Supporting Information

Synthesis, Binding Affinity and Structure-Activity Relationships of Novel, Selective and Dual Targeting CCR2 and CCR5 Receptor Antagonists

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1. Purity data of the test compounds

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2. Experimental, Chemistry

2.1. Chemistry General

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. THF and 1,4-dioxane were dried with sodium/benzophenone and freshly distilled before use. Flash column chromatography (fc): Silica gel 60, 40–64 µm; parentheses include: eluent, Rf value. Melting point: melting point apparatus Stuart Scientific® SMP 3, uncorrected. IR: IR spectrophotometer FT-ATR-IR (Jasco®). 1H NMR (400 MHz): Unity Mercury Plus 400 spectrometer (Varian®), AV400 (Bruker®), JEOL JNM-ECA-400. 13C NMR (100 MHz): Unity Mercury plus 400 spectrometer (Varian®) JEOL JNM-ECA-400; δ in ppm relative to tetramethysilane; coupling constants are given with 0.5 Hz resolution, the assignments of 13C and 1H NMR signals were supported by 2D NMR techniques; MS: APCl = atmospheric pressure chemical ionization, EI = electron impact, ESI = electro-spray ionization: MicroTof (Bruker Daltronic, Bremen), calibration with sodium formate clusters before measurement. HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method: column: LiChrospher® 60 RP-select B (5 µm), 250x4 mm² column; flow rate: 1.00 mL/min; injection volume: 5.0 µL; detection at ė = 210 nm; solvents: A: water with 0.05 % (v/v) trifluoroacetic acid; B: acetonitrile with 0.05 % (v/v) trifluoroacetic acid; gradient elution: (A %): 0-4 min: 90 %, 4-29 min: gradient from 90 % to 0 %, 29-31 min: 0 %, 31-31.5 min: gradient from 0 % to 90 %, 31.5-40 min: 90 %. Thin layer chromatography (tlc): all reactions were monitored by tlc. Tlc aluminium foils (by Merck®, silica gel 60 F254) were used in tlc chambers in saturated atmosphere at rt. The spots were visualized using UV light (254 nm). The reported Rf values should be taken as approximate values. The ratio of (highly volatile) solvent mixtures strongly depend on temperature and opening the tlc chamber might change the solvent composition and hence the Rf value.

2.2. Synthetic procedures

General procedure A: Suzuki-Miyaura cross-coupling

A 20 mL Schlenk flask was equipped with a Dimroth condenser, a magnetic stirring bar and closed. The flask was flame-dried in vacuo and filled with N2. Under a permanent flow of N2, amide 7 (1 eq.), PdCl2(dppe) (5 mol%), base (K2CO3, KOAc, NaOCH3) (2 eq.) and arylboronic acid (1.1-1.5 eq.) were suspended in dry dimethoxyethane (5-15 mL). The flask was sealed and heated to reflux for 12 h. After cooling to rt, the mixture was
filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product, which was purified by fc. Recrystallization from acetonitrile afforded the final product.

2-(4-Methylphenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxylic acid\(^{37}\) (6)

A 50 mL Schlenk flask was equipped with a Dimroth condenser, a magnetic stirring bar and closed. The flask was flame-dried in vacuo and filled with N\(_2\). Under a permanent flow of N\(_2\), ester 3 (1.0 g, 3.5 mmol), PdCl\(_2\)(dppf) (130 mg, 0.17 mmol, 5 mol%), KOAc (700 mg, 7.0 mmol, 2 eq.) and 4-methylphenylboronic acid (525 mg, 3.85 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (10 mL). The flask was sealed and heated to reflux for 12 h. After cooling down to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by fc (EtOAc : MeOH = 95:5) to yield 1.02 g (99 %) of the ester 5 as a colorless oil.

The ester 5 (1.02 g, 3.48 mmol) was dissolved in MeOH (50 mL) and 5 M NaOH (50 mL) was added. The mixture was heated to reflux for 3 h. After cooling down to rt, the mixture was concentrated in vacuo and acidified with conc. HCl to give a precipitate. The solid was filtered off, washed with 1 M HCl, water, dried and recrystallized from acetonitrile to give 6 as a colorless solid. \(R_f = 0.42\) (CH\(_2\)Cl\(_2\) : MeOH=95:5), mp 189-190 °C, yield 950 mg (97 %), C\(_{19}\)H\(_{18}\)O\(_2\) (278.3 g/mol). Purity (HPLC): 99 %, \(t_R = 21.40\) min. HRMS (APCI): \(m/z = \text{calcd. for } C_{19}H_{19}O_2 [\text{MH}^+] 279.1380, \text{found } 279.1381.\)

