Supporting Information

Design, synthesis and preliminary pharmacological evaluation of new quinoline derivatives as nicotinic ligands

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Available Supporting Information:

Experimental details of the synthesis of compounds **3**-**5**.

Assessment of enantiomeric excess

Table of elemental analysis of the new compounds.

Experimental details of the synthesis of compounds 3-5.

Chemistry. All melting points were taken on a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Brucker Avance 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C). Optical rotation was measured at a concentration of 1 g/100 mL (*c* = 1), unless otherwise stated, with a Perkin-Elmer polarimeter (accuracy (0.002°). GC-MS analysis were performed on a Perkin Elmer Turbomass - Autosystem XL; alternatively, mass spectra were recorded on a Linear Ion Trap (LTQ)-Thermo-Finnigan spectrometer. Chromatographic separations were performed on a silica gel column by gravity chromatography (Kieselgel 40, 0.063- 0.200 mm; Merck) or flash chromatography (Kieselgel 40, 0.040-0.063 mm; Merck). Yields are given after purification, unless differently stated. Where analyses are indicated by symbols, the analytical results are within 0.4% of the theoretical values. When reactions were performed under anhydrous conditions, the mixtures were maintained under nitrogen. Compounds were named following IUPAC rules as applied by Beilstein-Institute AutoNom (version 2.1) software for systematic names in organic chemistry.

Synthesis of amines 3a,b. A mixture of 4-(quinolin-6-yl)butynyl methanesulfonate[1] (0.48 g, 1.7 mmol) in isopropanol (5 mL) and an excess (10 mL) of methylamine or dimethylamine (33% solution in ethanol) was heated at 60 °C for 1,5 hr. The solvent was removed under vacuum, and the residue was treated with Et_2O and extracted 3-4 times with a saturated solution of NH_4Cl. The aqueous layers were collected, made alkaline with NaOH (10% solution in H_2O) and extracted with Et_2O. Anhydrification (Na_2SO_4) and removal of the solvent gave the desired compounds **3a** (82% yield) or **3b** (46% yield).

3a [^{1}H]-NMR ($CDCl_3$) δ 1.64 (bs, 1H, NH); 2.51 (s, 3H, NCH_3); 2.67 (t, 2H, *J* = 6.6 Hz, $C{\equiv}CCH_2$); 2.86 (t, 2H, *J* = 6.6 Hz, CH_2N); 7.38 (dd, 1H, *J* = 8.4 Hz, 4.0 Hz, H-3); 7.68 (dd, 1H, *J* = 8.8 Hz, 2.0 Hz, H-7); 7.87 (s, 1H, H-5) 8.00 (d, 1H, *J* = 8.8 Hz, H-8); 8.07 (d, 1H, *J* = 8.4 Hz, H-4); 8.88 (dd, 1H, *J* = 4.0 Hz, 1.6 Hz, H-2) ppm. [^{13}C]-NMR-APT ($CDCl_3$) δ 20.46, 36.07, 50,26, 81.42, 89.54,

121.69,122.07, 128.05, 129.48, 130.99,132.50, 135.68, 147.51, 150.75 ppm. The oxalate salt melted at 187 °C.

3b [^{1}H]-NMR ($CDCl_3$) δ 2.32 (s, 6H, $2CH_3$); 2.64 (s, 4H, CH_2CH_2); 7.38 (dd, 1H, *J* = 8.4 Hz, 4 Hz, H-3); 7.68 (dd, 1H, *J* = 8.8 Hz, 1.6 Hz, H-7); 7.87 (s, 1H, H-5); 8.00 (d, 1H, *J* = 8.8 Hz, H-8); 8.07 (d, 1H, *J* = 8.4 Hz, H-4); 8.87 (dd, 1H, *J* = 4.0 Hz, 2.4 Hz, H-2) ppm. [^{13}C]-NMR-APT ($CDCl_3$) δ 18.55, 45.36, 58,45, 81.02, 89.98, 121.68, 122.29, 128.10, 129.49, 130.93, 132.54, 135.68, 147.57, 150.73 ppm. The oxalate salt melted at 157 °C.

Synthesis of amines 4a,b and 5a,b.

