79 (arom.), 133.96 (arom.), 136.01 (arom.), 144.75 (arom.), 145.69 (arom.), Not clear (CO) ppm. Elem. Anal. (C$_{21}$H$_{25}$N$_3$O$_2$ + 0.4CH$_3$OH) Calc.: C, 70.56; H, 7.36; N, 11.54. Found: C, 70.51; H, 7.61; N, 11.63. The synthesis was performed in analogy to the one of rivastigmine described in reference 7.

General procedure for synthesis of tetracyclic carbamates

Triethylamine (1.1 equiv) was added to a stirred solution of 6,8,13,13a-tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-ol **5b** (1 equiv) in dichloromethane and stirred at ambient temperature for 15 min. Isocyanate (1.1 equiv) was added and stirred for another 1 to 2 hours at room temperature. Upon completion (TLC), the reaction mixture was diluted with dichloromethane, washed with water, washed with brine, dried and evaporated under reduced pressure. The crude compound was purified by preparative thin layer chromatography

(dichloromethane:MeOH, 40:1) to get the carbamate compounds **8b-e**. The syntheses were performed in analogy to the ones described in reference 8.

6,8,13,13a-Tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-yl heptylcarbamate (8b)

The reaction was carried out according to the general procedure, starting from 6,8,13,13a-tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-ol **5b** (50 mg, 0.19 mmol) and 1-isocyanatoheptane (30 mg, 0.21 mmol). The title compound was obtained as a yellow viscous oil (60 mg, 78% yield). ESI-MS: 408.1 m/z $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.97 – 0.83 (m, 3H, CH_2CH_3), 1.29 (m, 8H, $CH_3(CH_2)_4CH_2$), 1.63 – 1.47 (m, 2H, $CONHCH_2CH_2CH_2$), 2.58 (s, 3H, NCH_3), 2.91 – 2.66 (m, 2H, NCH_2CH_2), 3.33 – 3.11 (m, 4H, CCH_2CH_2+ $CONHCH_2$), 4.14 – 3.78 (m, 2H, CCH_2N), 4.85 (s, 1H, NCHN), 4.97 (t, J = 5.6 Hz, 1H, NH), 6.78 (s, 1H, arom.), 6. 91 (d, J = 1.2 Hz, 2H, arom.), 7.15 (dd, J = 5.9, 3.0 Hz, 1H, arom.), 7.25 – 7.20 (m, 2H, arom.), 7.43 – 7.34 (m, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.10 (CH_2CH_3), 22.61 (hept.CH_2), 26.74 (hept.CH_2), 28.55 (CCH_2CH_2), 28.96 (hept.CH_2), 29.88 (hept.CH_2), 31.76 (hept.CH_2), 37.90 (NCH_3), 41.30 (hept.CH_2), 47.84 (NCH_2CH_2), 56.11 (CCH_2N), 76.36 (NCHN), 119.58 (arom.), 120.04 (arom.), 120.34 (arom.), 125.15 (arom.), 125.84 (arom.), 127.52 (arom.), 128.75 (arom.), 128.81 (arom.), 128.81 (arom.), 135.94 (arom.), 144.31 (arom.), 145.67 (arom.), 155.12 (CO) ppm. Elem. Anal. ($C_{25}H_{33}N_3O_2$ + 0.1 CH_3OH) Calc.: C, 73.39; H, 8.20; N, 10.23; O, 8. Found: C, 73.23; H, 8.04; N, 10.07.

13-Methyl-6,8,13,13a-tetrahydro-5*H*-isoquinolino[1,2-*b*]quinazolin-10-yl(3-methoxyphenyl) carbamate (8c)

The reaction was carried out according to the general procedure, starting from 6,8,13,13a-tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-ol **5b** (50 mg, 0.19 mmol) and 1-isocyanato-2-methoxybenzene (31 mg, 0.21 mmol). The title compound was obtained as a light yellow solid (65 mg, 82% yield). mp 190 - 193 °C. tR: 1.9999 min, HRESIMS ($C_{25}H_{25}N_3O_3$+H)$^+$, *m/z* calc: 416.1969; found: 416.1974. ^{1}H NMR (300 MHz, DMSO) δ: 2.52 (s, 3H, NCH_3), 2.90 – 2.60 (m, 2H, NCH_2CH_2), 3.07 – 2.90 (m, 1H, CCH_2CH_2), 3.26 – 3.13 (m, 1H, CCH_2CH_2), 3.72 (s, 3H, OCH_3), 4.03 – 3.81 (m, 2H, CCH_2N), 4.82 (s, 1H, NCHN), 6.62 (m, 1H, arom.), 6.87 (s, 1H, arom.), 6.93 (m, 2H, arom.), 7.06 (m, 1H, arom.), 7.23 (m, 5H, arom.), 7.39 – 7.32 (m, 1H, arom.), 10.13 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 27.61 (CCH_2CH_2), 37.56 (NCH_3), 46.64 (NCH_2CH_2), 54.91 (CCH_2N), 54.82 (OCH_3), 75.43 (NCHN), 108.01 (arom.), 119.41 (arom.), 119.66 (arom.), 120.32 (arom.), 125.17 (arom.), 125.55 (arom.), 127.29 (arom.), 128.18 (arom.), 128.65 (arom.), 129.47 (arom.), 129.57 (arom.), 133.69 (arom.), 135.76 (arom.), 139.83 (arom.), 143.32 (arom.), 145.19 (arom.), 148.36 (arom.), 152.00 (CO), 159.56 ($COCH_3$) ppm. Elem. Anal. ($C_{25}H_{25}N_3O_3$ + 0.2 CH_3OH) Calc.: C, 71.74; H, 6.16; N, 9.96; O, 12.14 Found: C, 71.53; H, 6.02; N, 10.04.

13-Methyl-6,8,13,13a-tetrahydro-5*H*-isoquinolino[1,2-*b*]quinazolin-10-yl o-tolylcarbamate (8d)

The reaction was carried out according to the general procedure, starting from 6,8,13,13a-tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-ol **5b** (50 mg, 0.19 mmol) and 1-isocyanato-2-methylbenzene (28 mg, 0.21 mmol). The title compound was obtained as a colorless viscous oil (70 mg, 92 % yield). tR: 2.012 min,

HRESIMS ($C_{25}H_{25}N_3O_2$+H)$^+$, *m/z* calc: 400.202; found: 400.2019. ^{1}H NMR (300 MHz, $CDCl_3$+ MeOD) δ: 2.15 (s, 3H, CCH_3), 2.45 (s, 3H, NCH_3), 2.98 – 2.53 (m, 3H, N*C*$H_2$$CH_2$+ C*C*$H_2$$CH_2$), 3.20 – 3.04 (m, 1H, C*C*$H_2$$CH_2$), 4.00 – 3.61 (q, *J* = 16.0 Hz, 2H, CCH_2N), 4.72 (s, 1H, NCHN), 6.68 (s, 1H, arom.), 6.93 – 6.76 (m, 2H, arom.), 7.08 – 6.95 (m, 5H, arom.), 7.62 – 7.44 (m, 2H, arom.), 7.88 – 7.64 (m, 1H, arom.) ppm.^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.42 (CCH_3), 31.75 (C*C*$H_2$$CH_2$), 41.13 ($NCH_3$), 51.00 (N*C*$H_2$$CH_2$), 59.26 (C*C*$H_2$N), 79.77 (NCHN), 122.36 (arom.), 123.57 (arom.), 124.42 (arom.), 127.75 (arom.), 128.26 (arom.), 129.73 (arom.), 130.42 (arom.), 130.45 (arom.), 131.66 (arom.), 131.75 (arom.), 132.57 (arom.), 132.83 (arom.), 134.40 (arom.), 137.44 (arom.), 139.34 (arom.), 147.59 (arom.), 148.87 (arom.), 157.73 (CO) ppm. Elem. Anal.($C_{25}H_{25}N_3O_2$ + 0.4 CH_2Cl_2) Calc.: C, 70.38; H, 6.00; N, 9.69; O, 7.38; Cl, 6,54 Found: C, 70.10; H, 6.30; N, 10.08.

