

Optimized glucuronidation of dual pharmacology β -2 agonists/M3 antagonists for the treatment of COPD

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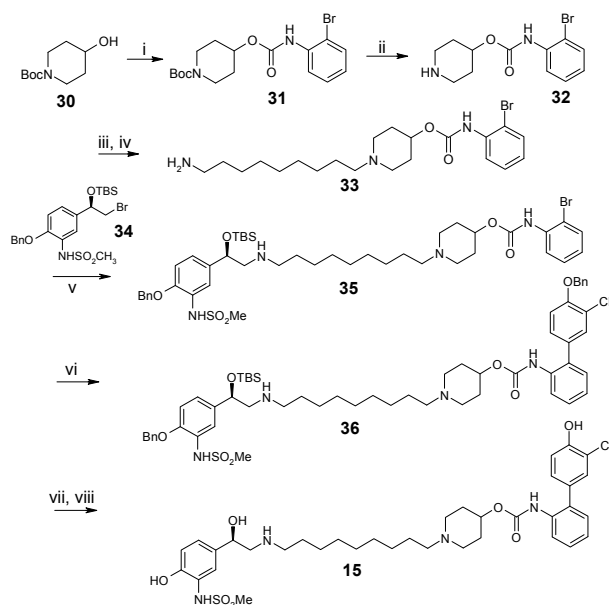
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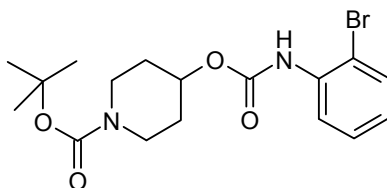
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General. Melting points were determined on a Gallenkamp melting point apparatus using glass capillary tubes and are uncorrected. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere, using commercially available anhydrous solvents. Thin-layer chromatography was performed on glass-backed pre-coated Merck silica gel (60 F254) plates, and FCC (flash column chromatography) was carried out using 40-63 μ m silica gel. NMR spectra were carried out on a Varian Mercury 400 spectrometer in the solvents specified. Mass spectra were recorded on a Waters Micromass ZQ using atmospheric pressure chemical ionization (APCI). Other abbreviations are used in conjunction with standard chemical practice.

Route to MABA 15

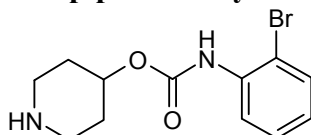


4-(2-Bromo-phenylcarbamoyloxy)-piperidine-1-carboxylic acid tert-butyl ester (31)



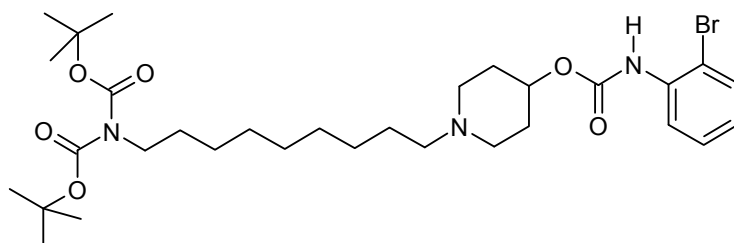
1-tert-Butoxycarbonyl-4-hydroxypiperidine 1.00 g, 5.0 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.70 mL, 5.0 mmol) was added and the reaction stirred at room temperature for 30 minutes. A solution of 2-bromophenylisocyanate (1.00 g, 5.0 mmol) in dichloromethane (5 mL) was added dropwise over 5 minutes and the reaction left stirring at room temperature for 12 hours. The solvent was removed in vacuo to furnish an oily solid that was slurried in pentane (20 mL) for 10 minutes, the solid was filtered off to furnish the title compound as a white solid, 1.35 g (68% yield): δ_{H} (400MHz, CDCl_3) 1.47 (9H, s), 1.68 (2H, m), 1.95 (2H, m), 3.22 (2H, m), 3.77 (2H, m), 4.93 (1H, m), 6.93 (1H, t), 7.11 (1H, br s), 7.31 (1H, t), 7.53 (1H, d), 8.13 (1H, d); LCMS m/z (APCI) 421/423 ($\text{M}+\text{Na}^+$), >95% pure.

(2-Bromo-phenyl)-carbamic acid piperidin-4-yl ester hydrochloride salt (32)



31 (35 g, 88 mmol) was dissolved in hydrochloric acid (175 mL of a 4 M solution in dioxane) and the reaction stirred at room temperature for 30 minutes. The solvent was removed in vacuo and the resulting solid slurried in diethyl ether (100 mL) for 30 minutes. The solid was isolated by filtration to furnish the title compound as a white solid, 27.3 g (84% yield): δ_{H} (400MHz, CDCl_3) 2.03 (2H, m), 2.18 (2H, m), 3.22 (2H, m), 3.30 (2H, m), 5.02 (1H, m), 7.19 (1H, m), 7.37 (1H, m), 7.58 (1H, m), 7.72 (1H, m); LCMS m/z (APCI) 299, 301 (M^+), >95% pure.

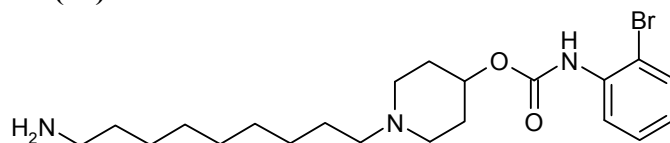
Di-tert-Butyl {9-[4-({[(2-bromophenyl)amino]carbonyl}oxy)piperidin-1-yl]nonyl}imidodicarbonate



32 (4.85 g, 14.5 mmol) was suspended in acetonitrile (40 mL) and triethylamine (4.0 mL, 28.9 mmol) was added at room temperature. A solution of (9-Bromo-nonyl)-dicarbamic acid tert-butyl ester (WO 2008041095, 6.10g, 14.4 mmol) in acetonitrile (20 mL) was added dropwise and the reaction heated at 50°C for 12 hours. The reaction was cooled to room temperature and the solvent removed in vacuo and the

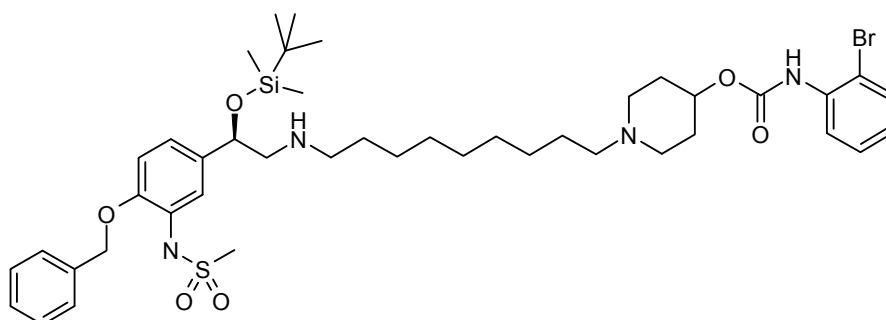
residue dissolved in dichloromethane (300 mL). The organics were washed with saturated aqueous sodium hydrogen carbonate (2 x 200 mL) and water (150 mL), dried (magnesium sulfate) and the solvent removed in vacuo to yield an oil. The oil was purified by column chromatography on silica gel eluting with pentane:ethyl acetate (50/50 by volume) to furnish the title compound, 6.50 g (71% yield): δ_{H} (400MHz, CD₃OD) 1.25 – 1.38 (10H, m), 1.44 (18H, s), 1.44 – 1.60 (6H, m), 1.77 (2H, m), 1.98 (2H, m), 2.25 – 2.39 (4H, m), 2.77 (2H, m), 4.73 (1H, m), 7.02 (1H, m), 7.35 (1H, m), 7.58 (1H, m), 7.73 (1H, m); LCMS m/z (APCI) 642, 644 (M+H)⁺, >95% pure.