***Cis* and *trans* 4-(6-Quinolinyl)-3-butenol**

To a solution of 4-(quinolin-6-yl)butynyl methanesulfonate[1] (0.2 g, 1 mmol) in an. THF (15 mL), $LiAlH_4$ (0.05 g, 1.5 mmol) was added under N_2. After heating under reflux for 2 hr, the mixture was treated with ice, the solvent was removed under vacuum, and the residue was partitioned between H_2O and Et_2O. The organic layer was collected and dried (Na_2SO_4), the solvent was evaporated under reduced pressure, giving 0.18 g of 1:3 *cis*-*trans* mixture of the alcohols.

[^{1}H]-NMR ($CDCl_3$) δ 2.51-2.55 (m, C*H*$_2$-CH=, 2H*trans*); 2.64-2.67 (m, C*H*$_2$-CH=, 2H*cis*); 3.03 (bs, 1H, OH); 3.77-3.82 (m, CH_2O, 2H*cis* + 2H*trans*); 5.83 (dt, *J* = 11.6 Hz, 7.2 Hz, C*H*=CH_2, 1H*cis*); 6.34 (dt, *J* = 16.0 Hz, 7.2 Hz, C*H*=CH_2, 1H*trans*); 6.59 (d, *J* = 16.0 Hz, C-CH=, 1H*trans*); 6.65 (d, *J* = 12.0 Hz, C-CH=, 1H*cis*); 7.29-7.33 (m, 1H*cis* + 1H*trans*, H-3); 7.55 (s, 1H*trans*, H-5); 7.61-7.71 (m, 2H*cis* + 1H*trans*, aromatics), 7.97-8.05 (m, 2H*cis* + 2H*trans*, aromatics); 8.78 (d, *J* = 4.0 Hz, 1H*trans*, H-2); 8.81 (d, *J* = 4.0 Hz, 1H*cis*, H-2) ppm.

N,N-Dimethyl-4-(6-quinolinyl)-3-butenamine 4b and 5b

To a solution of the cis-trans mixture of alcohols (0.25 g, 1.26 mmol) and anhydrous pyridine (0.85 mL, 10.5 mmol) in ethanol-free $CHCl_3$ (10 mL) cooled a 0°C and kept under N_2 athmosphere, mesyl chloride (0.17 g, 1.51 mmol) was slowly added; the mixture was allowed to warm to rt and

left under stirring for 2 h, then treated with H_2O and extracted with $CHCl_3$. After removal of the solvent, the residue was treated with HCl (0.1 M solution) and extracted with ether; the aqueous layer was made alkaline with NaOH 10 % and extracted with $CHCl_3$. Anhydrification (Na_2SO_4) and removal of the solvent under vacuum gave 0.31 g (89 % yield) of a *cis-trans* mixture of 4-(quinolin-6-yl)but-3-enyl methanesulfonate.

[^{1}H]-NMR ($CDCl_3$) δ 2.70-2.75 (m, C*H*$_2$-CH=, 2H*trans*); 2.83-2.86 (m, C*H*$_2$-CH=, 2H*cis*); 2.99 (s, SO_2CH_3, 3H*cis*); 3.02 (s, SO_2CH_3, 3H*trans*); 4.39-4.32 (m, CH_2OSO_2, 2H*cis* + 2H*trans*); 5.71-5.80 (m, =C*H*-CH_2, 1H*cis*); 6.32 (dt, *J* = 16.0 Hz, 6.8 Hz, =C*H*-CH_2, 1H*trans*); 6.68 (d, J = 16.0 Hz, C-CH=, 1H*trans*); 6.76 (d, J = 11.2 Hz, C-CH=, 1H*cis*); 7.36-7.42 (m, 1H*cis* + 1H*trans*), 7.59-7.70 (m, 2H*cis* + 2H *trans*), 8.00-8.15 (m, 2H*cis* + 2H*trans*) and 8.80-8.90 (m, 2H*cis* + 2H*trans*) (aromatics) ppm.