13-Methyl-6,8,13,13a-tetrahydro-5*H*-isoquinolino[1,2-*b*]quinazolin-10-yl(4-isopropylphenyl) carbamate (8e)

The reaction was carried out according to the general procedure, starting from 6,8,13,13a-tetrahydro-13-methyl-5*H*-isoquinolino[1,2-*b*]quinazolin-10-ol **5b** (50 mg, 0.19 mmol) and 1-isocyanato-4-isopropylbenzene (34 mg, 0.21 mmol). The title compound was obtained as a yellow viscous oil (69 mg, 85% yield). mp 78 - 80 °C. tR: 2.4048 min, HRESIMS ($C_{27}H_{29}N_3O_2$+H)$^+$, *m/z* calc: 428.2333; found: 428.2341. ^{1}H NMR (300 MHz, DMSO) δ: 1.18 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.52 (s, 3H, NCH_3) 2.91 – 2.61 (m, 3H, N*C*$H_2$$CH_2$+ C*C*$H_2$$CH_2$), 3.09 – 2.91 (m, 1H, C*C*$H_2$$CH_2$), 3.29 – 3.11 (m, 1H, C*H*$(CH_3)_2$), 3.91 (q, *J* = 16.0 Hz, 2H, CCH_2N), 4.81 (s, 1H, NCHN), 6.86 (s, 1H, arom.), 6.94 (d, *J* = 1.2 Hz, 2H, arom.), 7.28 – 7.14 (m, 5H, arom.), 7.46 – 7.30 (m, 3H, arom.), 10.03 (s, 1H, N*H*) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 23.87 ($CH(CH_3)_2$), 27.70 (C*C*$H_2$$CH_2$), 32.69 ($CH(CH_3)_2$), 37.59 ($NCH_3$), 46.88 (N*C*$H_2$$CH_2$), 54.96 (C*C*$H_2$N) 75.47 (NCHN), 118.35 (arom.), 119.50 (arom.), 119.63 (arom.), 120.35 (arom.), 125.21 (arom.), 125.55 (arom.), 126.45 (arom.), 127.30 (arom.), 128.15 (arom.), 128.64 (arom.), 133.75 (arom.), 135.73 (arom.), 136.35 (arom.), 142.78 (arom.), 143.42 (arom.), 145.21 (arom.), 152.10 (CO) ppm. Elem. Anal. ($C_{27}H_{29}N_3O_2$ + 0.2 CH_2Cl_2) Calc.: C, 73.49; H, 6.67; N, 9.45; O, 7.20; Cl, 3.19 Found: C, 73.55; H, 6.66; N, 9.63.

2,3-Dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (9a)[9]

Pyrrolidin-2-one (1.00 g, 12.25 mmol) and isatoic anhydride **1a** (1.00 g, 6.13 mmol) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The sealed reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 130 °C (temperature monitored by a built-in infrared sensor), power 10–200 W, and pressure 50–100 psi for 1 hr. The residue was purified by column chromatography using (2:1) CH_2Cl_2: acetone as eluent system to afford the title compound as a yellow solid (900 mg, 79% yield) mp 105-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.25 – 2.11 (m, 2H, CH_2*C*$H_2$$CH_2$), 3.08 (t, *J* = 7.9 Hz, 2H, C*C*$H_2$$CH_2$), 4.14 – 3.96 (m, 2H, N*C*$H_2$$CH_2$), 7.50 – 7.43 (m, 1H, arom.), 7.60 (d, *J* = 7.7 Hz, 1H, arom.), 7.78 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, arom.), 8.11 (dd, *J* = 7.9, 1.4 Hz, 1H, arom.) ppm. Spectral data is in accordance with literature data.[10]

2,3-Dihydro-7-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (9b)

Pyrrolidin-2-one (950 mg, 11.17 mmol) and 6-hydroxy-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **1b** (1.00 g, 5.58 mmol) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The sealed reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 130 °C (temperature monitored by a built-in infrared sensor), power 10–200 W, and pressure 50–100 psi for 1 hr. The residue was purified by column chromatography using (2:1) CH_2Cl_2 : acetone as eluent system to afford the title compound as a yellow solid (900 mg, 80% yield). mp 248-251 °C. ^{1}H NMR (300 MHz, DMSO) δ: 2.21 – 2.10 (m, 2H, $CH_2CH_2CH_2$), 3.08 – 2.94 (m, 2H, CCH_2CH_2), 4.12 – 3.94 (m, 2H, NCH_2CH_2), 7.23 (dd, *J* = 8.8, 2.9 Hz, 1H, arom.), 7.39 (d, *J* = 2.8 Hz, 1H, arom.), 7.47 (d, *J* = 8.8 Hz, 1H, arom.), 9.95 (s, 1H, COH) ppm. Spectral data is in accordance with literature data.[10]

7-(Benzyloxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (9c)

2,3-dihydro-7-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **9b** (400 mg, 1.98 mmol), K_2CO_3 (300 mg, 2.18 mmol) and benzyl bromide (510 mg, 2.97 mmol) were dissolved in DMF (10 mL) at room temperature and stirred for an additional 12 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with saturated brine (2 x 10 mL), dried over anhydrous MgSO4, and concentrated under reduced pressure. The residue was purified by column chromatography using (20:1) ethyl acetate: methanol as eluent system to afford the title compound as a yellow solid (450 mg, 78% yield). mp 188-190 °C. ESI-MS: 293.0 m/z $[MH]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.39 – 2.20 (m, 2H, $CH_2CH_2CH_2$), 3.25 – 3.08 (m, 2H, CCH_2CH_2), 4.30 – 4.11 (m, 2H, NCH_2CH_2), 5.17 (s, 2H, $COCH_2$), 7.44 – 7.29 (m, 5H, arom.), 7.47 (dd, *J* = 8.2, 1.2 Hz, 1H, arom.), 7.65 – 7.58 (m, 1H, arom.), 7.75 (d, *J* = 2.9 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.69 ($CH_2CH_2CH_2$), 32.25 (CCH_2CH_2), 46.57 (NCH_2CH_2), 70.51($COCH_2$), 107.14 (arom.), 124.90 (arom.), 127.71 (arom.), 128.20 (arom.), 128.24 (arom.), 128.66 (arom.), 131.25 (arom.), 136.34 (arom.), 149.10 (arom.), 157.18 (arom.), 157.41 (NCN), 160.76 (CO) ppm.