(2-Bromo-phenyl)-carbamic acid 1-(9-amino-nonyl)-piperidin-4-yl ester hydrochloride salt (33)



Di-tert-Butyl{9-[4-({[(2-bromophenyl)amino]carbonyl}oxy)piperidin-1-yl]nonyl}imidodicarbonate (20 g, 31 mmol) was dissolved in dioxane (200 mL) and hydrochloric acid (160 mL of a 4M solution in dioxane) added in one portion at room temperature. A white solid precipitated and water (50 mL) was added to dissolve the solid. The reaction was stirred at room temperature for 24 hours and the solvent removed in vacuo to furnish the title compound as an off white solid, 15 g (95% yield): δ_{H} (400MHz, CDCl₃) 1.21 – 1.37 (10H, m), 1.45 – 1.51 (4H, m), 1.78 (2H, m), 1.96 – 2.04 (4H, m), 2.20 – 2.37 (4H, m), 2.65 – 2.79 (4H, m), 4.74 (1H, m), 6.90 (1H, m), 7.10 (1H, m), 7.28 (1H, m), 7.49 (1H, m), 8.15 (1H, m); LCMS m/z (APCI) 440, 442 (M+H)⁺, >95% pure.

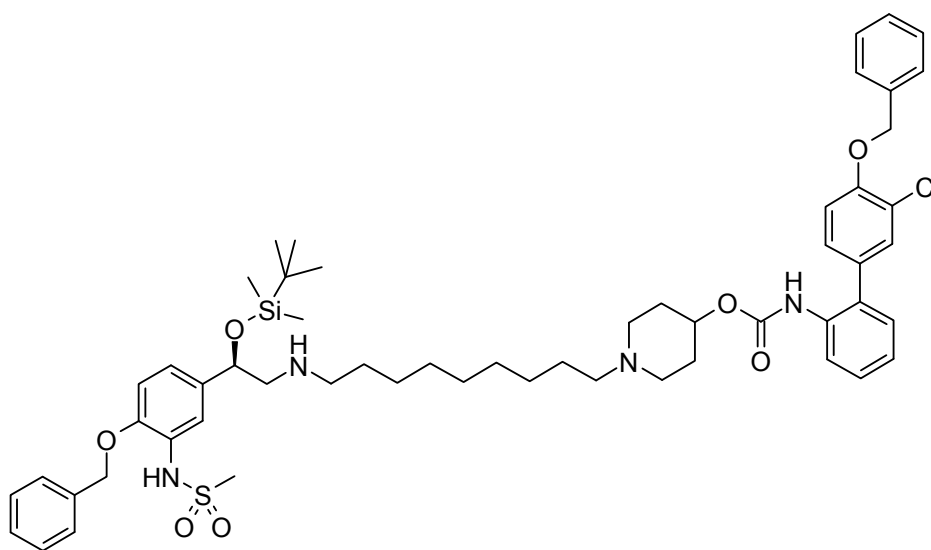
(2-Bromo-phenyl)-carbamic acid 1-{9-[2-(4-benzyloxy-3-methanesulfonylamino-phenyl)-2-(tert-butyl-dimethyl-silyloxy)-ethylamino]-nonyl}-piperidin-4-yl ester (35)



33 (16.0 g, 31.2 mmol) and N-{2-(benzyloxy)-5-[(1R)-2-bromo-1-[(tertbutyl (dimethyl)silyl]oxy}ethyl] phenyl}methanesulfonamide (WO 2005080324, 16.1 g, 31.2 mmol) and sodium hydrogencarbonate (13.1 g, 156 mmol) were heated in acetonitrile (200 mL) at 90°C for 72 hours. The reaction was cooled to room temperature and poured onto water (20 mL) and ethyl acetate (50 mL), the organics were separated and the aqueous extracted with ethyl acetate (2 x 40 mL). The

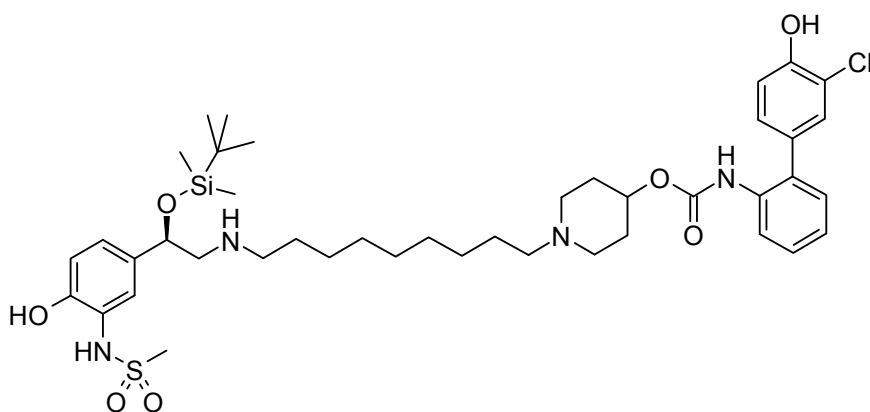
combined organics were dried (sodium sulfate) and the solvent removed in vacuo to furnish a brown oil. The oil was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98/2/1 by volume) to furnish the title compound as a colourless gum, 16.5 g (61% yield): δ_{H} (400MHz, CDCl_3) -0.17 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 1.25 – 1.33 (10H, m), 1.40 – 1.56 (4H, m), 1.78 (2H, m), 2.02 (4H, m), 2.21 – 2.38 (4H, m), 2.52 – 2.67 (2H, m), 2.72 – 2.84 (2H, m), 2.90 (3H, s), 4.75 – 4.82 (2H, m), 5.07 (2H, s), 6.80 (2H, m), 7.08 (2H, m), 7.35 – 7.41 (6H, m), 7.50 (2H, m), 8.15 (1H, m); LCMS m/z (APCI) 873, 875 (M+H)⁺, >95% pure.

(4'-Benzyloxy-3'-chloro-biphenyl-2-yl)-carbamic acid 1-{9-[2-(4-benzyloxy-3-methanesulfonylamino-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-ethylamino]-nonyl}-piperidin-4-yl ester (36)