The mixture of esters was dissolved in isopropanol (3 mL) and heated with dimethylamine (6 mL of a 33 % solution in abs. EtOH) at 60 °C for 1.5 h. The solvent was evaporated, the residue was treated with Et_2O and washed several times with a sat. solution of NH_4Cl. The combined aqueous fractions were made alkaline (10 % NaOH) and extracted with Et_2O. Anhydrification (Na_2SO_4) and removal of the solvent gave 0.16 g (63 % yield) of a residue (3:1 mixture of **4b** and **5b**) which was purified by column chromatography (WE2 as eluent), giving **4b** (0.05g, 19.8 % yield), **5b** (0.027g, 5.4 % yield), and 0.08g of mixed fraction. The amines were transformed into the oxalate salt by treatment with 1 eq. of oxalic acid in ethyl acetate

4b [^{1}H]-NMR ($CDCl_3$), δ 2.35 (s, 6H, $2CH_3$); 2.49-2.52 (m, 4H, CH_2-CH_2); 6.39 (dt, 1H, *J* = 16.0 Hz, 6.4 Hz, =C*H*-CH_2); 6.62 (d, 1H, *J* = 16.0 Hz, C-CH=); 7.36 (dd, 1H, *J* = 8.4 Hz, 4.4 Hz, H-3); 7.65 (s, 1H, H-5); 7.80 (dd, 1H, *J* = 8.8 Hz, 2.0 Hz, H-7); 8.01 (d, 1H, *J* = 8.8 Hz, H-8); 8.09 (d, 1H, *J* = 8.4 Hz, H-4); 8.83 (d, 1H, *J* = 4.4 Hz, H-2) ppm. [^{13}C]-NMR-APT ($CDCl_3$) δ 27.24, 45.48, 59.45, 121.45, 125.01, 127.47, 128.64, 129.66, 130.34, 130.48, 135.93, 135.99, 148, 149.95 ppm. mp (as oxalate salt) 150 °C.

5b [^{1}H]-NMR ($CDCl_3$), δ 2.26 (s, 6H, $2CH_3$); 2.47-2.51 (m, 2H, =CH-C*H*$_2$); 2.60-2.65 (m, 2H, CH_2N); 5.80 (dt, 1H, *J* = 11.6 Hz, 6.8 Hz, =C*H*-CH_2); 6.65 (d, 1H, *J* = 11.6 Hz, C-CH=); 7.38 (dd, 1H, *J* = 8.4 Hz, 4.0 Hz, H-3); 7.65 (d, 1H, *J* = 8.8 Hz, H-7); 7.70 (s, 1H, H-5); 8.05 (d, 1H, *J* = 8.8 Hz, H-8); 8.12 (d, 1H, *J* = 8.4 Hz, H-4); 8.87 (d, 1H, *J* = 4.0 Hz, H-2) ppm. [^{13}C]-NMR-APT ($CDCl_3$) δ 27.06, 45.35, 59.43, 121.45, 127.19, 128.32, 129.37, 129.66, 130.94, 131.42, 135.92, 136.13, 147.43, 150.36 ppm. mp (as oxalate salt) 154 °C,

N-Methyl-4-(6-quinolinyl)-3-butenamine 4a and 5a

The *cis-trans* mixture of the methanesulfonate esters (0.43 g, 1.55 mmol) was treated with methylamine (6 mL) as described for **4b** and **5b**. Usual work up gave **4a** (0.07 g, 21.3 % yield) and **5a** (0.03 g, 9.1 % yield)

4a [^{1}H]-NMR ($CDCl_3$), δ 2.48 (s, 3H, CH_3); 2.48-2.52 (m, 2H, =CH-C*H*$_2$); 2.78 (t, 2H, *J* = 6.8 Hz, CH_2N); 6.37 (dt, 1H, *J* = 15.8 Hz, 7.2 Hz, =C*H*-CH_2); 6.62 (d, 1H, *J* = 15.8 Hz, C-CH=); 7.37 (dd, 1H, *J* = 8.4 Hz, 4.4 Hz, H-3); 7.64 (s, 1H, H-5); 7.81 (dd, 1H, *J* = 8.8 Hz, 1.6 Hz, H-7); 8.01 (d, 1H, *J* = 8.4 Hz, H-8); 8.08 (d, 1H, *J* = 8.4 Hz, H-4); 8.83 (d, 1H, *J* = 4.4 Hz, H-2) ppm. [^{13}C]-NMR-APT ($CDCl_3$) δ 33.57, 36.4, 51.35, 121.52, 125.16, 127.39, 128.65, 129.73, 131.23, 135.82, 135.99, 148.05, 150.06 ppm. The oxalate salt melted at 160 °C.