4-Methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-4-ium iodide (10a)

A mixture of 2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **9a** (500 mg, 2.70 mmol) and (1.68 mL, 27.0 mmol,) of methyl iodide in 40 ml of dioxane was heated in sealed tube at 90 °C for 12 hr. After cooling, the product was filtered off and washed with dichloromethane to afford the title compound as a yellow solid (750 mg, 85% yield) mp 285-289 °C. ESI-MS: 201.0 m/z $[M]^+$. ^{1}H NMR (300 MHz, DMSO) δ: 2.44 – 2.25 (m, 2H, CCH_2CH_2), 3.74 (dd, *J* = 14.6, 6.7 Hz, 2H, $CH_2CH_2CH_2$), 4.02 (s, 3H, NCH_3), 4.30 (dd, J = 16.4, 8.7 Hz, 2H, NCH_2CH_2), 7.91 – 7.81 (m, 1H, arom.), 8.16 (tdd, *J* = 12.0, 7.6, 4.5 Hz, 2H, arom.), 8.35 (dd, *J* = 7.9, 1.2 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 17.80 (CCH_2CH_2), 33.92 ($CH_2CH_2CH_2$), 38.03 (NCH_3), 50.18 (NCH_2CH_2), 118.01 (arom.), 119.20 (arom.), 127.39 (arom.), 129.17 (arom.), 136.70 (arom.), 139.18 (arom.), 157.21 (NCN), 166.90 (CO) ppm. Synthetic procedure is described in ref. 11.

7-(Benzyloxy)-4-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-4-ium iodide (10c)

A mixture of 7-(benzyloxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **9c** (1.03 mmol, 300 mg) and (640 µL, 10.3 mmol) of methyl iodide in 20 mL of dioxane was heated in sealed tube at 90 °C for 12 h. After cooling, the product was filtered off and washed with dichloromethane to afford the title compound as a yellow solid (380 mg, 85% yield). mp 217-220 °C. ESI-MS: 307.1 m/z $[M]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.44 – 2.24 (m, 2H, C*CH*$_2$CH$_2$), 3.81 – 3.60 (m, 2H, CH$_2$*CH*$_2$CH$_2$), 4.00 (s, 3H, NCH_3), 4.28 (dd, *J* = 16.2, 8.5 Hz, 2H, N*CH*$_2$CH$_2$), 5.37 (s, 2H, OCH_2), 7.59 – 7.28 (m, 5H, benzyl CH's), 7.81 (dt, *J* = 9.2, 2.9 Hz, 2H, arom.), 8.08 (d, *J* = 9.2 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.96 (C*CH*$_2$CH$_2$), 33.45 (CH$_2$*CH*$_2$CH$_2$), 38.13 (NCH_3), 50.11 (N*CH*$_2$CH$_2$), 69.99 (OCH_2), 109.44 (arom.), 120.04 (arom.), 120.64 (arom.), 125.44 (arom.), 127.70 (arom. Benz.), 128.04 (arom. Benz.), 128.45 (arom. Benz.), 133.32 (arom.), 135.92 (arom.), 156.95 (arom.), 158.08 (NCN), 164.76 (CO) ppm. Synthetic procedure is described in ref. 11.

1,2,3,3a,4,9-Hexahydro-4-methylpyrrolo[2,1-*b*]quinazoline (11a)

A suspension of 4-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-4-ium iodide **10a** (500 mg, 1.52 mmol) in 75 mL of dry THF was added drop wise to a suspension of $LiAlH_4$ (290 mg, 7.62 mmol) in 75 mL of dry THF under an atmosphere of nitrogen. The mixture was heated to reflux for 2 hr. The excess of reducing agent was destroyed by slowly adding water, the reaction mixture then extracted with ethyl acetate, the organic extracts were dried and concentrated under vacuum. The residue was purified by column chromatography using (20:1) ethyl acetate: methanol as an eluent system to afford the title compound as a colorless oil (330 mg, 74% yield). ESI-MS: 188.2 m/z $[M]^+$. ^{1}H NMR (300 MHz, DMSO) δ: 2.04 – 1.74 (m, 3H, CH*CH*$_2$*CH*$_2$CH$_2$), 2.23 – 2.04 (m, 1H, CHCH$_2$*CH*$_2$CH$_2$), 2.70 – 2.55 (m, 1H, N*CH*$_2$), 2.81 (s, 3H, NCH_3), 3.16 – 2.97 (m, 1H, N*CH*$_2$), 3.95 – 3.80 (m, 3H, CCH_2N, NCHN), 6.70 (dd, *J* = 7.6, 5.9 Hz, 2H, arom.), 7.00 – 6.91 (m, 1H, arom.), 7.13 (td, J = 8.2, 1.5 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.97 (CH$_2$*CH*$_2$CH$_2$), 30.71 (CH*CH*$_2$CH$_2$), 34.71 (NCH_3), 51.86 (N*CH*$_2$CH$_2$), 51.92 (C*CH*$_2$N), 78.29 (N*CH*N), 112.38 (arom.), 117.41 (arom.), 121.52 (arom.), 126.80 (arom.), 127.61 (arom.), 146.01 (arom.) ppm. Elem. Anal. ($C_{12}H_{16}N_2$ + 0.1 CH_3OH) Calc.: C, 75.90; H, 8.63; N, 14.63; O, 0.84 Found: C, 75.73; H, 8.30; N, 14.68. Synthetic procedure is described in ref. 12.

7-(Benzyloxy)-1,2,3,3a,4,9-hexahydro-4-methylpyrrolo[2,1-*b*]quinazoline (11c)

A suspension of 7-(benzyloxy)-4-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-4-ium iodide **10c** (380 mg, 0.88 mmol) in 50 mL of dry THF was added dropwise to a suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in 75 mL of dry THF under an atmosphere of nitrogen. The mixture was heated to reflux for 3 hr. The excess of reducing agent was destroyed by slowly adding water, the reaction mixture then extracted with ethyl acetate, the organic extracts were dried and concentrated under vacuum. The residue was purified by column chromatography using (20:1) ethyl acetate: methanol as eluent system to afford the title compound as a beige solid (200 mg, 78% yield). mp 59-61°C. ESI-MS: 295.1 m/z $[MH]^+$. ^{1}H NMR (300 MHz, DMSO) δ: 2.03 – 1.71 (m, 3H, CH*CH*$_2$*CH*$_2$CH$_2$), 2.20 – 2.03 (m, 1H, CH*CH*$_2$CH$_2$), 2.66 – 2.49 (m, 1H, NCH_2), 2.76 (s, 3H, NCH_3), 3.09 (m,

1H, NCH_2), 3.67 (t, *J* = 6.1 Hz, 1H, NCHN), 3.83 (q, *J* = 14.6 Hz, 2H, CCH_2N), 4.99 (s, 2H, OCH_2benz), 6.72 – 6.62 (m, 2H, arom.), 6.84 – 6.75 (m, 1H, arom.), 7.46 – 7.27 (m, 5H, benzyl) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 20.96 ($CH_2CH_2CH_2$), 30.62($CHCH_2CH_2$), 35.45 (NCH_3), 52.25(NCH_2CH_2), 52.48 (CCH_2N), 70.68 (OCH_2), 78.87 (N*CH*N), 113.95 (arom.), 113.98 (arom.), 113.98 (arom.), 123.35 (arom.), 127.53 (arom.), 127.81 (arom.), 128.52 (arom.), 137.53 (arom.), 140.70 (arom.), 151.31 (arom.) ppm. Synthetic procedure is described in ref. 12.