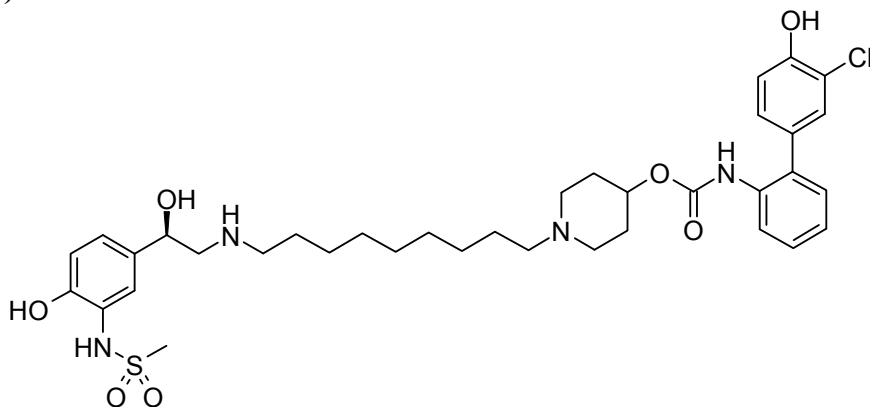
35 (1000 mg, 1.14 mmol), 4-benzyloxy-3-chlorophenyl boronic acid (450 mg, 1.72 mmol), sodium carbonate (485 mg, 4.58 mmol), palladium acetate (20 mg, 0.07 mmol) and tri(o-tolyl)phosphine (42 mg, 0.14 mmol) were heated in *N,N*-dimethylformamide (10 mL) at 100°C under microwave conditions for 10 minutes. The reaction was cooled to room temperature, filtered through celite and ethyl acetate (25 mL) added. The organics were washed with water (50 mL), dried (magnesium sulphate) and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95/5/0.5 by volume) to furnish the title compound as a yellow oil, 1.06 g (92% yield): δ_{H} (400MHz, CD_3OD) -0.18 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 1.20 – 1.38 (10H, m), 1.47 – 1.57 (4H, m), 1.64 (2H, m), 1.83 (2H, m), 2.32 – 2.45 (4H, m), 2.60 – 2.94 (9H, m), 4.60 (1H, m), 4.80 (1H, m), 5.20 (4H, m), 7.05 – 7.51 (20H, m); LCMS m/z (APCI) 1012 (M+H)⁺, >95% pure.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-(tert-butyl-dimethyl-silanyloxy)-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester



36 (1.50 g, 1.48 mmol) was dissolved in tert-butylmethyl ether (50 mL) and 10% palladium on carbon (25 mg) added in one portion. The reaction was hydrogenated at 10 psi at room temperature for 2 hours and 1.5 hours at 15 psi. The catalyst was removed by filtration through Arbocel and the solvent removed in vacuo to yield the title compound as a pale yellow solid, 1.08 g (89% yield): δ_{H} (400MHz, CD_3OD) -0.17 (3H, s), 0.04 (3H, s), 0.83 (9H, s), 1.25 – 1.39 (10H, m), 1.42 – 1.58 (4H, m), 1.60 – 2.00 (4H, m), 2.31 – 2.39 (4H, m), 2.58 – 2.75 (4H, m), 2.80 (2H, m), 2.89 (3H, s), 4.62 (1H, m), 4.76 (1H, m), 6.84 – 7.60 (10H, m); LCMS m/z (APCI) 832 (M+H)⁺, >95% pure.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (15)



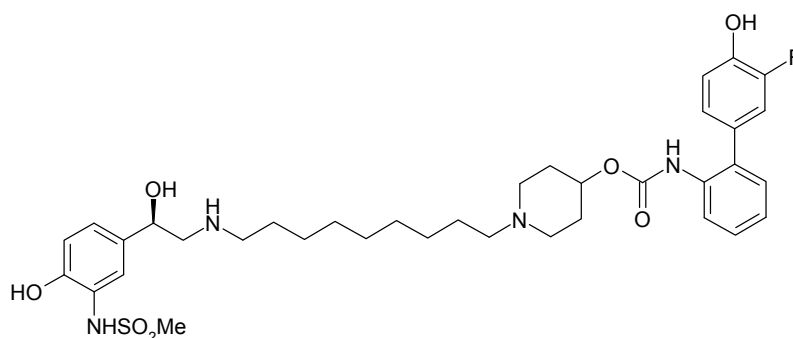
(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-(tert-butyl-dimethylsilyloxy)-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (215 mg, 0.26 mmol) was dissolved in THF (4 mL) and triethylaminetrihydrofluoride (208 mg, 1.29 mmol) added in one portion. The reaction was stirred at room temperature for 12 hours. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:880 ammonia (95/5/0.5 by volume) to furnish the title compound as a white foam, 180 mg (96% yield): δ_{H} (400MHz, CD_3OD) 1.22 – 1.37 (10H, m), 1.45 – 1.58 (4H, m), 1.65 (2H, m), 1.84 (2H, m), 2.30 – 2.36 (4H, m), 2.60 – 2.83 (6H, m), 2.92 (3H, s), 4.62 (1H, m), 4.75 (1H, m), 6.84 (1H, d), 6.95 (1H, m), 7.03 – 7.15 (2H, m), 7.23 – 7.37 (5H, m), 7.45 (1H, m); LCMS m/z (APCI) 717 (M+H)⁺, >95% pure; accurate mass, calc. 717.3083, found 717.3093.

Naphthalene-1,5-disulfonate salt of 15

15 (810 mg, 1.13 mmol) was dissolved in methanol (50 mL). A solution of 1,5-naphthalenedisulphonic acid tetrahydrate (367 mg, 1.13 mmol) in methanol (10 mL) was added and the solution was refluxed for 10 minutes and then allowed to cool slowly to room temperature. The mixture was filtered, washed with cold methanol and dried under vacuum to provide the desired salt (920 mg, 81% yield) as a white crystalline solid (mp 200°C): δ_{H} (400MHz, CD₃OD) 1.15 – 1.30 (10H, m), 1.57 – 1.69 (4H, m), 1.90 (2H, m), 2.07 (2H, m), 2.93 – 3.35 (13H, m), 4.84 (1H, m), 4.90 (1H, m), 6.93 (1H, m), 7.04 (1H, d), 7.12 (1H, m), 7.19 (1H, m), 7.27 – 7.38 (4H, m), 7.42 (1H, m), 7.50 (1H, m), 7.80 (2H, dd), 8.22 (2H, d), 9.03 (2H, dd).

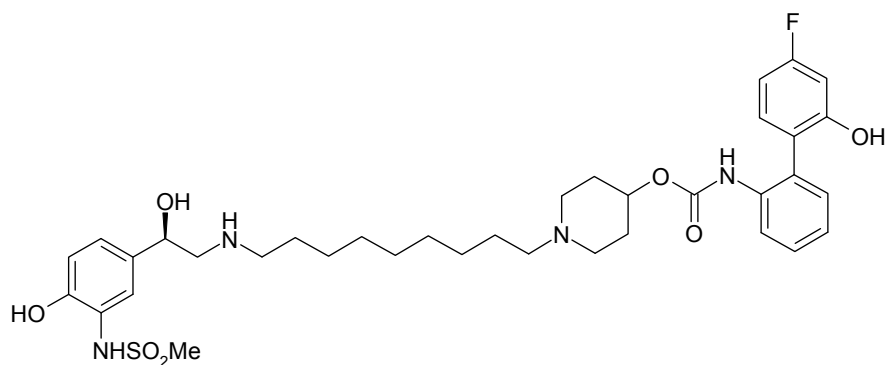
All derivatives were prepared using the same methodology described above and in WO 2008041095.

(3'-Fluoro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (13)



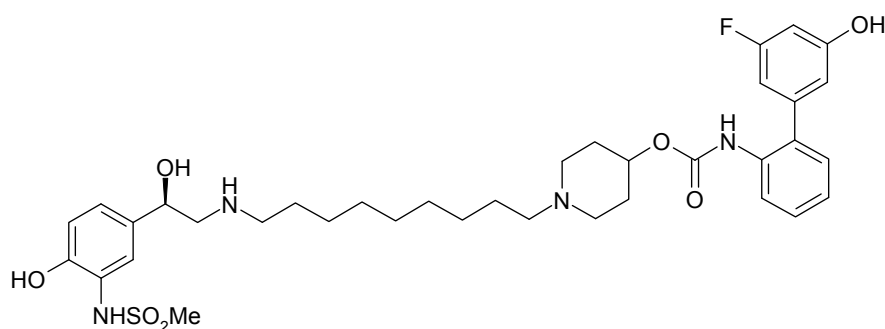
δ_{H} (400MHz, CD₃OD) 1.23 – 1.40 (10H, m), 1.42 – 1.60 (4H, m), 1.60 – 1.69 (2H, m), 1.83 – 1.95 (2H, m), 2.22 – 2.38 (4H, m), 2.65 – 2.74 (3H, m), 2.80 – 2.84 (2H, m), 2.92 (3H, s), 4.65 (1H, m), 4.73 (1H, m), 6.56 – 6.63 (2H, m), 6.85 (1H, d), 7.03 – 7.37 (6H, m), 7.60 (1H, m); LCMS *m/z* (APCI) 701 (M+H)⁺, >95% pure; accurate mass, calc. 701.3379, found 701.3369.