5a [^{1}H]-NMR ($CDCl_3$), δ 1.78 (bs, 1H, NH); 2.41 (s, 3H, CH_3); 2.58-2.63 (m, 2H, =CH-C*H*$_2$); 2.74 (t, *J* = 7.2 Hz, 2H, CH_2N); 5.78 (dt, 1H, *J* = 11.6 Hz, 7.2 Hz, =C*H*-CH_2); 6.65 (d, 1H, *J* = 11.6 Hz, C-CH=); 7.36 (dd, 1H, *J* = 8.4 Hz, 4.4 Hz, H-3); 7.65 (dd, 1H, *J* = 8.4 Hz, 1.6 Hz, H-7); 7.69 (s, 1H, H-5); 8.04 (d, 1H, *J* = 8.4 Hz, H-8); 8.11 (d, 1H, *J* = 8.4 Hz, H-4); 8.86 (dd, 1H, *J* = 4.4 Hz, 1.6 Hz, H-2) ppm. [^{13}C]-NMR-APT ($CDCl_3$) δ 29.21, 36.44, 51.88, 121.4, 127,2, 128.7, 129.29, 129.95, 130.95, 131.66, 135.88, 136.11, 147.37, 150.3 ppm. The oxalate salt melted at 165 °C**.**

Synthesis of the methiodides.

A solution of the amine in Et_2O (10 mL) was treated with 1-2 mL of iodomethane and left stirring for 24 h in the dark. A solid material was formed, which was collected by filtration, washed with Et_2O and dried under vacuum. The following compounds were obtained.

3c (73% yield) m.p.201°C [^{1}H]-NMR (D_2O) δ 3.14 (t, 2H, J = 6.7 Hz, C=CCH_2); 3.28 (s, 9H, NMe_3); 3.71 (t, 2H, *J* = 6.7 Hz, CH_2N); 7.58-7.62 (m, 1H), 7.78-7.81 (m, 1H), 7.98-8.02 (m, 1H), 8.07-8.08 (m, 1H), 8.34-8.36 (m, 1H), 8.84-8.87 (m, 1H) (aromatics) ppm. [^{13}C]-NMR (D_2O) δ 14.62, 53.39, 64.34, 82.66, 85.75, 120.45, 122.09, 127.54, 127.62, 131.54, 132.19, 137.16, 145.77, 150.69 ppm

4c (50% yield) m.p.205 °C [^{1}H]-NMR (D_2O) δ 2.71-2.77 (m, 2H, =CH-C*H*$_2$); 3.16 (s, 9H, $3CH_3$); 3.47 (t, 2H, *J* = 7.6 Hz, CH_2N); 6.24 (dt, 1H, *J* = 16.4 Hz, 6.8 Hz, =C*H*-CH_2); 6.64 (d, 1H, *J* = 16.4 Hz, C-CH=); 7.43 (dd, 1H, *J* = 8.4 Hz, 4.4 Hz, H-3); 7.58 (s, 1H, H-5); 7.72-7.77 (m, 2H, H-7 e H-8); 8.14 (d, 1H, *J* = 8.4 Hz, H-4); 8.66 (dd, 1H, *J* = 4.4 Hz, 1.6 Hz, H-2) ppm. [^{13}C]-NMR-APT (D_2O) δ 26.45, 53.03, 65.46, 121.8, 125.43, 125.66, 127.53, 128.21, 132.46, 134.99, 137.53, 146.03, 149.69 ppm.

5c (52% yield) m.p.205 °C [^{1}H-]-NMR (D_2O) δ 2.77-2.84 (m, 2H, =CH-C*H*$_2$); 3.07 (s, 9H, $3CH_3$); 3.43-3.49 (m, 2H, CH_2N); 5.72-5.77 (m, 1H, =C*H*-CH_2); 6.77 (d, 1H, *J* = 10.8 Hz, C-CH=); 7.50 (dd, 1H, *J* = 8.2 Hz, 4.2 Hz, H-3); 7.63 (d, 1H, *J* = 8.8 Hz, H-7); 7.69 (s, 1H, H-5); 7.92 (d, 1H, *J* = 8.8 Hz, H-8); 8.27 (d, 1H, *J* = 8.2 Hz, H-4); 8.76 (d, 1H, *J* = 4.2 Hz, H-2). [^{13}C]-NMR-APT (D_2O) δ 22.32, 52.95, 65.58, 121.91, 126.55, 127.4, 128.02, 130.88, 131.64, 132.48, 134.95, 137.64, 145.52, 150.22 ppm.