1,2,3,3a,4,9-Hexahydro-4-methylpyrrolo[2,1-*b*]quinazolin-7-ol (12)

To a mixture of 7-(benzyloxy)-1,2,3,3a,4,9-hexahydro-4-methylpyrrolo[2,1-*b*]quinazoline **11c** (170 mg, 0.58 mmol) and 10 % Pd-C (20 mg) was added 10 mL ethanol. The mixture was stirred at room temperature and under an atmosphere of H_2 for 24 hr. The mixture was filtered over celit to afford the title compound as a beige viscous oil (100 mg, 84% yield). ESI-MS: 205.1 m/z $[M+H]^+$. ^{1}H NMR (300 MHz, MeOD) δ: 2.02 – 1.65 (m, 3H, $CHCH_2CH_2$), 2.16 (dt, *J* = 9.2, 8.3 Hz, 1H, $CHCH_2CH_2$), 2.51 (m, 1H, NCH_2CH_2), 2.73 (s, 3H, NCH_3), 3.11 (m, 1H, NCH_2CH_2), 3.52 – 3.39 (m, 1H, NCHN), 3.71 (dt, *J* = 46.4, 12.3 Hz, 2H, CCH_2N), 6.46 (d, *J* = 2.7 Hz, 1H, arom.), 6.59 (dd, *J* = 8.7, 2.8 Hz, 1H, arom.), 6.68 (d, *J* = 8.8 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, MeOD) δ: 21.52 ($CHCH_2CH_2$), 31.35 ($CHCH_2CH_2$), 36.23 (NCH_3), 53.57 (NCH_2CH_2), 54.14 (CCH_2N), 80.92 (N*CH*N), 114.60 (arom.), 115.50 (arom.), 116.00 (arom.), 124.76 (arom.), 140.86 (arom.), 151.11 (arom.) ppm. Elem. Anal. ($C_{12}H_{16}N_2O$ + 0.1 $CHCl_3$) Calc.: C, 67.22; H, 7.51; N, 12.96; O, 7.40 Found: C, 67.61; H, 7.74; N, 13.21.

General procedure for synthesis of tricyclic carbamates

Triethylamine (1.1 equiv) was added to a stirred solution of 1,2,3,3a,4,9-hexahydro-4-methylpyrrolo[2,1-*b*]quinazolin-7-ol **12** (1 equiv) in dichloromethane and stirred at ambient temperature for 15 min. Isocyanate (1.1 equiv) was added and stirred for another 1 to 2 hours at room temperature. Upon completion (TLC), the reaction mixture was diluted with dichloromethane, washed with water and brine, dried and evaporated under reduced pressure. The crude compound was purified by preparative thin layer chromatography (dichloromethane : MeOH, 20:1) to get the carbamate compounds **13a-d.** Synthetic procedure is described in ref. 8.

1,2,3,3a,4,9-Hexahydro-4-methylpyrrolo[2,1-*b*]quinazolin-7-yl heptylcarbamate (13a)

The reaction was carried out according to the general procedure, starting from 1,2,3,3a,4,9-hexahydro-4-methylpyrrolo[2,1-*b*]quinazolin-7-ol **12** (50 mg, 0.24 mmol) and 1-isocyanatoheptane (18 mg , 0.26 mmol). The title compound was obtained as a yellow oil (55 mg, 83%). ESI-MS: 346.2 m/z $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94 – 0.81 (m, 3H, CH_2CH_3), 1.39 – 1.20 (m, 8H, $CH_3(CH_2)_4CH_2$), 1.50 (dd, *J* = 19.7, 12.9 Hz, 2H, $NHCH_2CH_2$), 1.97 – 1.72 (m, 3H, $CHCH_2CH_2$), 2.19 – 1.98 (m, 1H, $CHCH_2CH_2$), 2.66 – 2.52 (m, 1H, NCH_2CH_2), 2.77 (s, 3H, NCH_3), 3.13 – 2.96 (m, 1H, NCH_2CH_2), 3.20 (dd, *J* = 13.3, 6.8 Hz, 2H, $NHCH_2CH_2$), 3.90 – 3.71 (m, 3H, CCH_2N, NCHN), 5.07 (t, *J* = 5.5 Hz, 1H, NH), 6.61 (d, *J* = 8.8 Hz, 1H, arom.), 6.72 (d, *J* = 2.7 Hz, 1H, arom.), 6.85 (dd, *J* = 8.8, 2.7 Hz, 1H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.10 (CH_2CH_3), 21.01($CH_2CH_2CH_2$), 22.61 (hept.CH_2), 26.73 (hept.CH_2), 28.96 (hept.CH_2), 29.87 (hept.CH_2), 30.66 ($CHCH_2CH_2$), 31.76 (hept.CH_2), 34.98 (NCH_3), 41.27 (hept.CH_2), 51.74 (NCH_2CH_2), 51.83 (CCH_2N), 78.29

(NCHN), 112.85 (arom.), 119.9 (arom.), 120.39 (arom.), 122.37 (arom.), 142.37 (arom.), 143.61 (arom.), 155.37 (CO) ppm. Elem. Anal. ($C_{20}H_{31}N_3O_2$ + 0.7 CH_3OH) Calc.: C, 67.58; H, 9.26; N, 11.42; O, 11.74 Found: C, 67.62; H, 9.26; N, 11.41.

4-Methyl-1,2,3,3a,4,9-hexahydropyrrolo[2,1-*b*]quinazolin-7-yl (3-methoxyphenyl)carbamate (13b)

The reaction was carried out according to the general procedure, starting from 1,2,3,3a,4,9-hexahydro-4-methylpyrrolo[2,1-*b*]quinazolin-7-ol **12** (50 mg, 0.24 mmol) and 1-isocyanato-3-methoxybenzene (40 mg , 0.26 mmol). The title compound was obtained as a light brown viscous oil (70 mg, 83%). tR: 1.6360 min, HRESIMS $[C_{20}H_{23}N_3O_3+H]^+$, *m/z*, calc: 354.1812; found: 354.1826. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.00 – 1.73 (m, 3H, CH*CH*$_2$*CH*$_2$), 2.21 – 2.00 (m, 1H, CH*CH*$_2$*CH*$_2$), 2.72 – 2.58 (m, 1H, N*CH*$_2$CH$_2$), 2.79 (s, 3H, NCH_3), 3.04 (m, 1H, N*CH*$_2$CH$_2$), 3.78 (s, 3H, OCH_3), 3.91 – 3.82 (m, 3H, C*CH*$_2$N, NCHN), 6.70 – 6.59 (m, 2H, arom.), 6.79 (t, *J* = 4.7 Hz, 1H, arom.), 6.97 – 6.84 (m, 2H, arom.), 7.06 (s, 1H, NH), 7.20 (dd, *J* = 10.7, 5.5 Hz, 2H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.07 (CH$_2$*CH*$_2$CH$_2$), 30.59 (CH*CH*$_2$CH$_2$), 34.95 (NCH_3), 51.55 (N*CH*$_2$CH$_2$), 51.81 (C*CH*$_2$N), 55.30 (OCH_3), 78.25 (NCHN), 109.73 (arom.), 112.90 (arom.), 119.95 (arom.), 119.94 (arom.), 120.50 (arom.), 120.53 (arom.), 122.41 (arom.), 129.78 (arom.), 138.90 (arom.), 141.74 (arom.), 143.96 (arom.), 152.34 (CO), 160.32 (*C*OCH_3) ppm. Elem. Anal. ($C_{20}H_{23}N_3O_3$ + 0.6 CH_3OH) Calc.: C, 66.40; H, 6.87; N, 11.28; O, 15.46 Found: C, 66.00; H, 6.63; N, 10.98.