(4'-Fluoro-2'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (8)



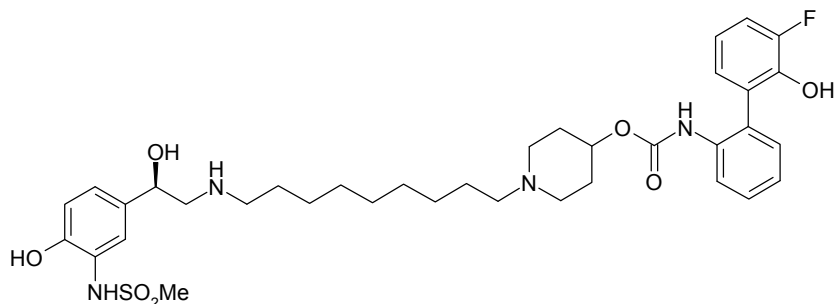
δ_{H} (400MHz, CD₃OD) 1.25 – 1.38 (10H, m), 1.43 – 1.74 (6H, m), 1.82 - 1.93 (2H, m), 2.25 – 2.37 (4H, m), 2.62 – 2.75 (3H, m), 2.85 (2H, m), 2.93 (3H, s), 4.61 (1H, m), 4.73 (1H, m), 6.85 (1H, d), 6.90 – 6.98 (2H, m), 7.02 – 7.06 (2H, m), 7.20 – 7.33 (3H, m), 7.37 (1H, m), 7.50 (1H, m); LCMS m/z (APCI) 701 (M+H)⁺, >95% pure; accurate mass, calc. 701.3379, found 701.3381.

(5'-Fluoro-3'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (12)



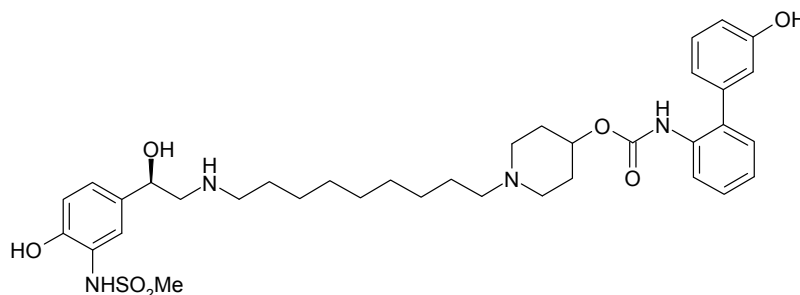
δ_{H} (400MHz, CD₃OD) 1.22 – 1.40 (10H, m), 1.47 – 1.60 (4H, m), 1.60 – 1.74 (2H, m), 1.82 – 1.92 (2H, m), 2.24 – 2.38 (4H, m), 2.63 – 2.75 (4H, m), 2.84 (2H, m), 2.92 (3H, s), 4.62 (1H, m), 4.70 (1H, m), 6.47 – 6.61 (3H, m), 6.85 (1H, d), 7.02 (1H, m), 7.22 – 7.36 (4H, m), 7.52 (1H, m); LCMS m/z (APCI) 701 (M+H)⁺, >95% pure; accurate mass, calc. 701.3379, found 701.3387.

(3'-Fluoro-2'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (9)



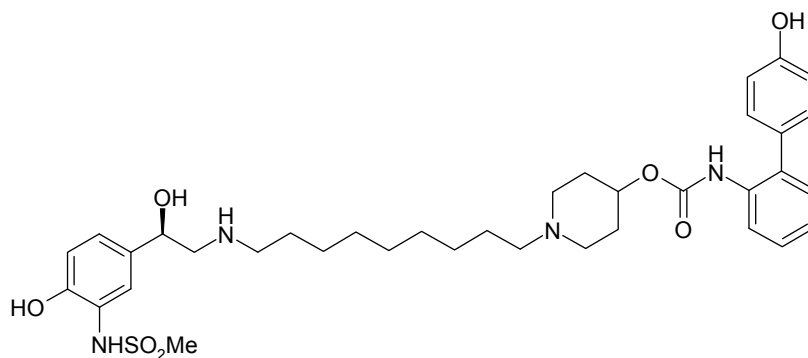
δ_{H} (400MHz, CD₃OD) 1.25 – 1.42 (10H, m), 1.45 – 1.76 (6H, m), 1.83 – 1.97 (2H, m), 2.22 – 2.43 (4H, m), 2.60 – 2.90 (6H, m), 2.92 (3H, s), 4.59 – 4.86 (2H, m), 6.72 (1H, m), 6.85 (1H, d), 6.96 (1H, d), 7.02 – 7.06 (2H, m), 7.19 (1H, m), 7.26 – 7.38 (3H, m), 7.60 (1H, m); LCMS m/z (APCI) 701 (M+H)⁺, >95% pure; accurate mass, calc. 701.3379, found 701.3367.

(3'-Hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (6)



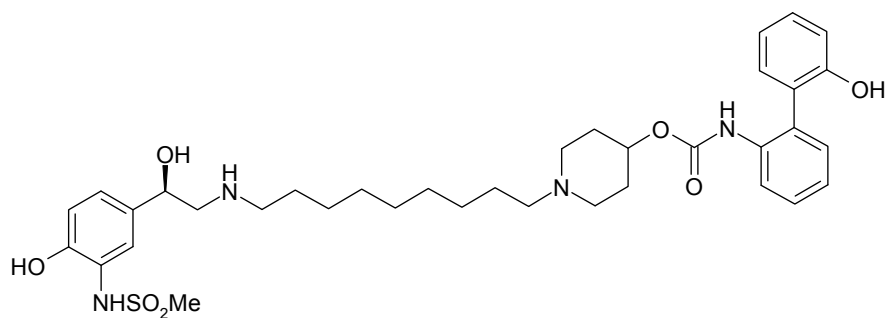
δ_{H} (400MHz, CD₃OD) 1.25 – 1.40 (10H, m), 1.45 – 1.55 (4H, m), 1.59 – 1.72 (2H, m), 1.84 – 1.93 (2H, m), 2.22 – 2.35 (4H, m), 2.61 – 2.76 (4H, m), 2.78 (2H, m), 2.92 (3H, s), 4.60 – 4.70 (2H, m), 6.85 (1H, d), 6.96 (2H, m), 7.10 (1H, m), 7.15 – 7.30 (4H, m), 7.28 – 7.35 (2H, m), 7.60 (1H, m); LCMS m/z (APCI) 684 (M+H)⁺, >95% pure.