References

1. Guandalini, L.; Martini, E.; Dei, S.; Manetti, D.; Scapecchi, S.; Teodori, E.; Romanelli, M. N.; Varani, K.; Greco, G.; Spadola, L.; Novellino, E. Design of novel nicotinic ligands through 3D database searching. *Bioorg. Med. Chem.* **2005,** 13, 799-807.

Assessment of enantiomeric excess

The enantiomeric excess was determined by enantiomeric HPLC analysis of the secondary amines (*R*)-(+)- and (*S*)-(-)-**1a** (Fig. 1), obtained by hydrolysis of amides **10** and **9**, and on the tertiary amines (*R*)-(+)- and ()-(-)-**1b** (Fig. 2), obtained by fractional crystallization of the salt of *rac*-**1b** with O,O'-di-p-toluoyl-tartaric acid.

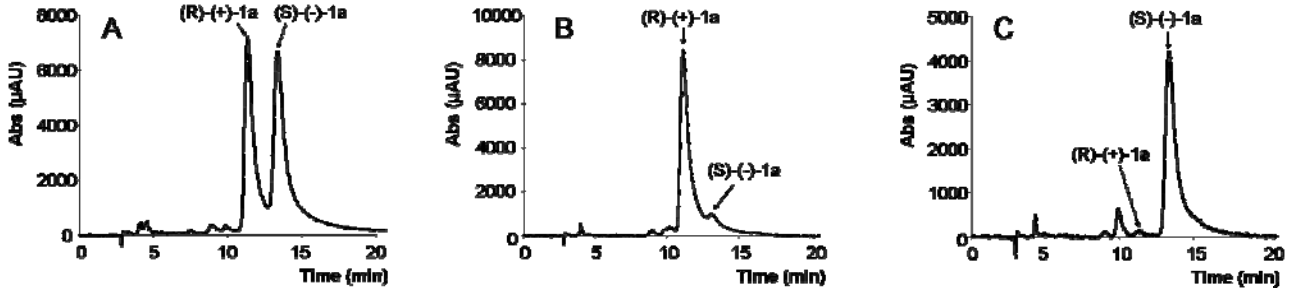

Figure 1. Enantioselective HPLC of *rac*-**1a** (A); enantiomeric excess assay of (*R*)-(+)-**1a** (B) and (*S*)-(-)-**1a** (C) samples.

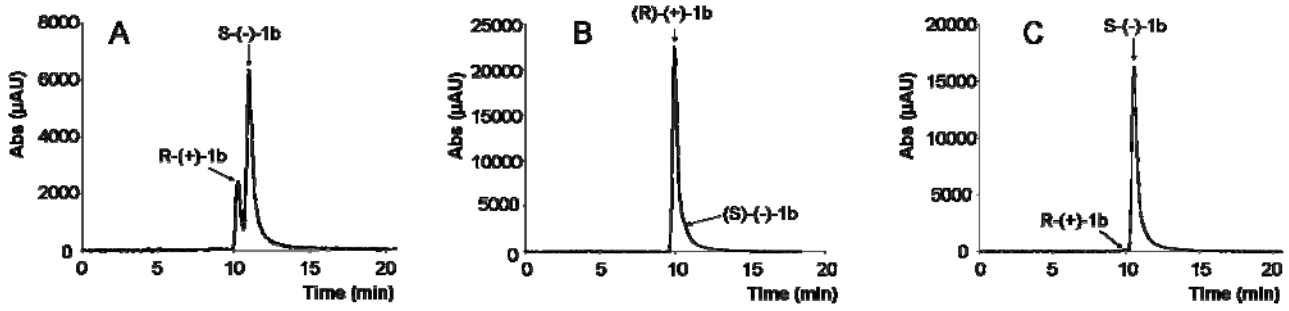

Figure 2. Enantioselective HPLC of enriched of (*S*)-(-)-**1b** sample (A); enantiomeric excess assay of (*R*)-(+)-**1b** (B) and (*S*)-(-)-**1b** (C) samples.

Table of elemental analysis of the new compounds.