4-Methyl-1,2,3,3a,4,9-hexahydropyrrolo[2,1-*b*]quinazolin-7-yl o-tolylcarbamate (13c)

The reaction was carried out according to the general procedure, starting from 1,2,3,3a,4,9-hexahydro-4-methylpyrrolo[2,1-*b*]quinazolin-7-ol **12** (50 mg, 0.24 mmol) and 1-isocyanato-2-methylbenzene (35 mg, 0.26 mmol). The title compound was obtained as a light yellow viscous oil (66 mg, 82%). tR: 1.6517 min, HRESIMS $(C_{20}H_{23}N_3O_2+H)^+$, *m/z*, calc: 338.1863; found: 338.1872. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.99 – 1.75 (m, 3H, CH*CH*$_2$*CH*$_2$), 2.15 – 2.04 (m, 1H, CH*CH*$_2$*CH*$_2$), 2.32 (s, 3H, CCH_3), 2.70 – 2.52 (m, 1H, N*CH*$_2$CH$_2$), 2.80 (s, 3H, NCH_3), 3.12 – 2.98 (m, 1H, N*CH*$_2$CH$_2$), 3.87 (m, 3H, C*CH*$_2$N, NCHN), 6.66 (d, *J* = 8.8 Hz, 1H, arom.), 6.73 (s, 1H, arom.), 6.82 (t, *J* = 2.8 Hz, 1H, arom.), 6.94 (dd, *J* = 8.8, 2.8 Hz, 1H, arom.), 7.08 (m, 1H, arom.), 7.25 – 7.15 (m, 2H, arom.), 7.84 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.73 (CCH_3), 21.05 (CH$_2$*CH*$_2$CH$_2$), 30.63 (CH*CH*$_2$CH$_2$), 34.94 (NCH_3), 51.61 (N*CH*$_2$CH$_2$), 51.81 (C*CH*$_2$N), 78.25 (NCHN), 112.86 (arom.), 119.89 (arom.), 120.43 (arom.), 122.40 (arom.), 124.39 (arom.), 125.52 (arom.), 126.99 (arom.), 130.46 (arom.), 130.83 (arom.), 135.62 (arom.), 141.90 (arom.), 143.91 (arom.), 152.34 (CO) ppm. Elem. Anal. ($C_{20}H_{23}N_3O_2$ + 0.8 CH_3OH) Calc.: C, 68.81; H, 7.27; N, 11.57; O, 12.34 Found: C, 68.54; H, 6.88; N, 11.87.

4-Methyl-1,2,3,3a,4,9-hexahydropyrrolo[2,1-*b*]quinazolin-7-yl (4-isopropylphenyl)carbamate (13d)

The reaction was carried out according to the general procedure, starting from 1,2,3,3a,4,9-hexahydro-4-methylpyrrolo[2,1-*b*]quinazolin-7-ol **12** (50 mg, 0.24 mmol) and 1-isocyanato-4-isopropylbenzene (42 mg, 0.26 mmol). The title compound was obtained as a white solid (70 mg, 80%). mp 171 - 173 °C. tR: 2.1041 min, HRESIMS $(C_{22}H_{27}N_3O_2+H)^+$, *m/z*, calc: 366.2176; found: 366.2187. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, *J* =

6.9 Hz, 6H,CH ($C\mathit{H}_3$)$_2$), 2.01 – 1.74 (m, 3H, CH$\mathit{CH}_2\mathit{CH}_2$), 2.18 – 2.04 (m, 1H, CH$\mathit{CH}_2\mathit{CH}_2$), 2.67 (m, 1H, N$\mathit{CH}_2CH_2$), 2.80 (s, 3H, NCH$_3$), 2.89 (dq, J = 13.8, 6.9 Hz, 1H, CH(CH$_3$)$_2$), 3.01 – 3.12 (m, 1H, NCH_2CH$_2$), 3.99 – 3.78 (m, 3H, CCH_2N, NCHN), 6.66 (d, J = 8.8 Hz, 1H, arom.), 6.80 (d, J = 2.7 Hz, 1H, arom.), 6.98 – 6.83 (m, 2H, arom.), 7.25 – 7.10 (m, 2H, arom.), 7.35 (d, J = 8.4 Hz, 2H, arom.) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.11 (CH$_2\mathit{CH}_2$CH$_2$), 24.06 (CH (CH_3)$_2$), 30.57(CHCH_2CH$_2$), 33.53 (CH (CH$_3$)$_2$), 34.95 (NCH$_3$), 51.50 (NCH_2CH$_2$), 51.82 (CCH_2N), 78.26 (NCHN), 112.94 (arom.), 119.97 (arom.), 120.55 (arom.), 122.37 (arom.), 127.02 (arom.), 127.02 (arom.), 127.02 (arom.), 135.29 (arom.), 141.94 (arom.), 143.84 (arom.), 157.50 (CO) ppm. Elem. Anal. Elem. Anal. ($C_{22}H_{27}N_3O_2$ + 0.1 CH_3OH) Calc.: C, 72.00; H, 7.49; N, 11.40; O, 9.11 Found: C, 71.79; H, 7.19; N, 11.42.

Enzyme inhibition

Acetyl- and butyrylcholinesterase inhibition assay

AChE (E.C.3.1.1.7, Type VI-S, from Electric Eel) and BChE (E.C.3.1.1.8, from equine serum) were purchased from Sigma-Aldrich (Steinheim, Germany). DTNB (Ellman's reagent), ATC and BTC iodides were obtained from Fluka (Buchs, Switzerland).

The assay was performed as described in the following procedure [cf. reference 9 in the main article]: stock solutions of the test compounds were prepared in ethanol, 100 µL of which gave a final concentration of 10-3 M when diluted to the final volume of 3.32 mL. The highest concentration of the test compounds applied in the assay was 10-4 M (10 % EtOH in the stock solution did not influence enzyme activity). In order to obtain an inhibition curve, at least five different concentrations (normally 10^{-4} – 10^{-9} M) of the test compound were measured at 25 °C and 412 nm, each concentration in triplicate.

For buffer preparation, 1.36 g of potassium dihydrogen phosphate (10 mmol) were dissolved in 100 mL of water and adjusted with NaOH to pH = 8.0 ± 0.1. Enzyme solutions were prepared to give 2.5 units mL-1 in 1.4 mL aliquots. Furthermore, 0.01 M DTNB solution, 0.075 M ATC and BTC solutions, respectively, were used. A cuvette containing 3.0 mL of phosphate buffer, 100 µL of the respective enzyme, and 100 µL of the test compound solution was allowed to stand for 4.5 min, then 100 µL of DTNB were added, and the reaction was started by addition of 20 µL of the substrate solution (ATC/BTC). The solution was mixed immediately, and exactly 2 min after substrate addition the absorption was measured. For the reference value, 100 µL of water replaced the test compound solution. For determining the blank value, additionally 100 µL of water replaced the enzyme solution. The inhibition curve was obtained by plotting the percentage enzyme activity (100% for the reference) versus logarithm of test compound concentration.