(4'-Hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (5)



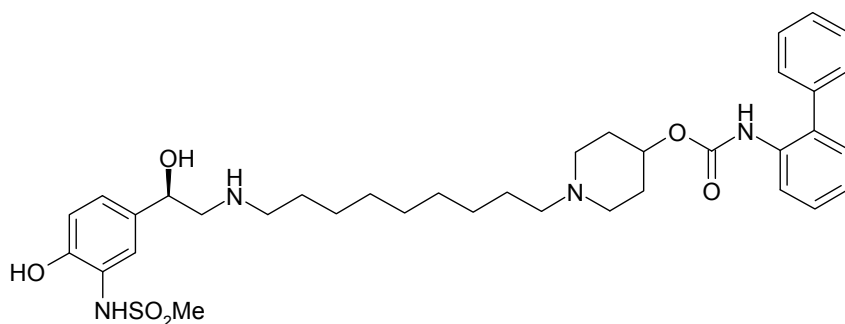
δ_{H} (400MHz, CD₃OD) 1.25 – 1.40 (10H, m), 1.42 – 1.52 (4H, m), 1.60 – 1.70 (2H, m), 1.82 – 1.91 (2H, m), 2.25 – 2.37 (4H, m), 2.63 – 2.77 (4H, m), 2.81 (2H, m), 2.92 (3H, s), 4.60 – 4.70 (2H, m), 6.85 (1H, d), 6.96 (2H, m), 7.05 – 7.25 (5H, m), 7.30 – 7.65 (3H, m); LCMS m/z (APCI) 684 (M+H)⁺, >95% pure.

(2'-Hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (7)



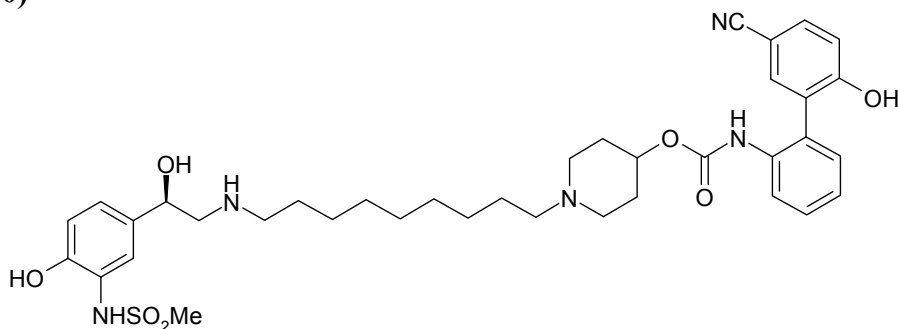
δ_{H} (400MHz, CD_3OD) 1.25 – 1.38 (10H, m), 1.45 – 1.57 (4H, m), 1.60 – 1.72 (2H, m), 1.84 – 1.95 (2H, m), 2.22 – 2.37 (4H, m), 2.63 – 2.75 (4H, m), 2.80 (2H, m), 2.91 (3H, s), 4.60 – 4.71 (2H, m), 6.85 (1H, d), 6.96 (2H, m), 7.06 (1H, m), 7.15 – 7.27 (4H, m), 7.31 – 7.35 (2H, m), 7.65 (1H, m); LCMS m/z (APCI) 684 ($\text{M}+\text{H}$)⁺, >95% pure.

Biphenyl-2-yl-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (4)



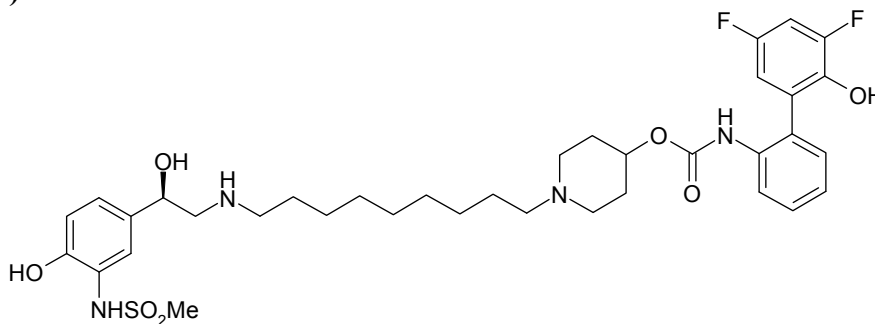
δ_{H} (400MHz, CD_3OD) 1.24 – 1.40 (10H, m), 1.45 – 1.68 (6H, m), 1.83 (2H, m), 2.23 – 2.37 (4H, m), 2.62 – 2.69 (4H, m), 2.77 – 2.82 (2H, m), 2.94 (3H, s), 4.60 (1H, m), 4.70 (1H, m), 6.85 (1H, d), 7.04 (1H, d), 7.22 – 7.45 (9H, m), 7.57 (1H, m); LCMS m/z (APCI) 667 ($\text{M}+\text{H}$)⁺, >95% pure.

(5'-Cyano-2'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (10)



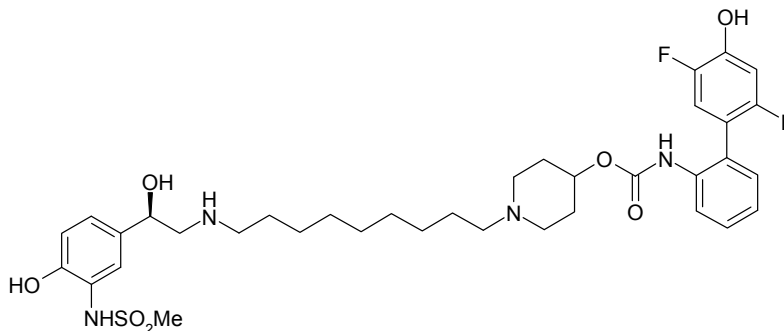
δ_{H} (400MHz, CD_3OD) 1.27 – 1.40 (10H, m), 1.53 (2H, m), 1.60 – 1.75 (4H, m), 1.90 (2H, m), 2.36 – 2.47 (4H, m), 2.77 (2H, m), 2.86 – 2.92 (5H, m), 3.00 (2H, m), 4.68 (1H, m), 4.78 (1H, m), 6.83 (1H, d), 6.89 (1H, d), 7.10 (1H, m), 7.18 (1H,), 7.29 – 7.44 (5H, m), 7.59 (1H, m); LCMS m/z (APCI) 709 (M+H)⁺, >95% pure; accurate mass, calc. 708.3437, found 708.3425.

(3',5'-Difluoro-2'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (11)



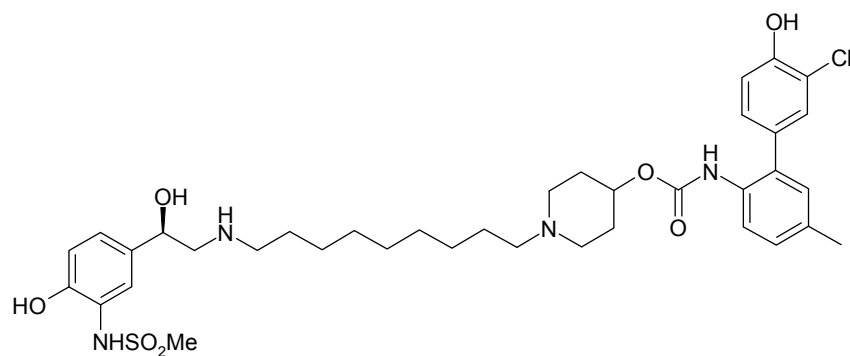
δ_{H} (400MHz, CD_3OD) 1.25 – 1.40 (10H, m), 1.43 – 1.88 (6H, m), 1.90 (2H, m), 2.31 – 2.42 (4H, m), 2.70 – 2.95 (6H, m), 2.96 (3H, s), 4.65 (1H, m), 4.79 (1H, m), 6.76 (1H, m), 6.85 – 6.95 (2H, m), 7.09 (1H, m), 7.19 – 7.36 (3H, m), 7.60 (1H, m); LCMS m/z (APCI) 719 (M+H)⁺, >95% pure; accurate mass, calc. 719.3285, found 719.3284.