N	formula	Calculated			Found		
		C	H	N	C	H	N
(-)-**1a**.oxa	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.72	62.15	5.71	9.62
(+)-**1a**.oxa	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.72	62.16	5.95	9.85
(-)-**1b**.oxa	$C_{16}H_{18}N_2O_4$	63.56	6.00	9.27	63.36	5.75	9.42
(+)-**1b**.oxa	$C_{16}H_{18}N_2O_4$	63.56	6.00	9.27	63.72	5.71	9.20
(-)-**1c**	$C_{15}H_{19}IN_2$	50.86	5.41	7.91	50.99	5.63	7.63
(+)-**1c**	$C_{15}H_{19}IN_2$	50.86	5.41	7.91	50.62	5.20	7.65
(*R*)-**2a**.oxa	$C_{16}H_{18}N_2O_5$	60.37	5.70	8.80	60.23	5.42	8.62
(*S*)-**2a**.oxa	$C_{16}H_{18}N_2O_5$	60.37	5.70	8.80	60.12	5.36	8.53
(*R*)-**2b**.oxa	$C_{17}H_{20}N_2O_5$	61.44	6.07	8.43	61.10	6.25	8.09
(*S*)-**2b**.oxa	$C_{17}H_{20}N_2O_5$	61.44	6.07	8.43	61.12	6.21	8.10
(*R*)-**2c**	$C_{16}H_{21}IN_2O$	50.01	5.51	7.29	49.73	5.12	7.01
(*S*)-**2c**	$C_{16}H_{21}IN_2O$	50.01	5.51	7.29	49.76	5.10	7.07
3a.oxa	$C_{16}H_{16}N_2O_4$	63.99	5.37	9.33	63.75	5.01	9.03
3b.oxa	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91	64.57	5.51	8.68
3c	$C_{16}H_{19}IN_2$	52.47	5.23	7.65	52.12	5.01	7.36
4a.oxa	$C_{16}H_{18}N_2O_4$	63.56	6.00	9.27	63.16	5.75	9.02
4b.oxa	$C_{17}H_{20}N_2O_4$	64.54	6.37	8.86	64.72	6.02	8.53
4c	$C_{16}H_{21}IN_2$	52.18	5.75	7.61	52.01	5.90	7.36
5a.oxa	$C_{16}H_{18}N_2O_4$	63.56	6.00	9.27	63.21	5.87	9.02
5b.oxa	$C_{17}H_{20}N_2O_4$	64.54	6.37	8.86	64.20	6.52	8.68
5c	$C_{16}H_{21}IN_2$	52.18	5.75	7.61	51.98	5.45	7.52
6a.oxa	$C_{15}H_{14}N_2O_4$	62.93	4.93	9.79	62.90	4.75	9.81
6b.oxa	$C_{16}H_{16}N_2O_4$	63.99	5.37	9.33	64.15	5.48	9.52
6c	$C_{15}H_{17}IN_2$	51.15	4.86	7.95	51.02	4.62	7.73
7a.oxa	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.72	62.59	5.65	9.81
7b.oxa	$C_{16}H_{18}N_2O_4$	63.56	6.00	9.27	63.78	5.82	9.13
7c	$C_{15}H_{19}IN_2$	50.86	5.41	7.91	50.49	5.35	7.70
8a.oxa	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.72	62.35	5.50	9.67
8b.oxa	$C_{16}H_{18}N_2O_4$	63.56	6.00	9.27	63.22	5.71	9.01
8c	$C_{15}H_{19}IN_2$	50.86	5.41	7.91	50.62	5.35	7.72
9	$C_{23}H_{24}N_2O_2$	76.64	6.71	7.77	76.20	6.54	7.39
10	$C_{23}H_{24}N_2O_2$	76.64	6.71	7.77	76.31	6.59	7.60
(*R*)-**11**	$C_{22}H_{22}N_2O_3$	72.91	6.12	7.73	72.54	5.85	7.39
(*S*)-**11**	$C_{22}H_{22}N_2O_3$	72.91	6.12	7.73	72.61	6.33	7.52
12	$C_{12}H_9NO$	78.67	4.95	7.65	78.51	5.23	7.82
13	$C_{12}H_{11}NO$	77.81	5.99	7.56	77.45	5.72	7.19
14	$C_{12}H_{11}NO$	77.81	5.99	7.56	78.03	6.00	7.23