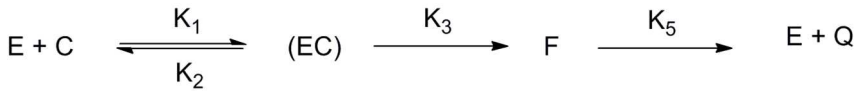
We evaluated putative changes in inhibitory activities of some of our most potent carbamate structures by elongating incubation times from 4.5 min to 20 min.

Table 1: BChE inhibition results after 20 min incubation time.

Compound	IC_{50}(BChE), µM ± SEM
Physostigmine	0.034 ± 0.123
7	0.040 ± 0.035
8b	0.056 ± 0.025
8d	0.11 ± 0.306

Kinetic studies

The inhibition of AChE by carbamates involves a reversible complex (EC) formation, followed by production of a covalent adduct (F) by carbamoylation of the enzyme. The carbamoylated enzyme is then hydrolyzed to regenerate the free enzyme [cf. ref. 17 of the main article]. The whole mechanism can be represented as follows:



(1)

After the reversible complex formation (EC; equilibrium constant: $K_C=k_2/k_1$), the carbamoylation phase of the reaction is considerably more rapid than the decarbamoylation phase (i.e., $k_3 >> k_5$). Therefore, we investigated the carbamoylation phase of the inhibition process, by determining k_3 in order to determine the velocity of the carbamoylation process in comparison to physostigmine. A stopped time assay was performed to characterize the carbamoylation step, AChE or BChE and inhibitor were mixed in the assay buffer, and aliquots were transferred to a spectrophotometer cell at various times for the determination of the residual AChE or BChE activity. The data were fitted to the following equation

$$R = R_0 \exp(-k_{obs}t) + R_\alpha \qquad (2)$$

Where R, R_0, and R_α are ratios of the inhibited enzyme activity (v_i) to the control activity (v_0) at times t, 0, and α, respectively. In this way, the values of the observed pseudo-first-order inhibition rate constant (k_{obs}) for each concentration of inhibitor were obtained. Double reciprocal plots of k_{obs} versus inhibitor concentration [I] were then used to compute k_3 and K_C from the intercept and from the ratio of the slope to the intercept, respectively, according to the equation:

$$1/k_{obs} = K_C/k_3 \; 1/[I] + 1/k_3 \qquad (3)$$

The equilibrium constant of the inhibitor-ChE complexes (K_C) and rate constants (k_3) of **8a**, **8b**, and physostigmine were determined from eq (3) following the method reported by Feaster and Quinn.[13]

Stability study

The stability of selected test compounds was investigated in aqueous phosphate buffer (pH 8) at different incubation times (0, 20, and 40 min, respectively) at which also the kinetic studies were performed. Two target compounds (**8a** and **8b**) were investigated as representatives.

LC/MS analysis:

HPLC experiments were carried out on an Agilent Technologies 1240 UHPLC. Electrospray mass spectrometry measurements were performed on a MSD quadrupole mass spectrometer (Agilent Technologies, Palo Alto, CA, USA) interface to the 1240 HPLC system. MS measurements were acquired simultaneously in positive ion full

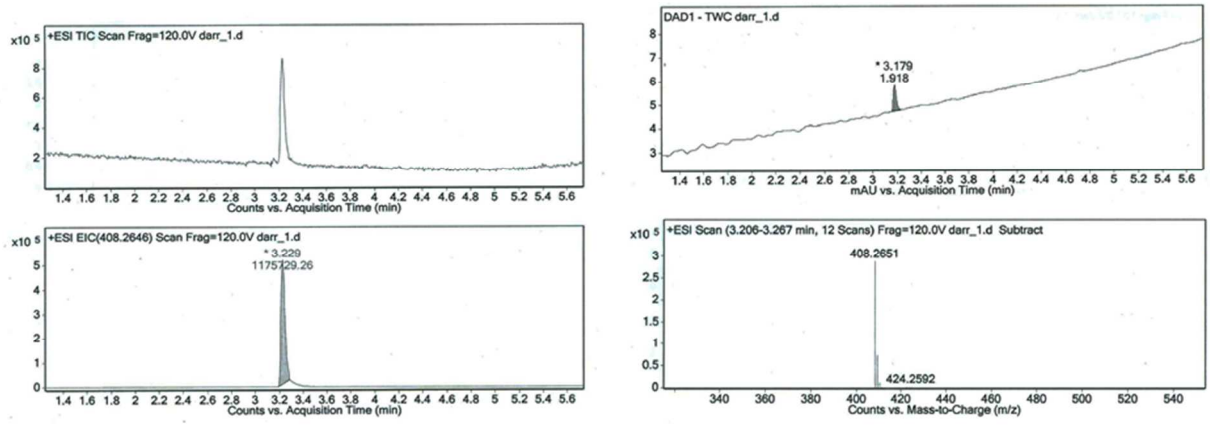
scan modes from 100 to 1400, using 120V of fragmentator voltage to determine the molecular weights of the degradants. Drying gas flow and temperature were 8 L/min and 320 °C, respectively. The nebulizador pressure was 35 psi and the capillary voltage 3500V. Data acquisition and integration for LC–UV and MS detection were collected using Mass Hunter B05.00 software (Agilent Technologies).

Sample preparation:

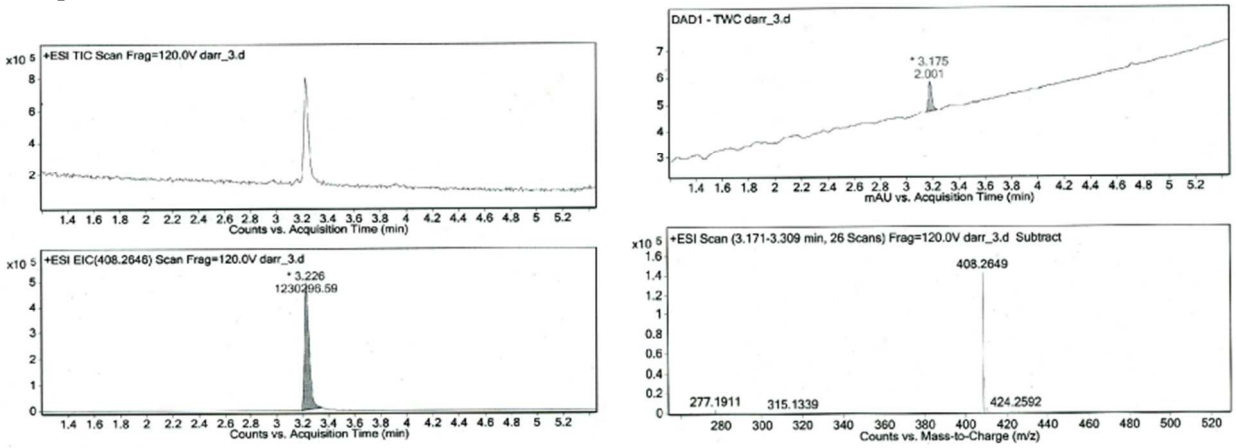
A 100 µM stock solution of compounds **8a** and **8b**, respectively, was prepared by dilution of a 100 µL solution of **8a** or **8b** in ethanol/water 1/1 mixture to 3220 µL phosphate buffer (pH 8) in the same way as preparing stock solutions for enzyme testing.