(2',5'-Difluoro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (14)



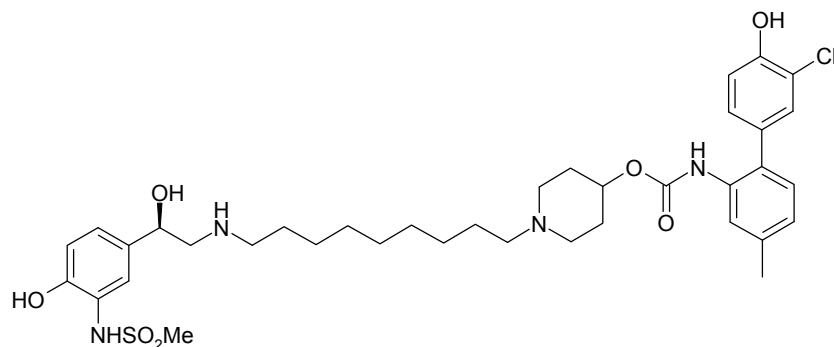
δ_{H} (400MHz, CD_3OD) 1.30 – 1.43 (10H, m), 1.59 – 1.78 (6H, m), 1.89 (2H, m), 2.30 – 2.40 (4H, m), 2.68 (2H, m), 2.83 (2H, m), 2.94 – 2.98 (5H, m), 4.65 (1H, m), 4.77 (1H, m), 6.66 (1H, m), 6.90 (1H, d), 6.98 (1H, m), 7.10 – 7.37 (5H, m), 7.52 (1H, m); LCMS m/z (APCI) 719 (M+H)⁺, >95% pure; accurate mass, calc. 719.3285, found 719.3277.

(2'-Chloro-4'-hydroxy-5-methyl-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (16)



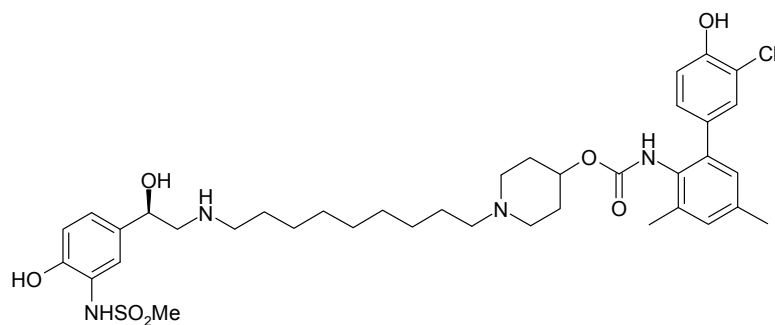
δ_{H} (400MHz, CD_3OD) 1.26 – 1.37 (10H, m), 1.45 – 1.70 (6H, m), 1.85 (2H, m), 2.27 – 2.38 (7H, m), 2.60 – 2.77 (4H, m), 2.83 (2H, m), 2.95 (3H, s), 4.60 (1H, m), 4.70 (1H, m), 6.87 (1H, d), 6.92 (1H, d), 7.05 – 7.13 (4H, m), 7.28 – 7.34 (2H, m), 7.37 (1H, m); LCMS m/z (APCI) 731 ($\text{M}+\text{H}$)⁺, >95% pure; accurate mass, calc. 731.3240, found 731.3238.

(2'-Chloro-4'-hydroxy-4-methyl-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (17)



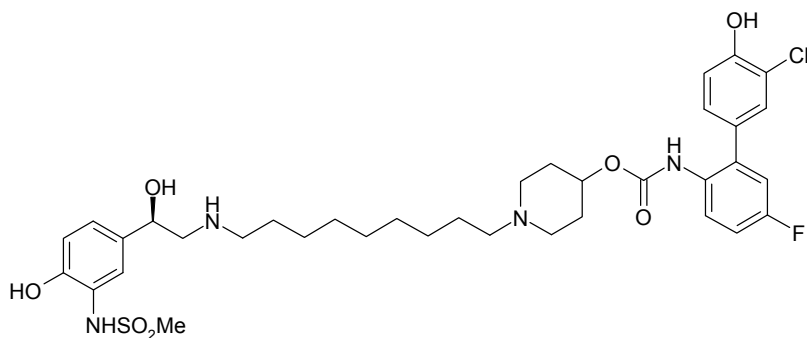
δ_{H} (400MHz, CD_3OD) 1.26 – 1.40 (10H, m), 1.46 – 1.60 (4H, m), 1.69 (2H, m), 1.85 (2H, m), 2.30 – 2.37 (7H, m), 2.60 – 2.75 (4H, m), 2.79 – 2.86 (2H, m), 2.94 (3H, s), 4.62 (1H, m), 4.71 (1H, m), 6.85 (1H, d), 6.93 (1H, d), 7.06 – 7.10 (4H, m), 7.27 – 7.30 (2H, m), 7.35 (1H, m); LCMS m/z (APCI) 731 ($\text{M}+\text{H}$)⁺, >95% pure; accurate mass, calc. 731.3240, found 731.3232.

(2'-Chloro-4'-hydroxy-3,5-dimethyl-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (18)



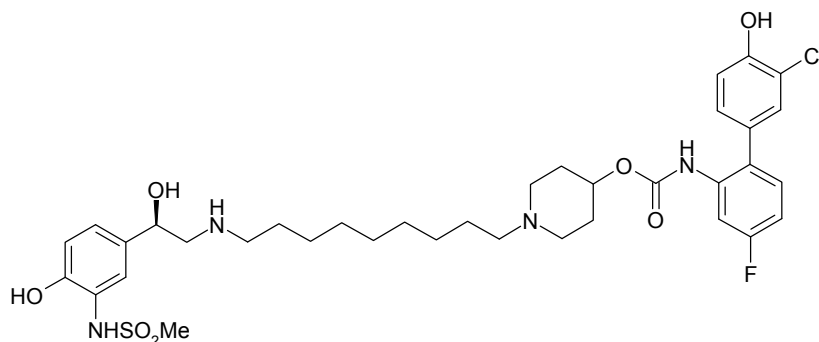
δ_{H} (400MHz, CD_3OD) 1.25 – 1.37 (10H, m), 1.50 – 1.70 (6H, m), 1.82 (2H, m), 2.24 (3H, s), 2.32 – 2.38 (7H, m), 2.58 – 2.74 (4H, m), 2.80 (2H, m), 2.92 (3H, s), 4.57 (1H, m), 4.70 (1H, m), 6.83 – 6.90 (2H, m), 6.95 (1H, m), 7.04 – 7.09 (3H, m), 7.26 (1H, m), 7.35 (1H, m); LCMS m/z (APCI) 745 ($\text{M}+\text{H}$)⁺, >95% pure; accurate mass, calc. 745.3396, found 745.3382.

(2'-Chloro-5-fluoro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (19)



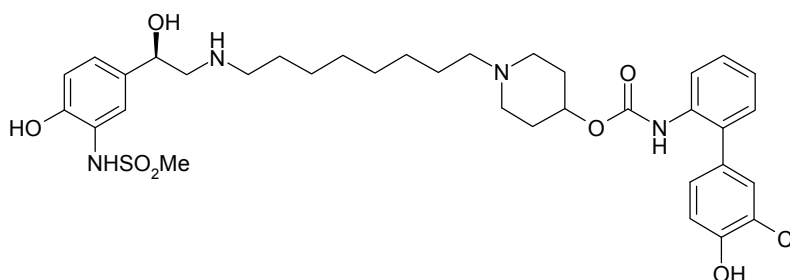
δ_{H} (400MHz, CD_3OD) 1.25 – 1.38 (10H, m), 1.46 – 1.71 (6H, m), 1.83 (2H, m), 2.30 – 2.37 (4H, m), 2.60 – 2.85 (6H, m), 2.94 (3H, s), 4.60 (1H, m), 4.71 (1H, m), 6.85 (1H, d), 6.91 (1H, d), 7.02 – 7.09 (3H, m), 7.15 (1H, m), 7.32 (1H, m), 7.38 (1H, m), 7.40 (1H, m); LCMS m/z (APCI) 735 ($\text{M}+\text{H}$)⁺, >95% pure; accurate mass, calc. 735.2989, found 735.2997.

(2'-Chloro-4-fluoro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-piperidin-4-yl ester (20)



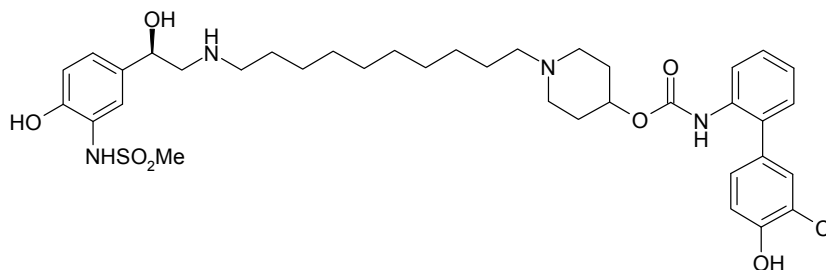
δ_{H} (400MHz, CD₃OD) 1.30 – 1.38 (10H, m), 1.51 – 1.60 (4H, m), 1.70 (2H, m), 1.89 (2H, m), 2.31 – 2.39 (4H, m), 2.63 – 2.77 (4H, m), 2.84 (2H, m), 2.94 (3H, s), 4.64 – 4.75 (2H, m), 6.85 (1H, d), 6.96 (2H, m), 7.08 (2H, m), 7.21 – 7.26 (2H, m), 7.36 (1H, m), 7.42 (1H, m); LCMS m/z (APCI) 735 (M+H)⁺, >95% pure.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{8-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-octyl}-piperidin-4-yl ester (21)



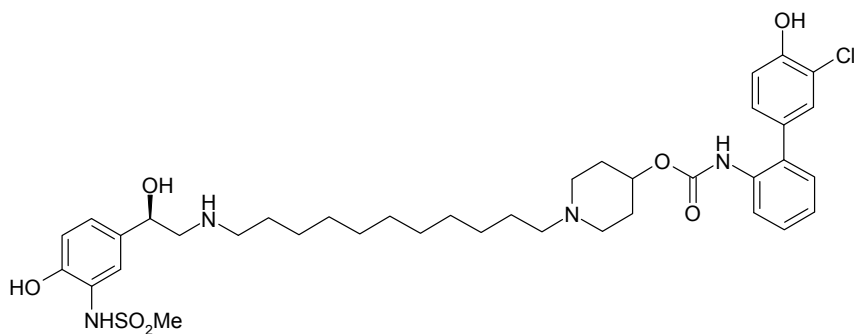
δ_{H} (400MHz, CD₃OD) 1.25 – 1.30 (8H, m), 1.46 – 1.69 (6H, m), 1.86 (2H, m), 2.60 – 2.78 (4H, m), 2.82 (2H, m), 2.94 (3H, s), 4.62 (1H, m), 4.71 (1H, m), 6.81 – 6.84 (2H, m), 7.05 (1H, m), 7.18 – 7.30 (5H, m), 7.38 (1H, m), 7.55 (1H, m); LCMS m/z (APCI) 703 (M)⁺, >95% pure.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{10-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-decyl}-piperidin-4-yl ester (22)



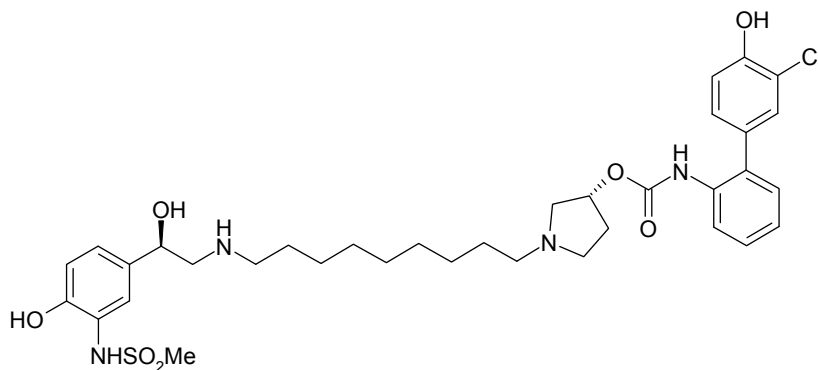
δ_{H} (400MHz, CD₃OD) 1.23 – 1.39 (12H, m), 1.45 – 1.75 (6H, m), 1.88 (2H, m), 2.25 – 2.38 (4H, m), 2.60 – 2.80 (4H, m), 2.87 (2H, m), 2.95 (3H, m), 4.63 (1H, m), 4.75 (1H, m), 6.84 (1H, d), 6.95 (1H, d), 7.06 (1H, m), 7.12 (1H, m), 7.22 – 7.38 (5H, m), 7.49 (1H, m); LCMS m/z (APCI) 731 (M+H)⁺, >95% pure; accurate mass, calc. 731.3240, found 731.3219.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{11-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-undecyl}-piperidin-4-yl ester (23)



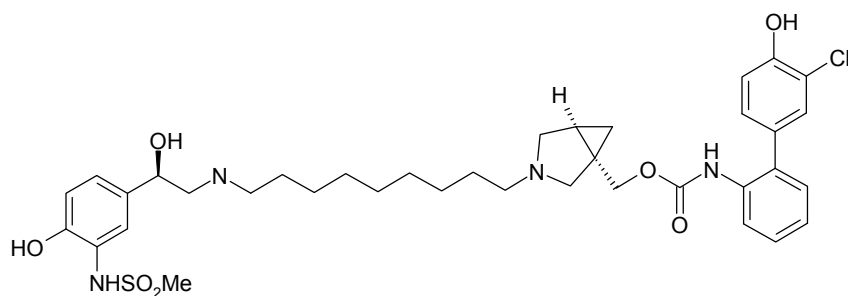
δ_{H} (400MHz, CD_3OD) 1.25 – 1.40 (14H, m), 1.46 – 1.75 (6H, m), 1.85 (2H, m), 2.26 – 2.39 (4H, m), 2.61 – 2.78 (4H, m), 2.82 (2H, m), 2.92 (3H, s), 4.61 (1H, m), 4.71 (1H, m), 6.85 (1H, d), 6.96 (1H, d), 7.05 – 7.13 (2H, m), 7.24 – 7.38 (5H, m), 7.47 (1H, m); LCMS m/z (APCI) 745 ($\text{M}+\text{H}$)⁺, >95% pure.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-pyrrolidin-3-yl ester (24)