Chromatograms:

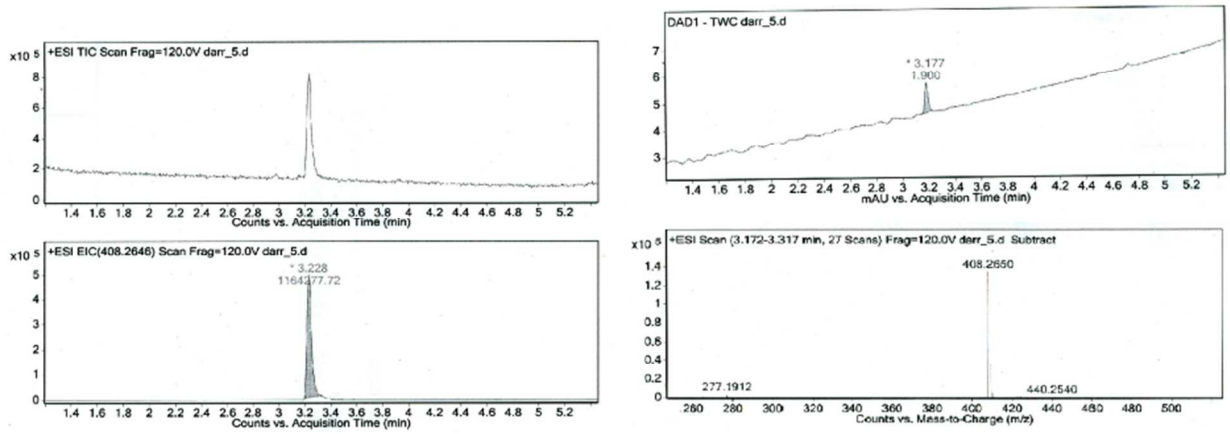
Compound **8b** at t= 0 min.



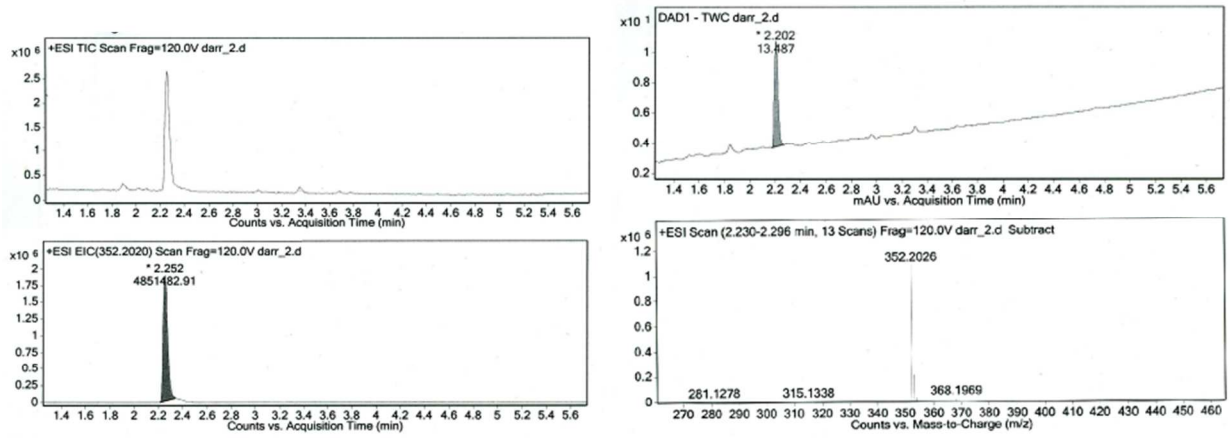
Compound **8b** at t= 20 min.



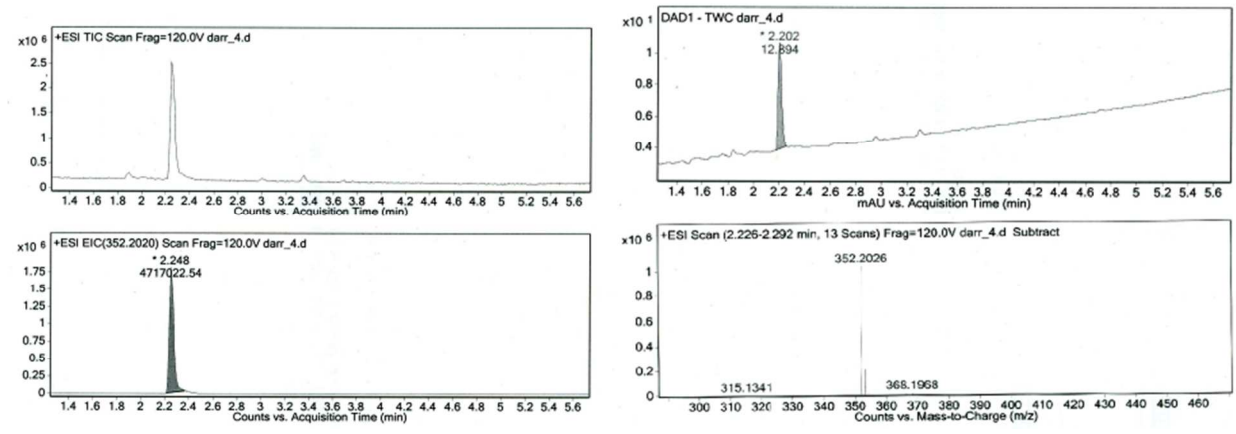
Compound **8b** at t= 40 min.



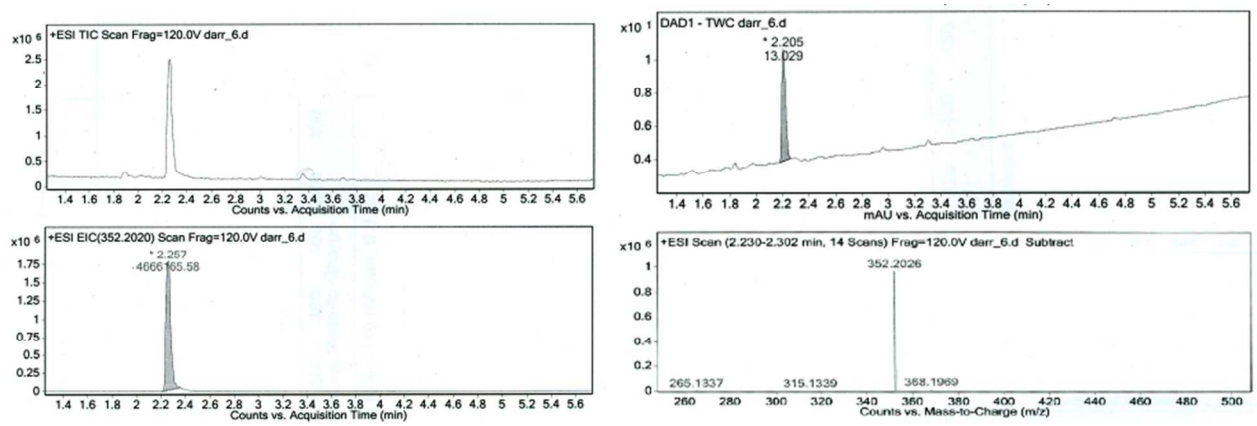
Compound **8a** at t= 0 min.