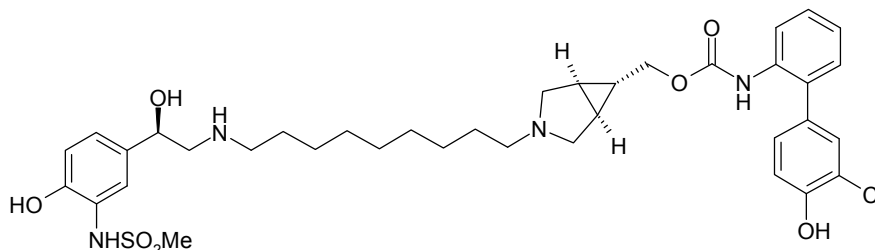
δ_{H} (400MHz, CD_3OD) 1.30 – 1.40 (12H, m), 1.51 (2H, m), 1.62 (2H, m), 2.43 (4H, m), 2.71 (2H, m), 2.82 (2H, m), 2.96 (3H, s), 2.98 (2H, m), 4.76 (1H, m), 5.05 (1H, m), 6.87 (1H, d), 6.91 (1H, d), 7.20 – 7.37 (4H, m), 7.39 (1H, m), 7.50 (1H, m); LCMS m/z (APCI) 703 ($\text{M}+\text{H}$)⁺, >95% pure.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 3-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-3-azabicyclo[3.1.0]hex-1-ylmethyl ester (25)



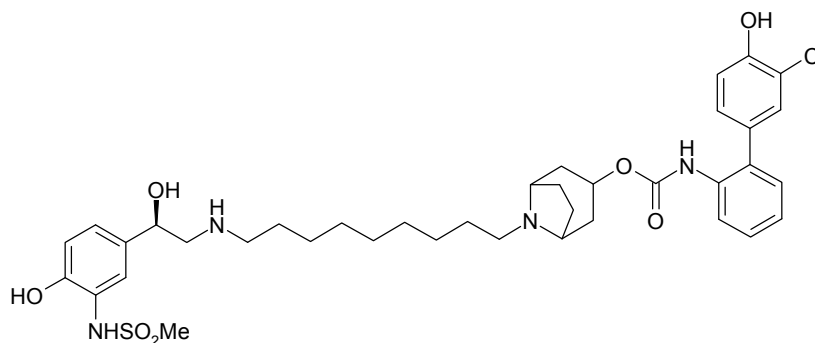
δ_{H} (400MHz, DMSO- d_6) 0.40 (1H, m), 0.83 (1H, m), 1.10 – 1.25 (15H, m), 2.15 (2H, m), 2.30 (2H, m), 2.49 – 2.60 (4H, m), 2.82 (2H, m), 2.89 (3H, s), 3.97 (1H, d), 4.10 (1H, d), 4.50 (1H, m), 6.79 (1H, m), 6.95 – 6.99 (2H, m), 7.10 – 7.18 (2H, m), 7.22 – 7.37 (5H, m), 8.66 (1H, br s); LCMS m/z (APCI) 729 (M+H)⁺, >95% pure.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 3-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-3-aza-bicyclo[3.1.0]hex-6-ylmethyl ester (26)



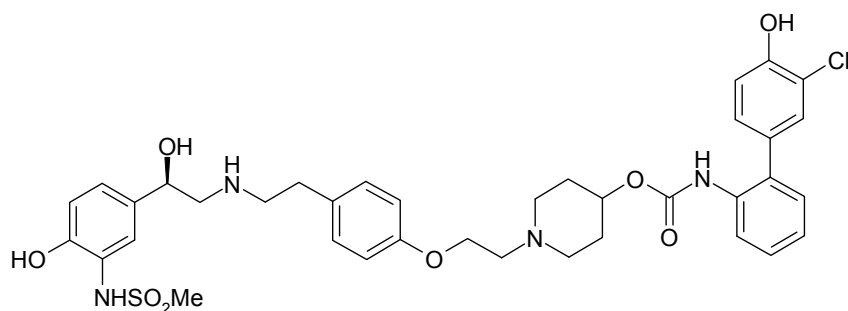
δ_{H} (400MHz, CD₃OD) 1.20 – 1.60 (17H, m), 2.38 – 2.41 (4H, m), 2.73 (2H, m), 2.84 (2H, m), 2.95 (3H, s), 3.02 (2H, m), 3.86 (2H, m), 4.73 (1H, m), 6.78 (1H, d), 6.94 (1H, d), 7.04 – 7.15 (2H, m), 7.20 – 7.37 (5H, m), 7.54 (1H, m); LCMS m/z (APCI) 729 (M+H)⁺, >95% pure; accurate mass, calc. 729.3083, found 729.3086.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 8-{9-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-nonyl}-8-aza-bicyclo[3.2.1]oct-3-yl ester (27)



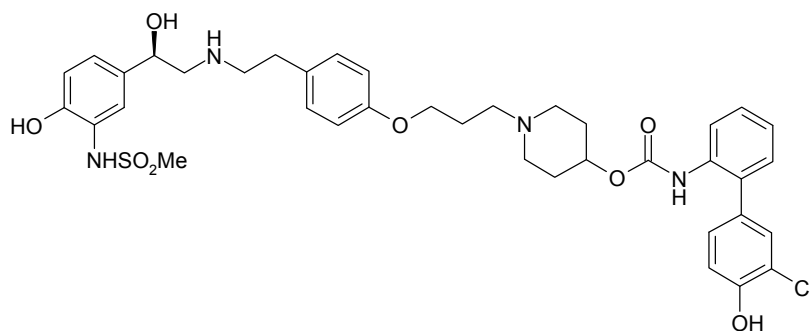
δ_{H} (400MHz, CD₃OD) 1.27 – 1.37 (12H, m), 1.48 – 1.59 (4H, m), 1.70 (2H, m), 1.85 – 2.05 (4H, m), 2.11 (2H, m), 2.47 (2H, m), 2.70 (2H, m), 2.83 (2H, m), 2.94 (3H, s), 4.70 (1H, m), 4.79 (1H, m), 6.86 (1H, d), 6.90 (1, d), 7.06 (1H, m), 7.12 (1H, m), 7.24 – 7.38 (5H, m), 7.41 (1H, m); LCMS m/z (APCI) 743 (M+H)⁺, >95% pure; accurate mass, calc. 743.3240, found 743.3241.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-[2-(4-{2-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-ethyl}-phenoxy)-ethyl]-piperidin-4-yl ester (28)



δ_{H} (400MHz, CD₃OD) 1.70 (2H, m), 1.88 (2H, m), 2.45 (2H, m), 2.77 – 2.96 (13H, m), 4.10 (2H, m), 4.60 – 4.70 (2H, m), 6.84 – 6.90 (3H, m), 6.97 (1H, d), 7.05 (1H, m), 7.10 – 7.18 (3H, m), 7.25 – 7.38 (5H, m), 7.47 (1H, m); LCMS m/z (APCI) 739 (M+H)⁺, >95% pure; accurate mass, calc. 739.2563, found 739.2553.

(3'-Chloro-4'-hydroxy-biphenyl-2-yl)-carbamic acid 1-[3-(4-{2-[2-hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-ethyl}-phenoxy)-propyl]-piperidin-4-yl ester (29)



δ_{H} (400MHz, CD₃OD) 1.68 (2H, m), 1.87 (2H, m), 1.98 (2H, m), 2.39 (2H, m), 2.56 (2H, m), 2.63 – 2.90 (8H, m), 2.90 (3H, s), 3.99 (2H, m), 4.65 (2H, m), 6.80 – 6.84 (3H, m), 6.87 (1H, d), 7.02 (1H, m), 7.10 – 7.14 (3H, m), 7.21 – 7.35 (5H, m), 7.44 (1H, m); LCMS m/z (APCI) 753 (M+H)⁺, >95% pure.