Compound **8a** at t= 20 min.



Compound **8a** at t= 40 min.



Results

Compounds **8a** and **8b** are totally stable in aqueous phosphate buffer (pH 8) at incubation times 0, 20, and 40 min, respectively, i. e. no decarbamoylation or hydrolysis of the heterocyclic aminal structure could be observed.

Cells and cell culture

HT-22 cells[14,15] were derived from murine hippocampal tissue.[16]

HT-22 cells are grown in high glucose Dulbecco's Modified Eagle's Medium (DMEM, Invitrogen, Karlsruhe, Germany) supplemented with 10 % (v/v) heat-inactivated fetal calf serum (FCS) (Biochrom, Berlin, Germany). Cells were kept under standard cell culture conditions at 37 °C under 5 % CO_2 in a humidified incubator. Cells were subcultured every 2 days.

Neuroprotection and neurotoxicity assay

Cell viability was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay[17,18] according to reference 11a in the main text. Briefly, cells were seeded in 96-well plates at a densitiy of $5x10^3$ per well and cultured for 24 hr. Subsequently cells were incubated for another 24 hr either with medium, compounds, or solvent only in presence (neuroprotection assay) or absence (neurotoxicity assay) of 5 mM glutamate (Monosodium-L-glutamate, Merck, Darmstadt, Germany). Quercetin (Sigma, Steinheim, Germany) in a concentration of 25 µM served as positive control in the neuroprotection assay. MTT (Sigma, Steinheim, Germany) solution (4 mg/mL in PBS) was diluted 1:10 with medium and the mixture was added to the wells after removal of previous medium. The plates were then incubated for another 3 hr. Afterwards, supernatants were removed and 100 µL of lysis buffer (10% SDS, pH 4.1) was added to the wells. Absorbance at 560 nM was determined on the next day with a multiwall plate photometer (Spectra Fluor Plus, Crailsheim, Germany). Results of cell viability are expressed as percentage to untreated control cells. All compounds were dissolved in DMSO and diluted with fresh medium. DMSO concentration in final dilutions was ≤ 0.1%.

Statistical Analysis:

Data are expressed as mean +/- SD of at least 3 different independent experiments. Data were subjected to one-way ANOVA followed by Dunnett's multiple comparison post test using GraphPad Prism 4 Software. (Levels of significance * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)

Additional graphs for neuroprotection and neurotoxicity.

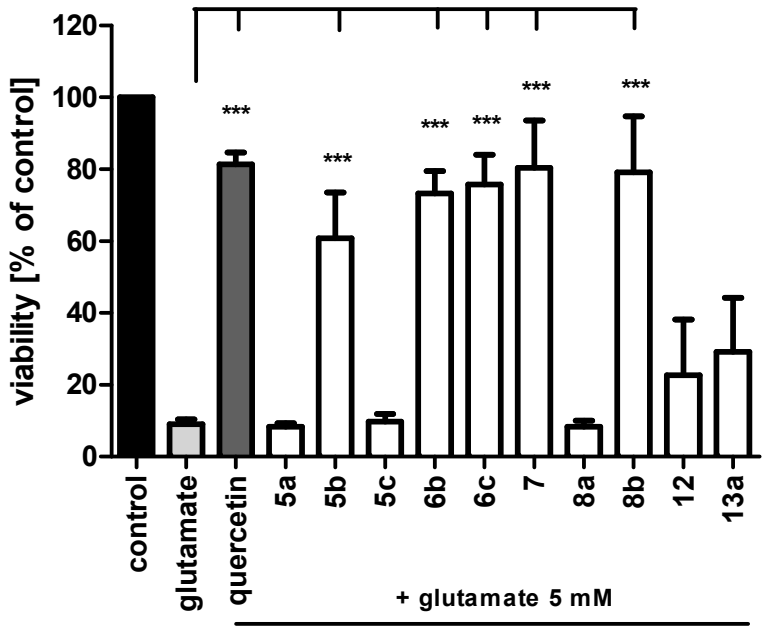


Figure 1: Evaluation of neuroprotection of target compounds at 5 µM against glutamate induced oxidative stress on HT-22 cells via modified MTT assay. Compounds were incubated for 24 h. Results of cell viability are expressed as percentage to untreated control cells. Data were subjected to one-way ANOVA followed by Dunnett's multiple comparison post test using GraphPad Prism 4 Software (Level of significance *** $p < 0.001$).

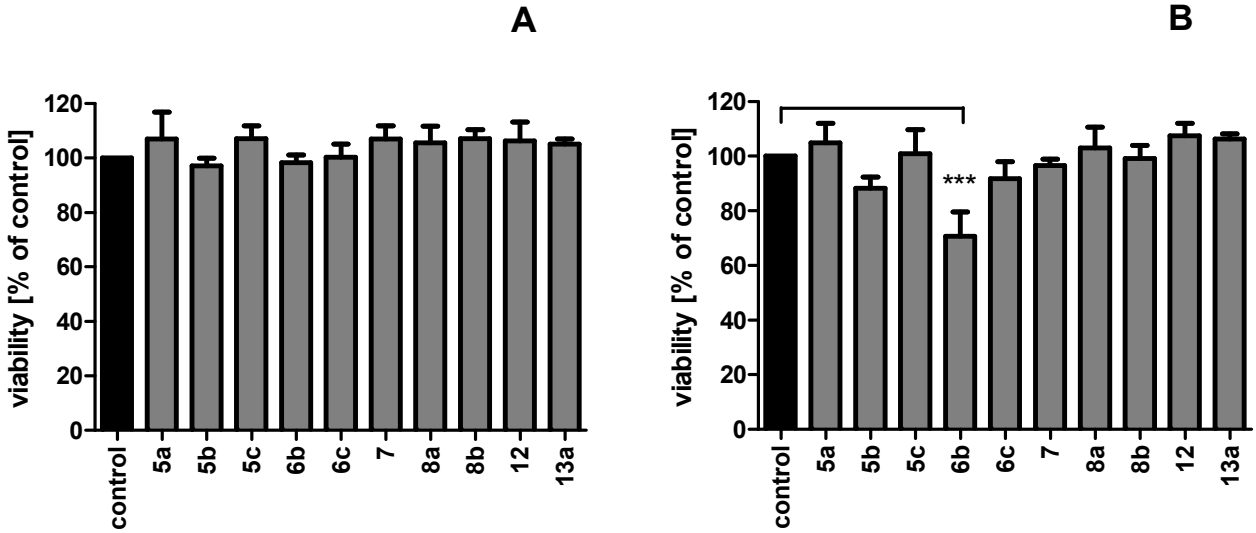


Figure 2: Evaluation of self-toxicity of target compounds at 5 µM (**A**) and 10 µM (**B**) towards HT-22 neuronal cells via MTT assay. Compounds were incubated for 24 h. Results of cell viability are expressed as percentage to untreated control cells. Data were subjected to one-way ANOVA followed by Dunnett's multiple comparison post test using GraphPad Prism 4 Software (Level of significance *** $p < 0.001$).

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