\(^1\)H NMR (CDCl\(_3\)): \(\delta (ppm) = 1.92-2.17\) (m, 2H, 6\(-\)C\(\text{H}_2\)), 2.40 (s, 3H, C\(\text{H}_3\)tolyl), 2.70 (t, \(J = 5.6\) Hz, 2H, 7\(-\)C\(\text{H}_2\)), 2.89 (t, \(J = 5.6\) Hz, 2H, 5\(-\)C\(\text{H}_2\)), 7.18-7.30 (m, 3H, 3\(-\)C\(\text{H}_2\)phenyl, 5\(-\)C\(\text{H}_2\)phenyl, 4\(-\)C\(\text{H}_2\)), 7.46 (dd, \(J = 7.8/2.1\) Hz, 1H, 3\(-\)CH\(_3\)phenyl), 7.49 (d, \(J = 8.1\) Hz, 2H, 2\(-\)CH\(_3\)phenyl, 6\(-\)CH\(_3\)phenyl)), 7.57 (d, \(J = 2.0\) Hz, 1H, 1\(-\)CH\(_3\)), 7.92 (s, 1H, 9\(-\)CH\(_3\)). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta (ppm) = 21.6\) (CH\(_3\)tolyl), 27.6 (C-6), 30.6 (C-7), 35.4 (C-5), 127.2 (C-2\(_3\)tolyl, C-6\(_3\)tolyl), 128.0 (C-3), 130.0 (C-3\(_3\)tolyl, C-5\(_3\)tolyl), 130.4 (C-4), 132.1 (C-1), 132.2 (C-4\(_3\)tolyl), 134.7 (C-4a), 137.6 (C-1\(_3\)tolyl), 137.9 (C-2), 139.6 (C-9a), 142.3 (C-9), 142.6 (C-8), 174.3 (O=COH). FT-IR (neat): \(\tilde{\nu} (\text{cm}^{-1}) = 2920, 2840\) (C-H\(_{\text{alkyl}}\)), 2634, 2549 (COOH), 1732, 1680 (C=O).

2-(4-Methylphenyl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide\(^{39}\) (8a)

According to general procedure A amide 7 (200 mg, 0.42 mmol), PdCl\(_2\)(dppf) (20 mg, 0.02 mmol, 5 mol%), K\(_2\)CO\(_3\) (174 mg, 1.26 mmol, 3 eq.) and 4-methylphenylboronic acid
(86 mg, 0.63 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (15 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 8a as a colorless solid. Rf = 0.28 (CH2Cl2 : MeOH = 95:5), mp 160-162 °C, yield 74 mg (90 %). C32H36N2O2 (480.6 g/mol). Purity (HPLC): 99 %, tr = 21.31 min. HRMS (APCI): m/z = calcd. for C32H37N2O2 [M+H] 481.2850, found 481.2835. 1H NMR (CDCl3): δ (ppm) = 1.52-1.79 (m, 4H, 3-CH2pyran, 5-CH2pyran), 2.03-2.11 (m, 2H, 6-Ch2), 2.15 (s, 3H, N-CH3), 2.33 (s, 3H, CH3tolyl), 2.51-2.68 (m, 3H, 4-Hpyran, 7-Ch2), 2.74-2.89 (m, 2H, 5-Ch2), 3.30 (td, J = 11.5/2.5 Hz, 2H, CH2axial-O-CH2axial), 3.52 (s, 2H, N-Ch2), 3.89-4.02 (m, 2H, CH2equat.-O-CH2equat.), 7.13-7.18 (m, 3H, 4-Ch, 3-Htolyl, 5-Htolyl), 7.25 (d, J = 8.4 Hz, 2H, 3-Hphenyl, 5-Hphenyl), 7.31-7.39 (m, 2H, 3-Ch, 9-Ch), 7.41 (d, J = 8.1 Hz, 2H, 2-Htolyl, 6-Htolyl), 7.44 (d, J = 1.9 Hz, 1H, 1-Ch), 7.50 (d, J = 8.5 Hz, 2H, 2-Hphenyl, 6-Hphenyl), 7.65 (s, 1H, N-H). 13C NMR (CDCl3): δ (ppm) = 21.6 (CH3tolyl), 28.4 (C-6), 29.6 (C-3pyran, C-5pyran), 30.9 (C-7), 35.1 (C-5), 38.0 (N-Ch3), 57.8 (Ph-Ch2), 60.0 (C-4pyran), 68.2 (C-2pyran, C-6pyran), 120.5 (C-2phenyl, C-6phenyl), 127.2 (C-2tolyl, C-6tolyl), 127.3 (C-3), 129.8 (C-3tolyl, C-5tolyl), 130.0 (C-3phenyl, C-5phenyl), 130.3 (C-4), 130.3 (C-4tolyl), 131.1 (C-1), 134.7 (C-9), 135.1 (C-4a), 137.3 (C-4phenyl), 137.6 (C-1tolyl), 138.0 (C-2), 138.4 (C-1phenyl), 139.6 (C-9a), 141.9 (C-8), 168.5 (O=C-NH). FT-IR (neat): ν (cm⁻¹) = 3298 (N-H), 2970, 2920 (C-Halkyl), 1644 (C=O), 1095, 1014 (C-O).

N-[4-Diethylamino]phenyl]-2-(4-methylphenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (8b)

N,N'-Diethylbenzene-1,4-diamine (60 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 6 (100 mg, 0.36 mmol), triethylamine (73 mg, 0.72 mmol, 2 eq.) and HATU™ (153 mg, 0.40 mmol, 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo and the residue was purified by fc (EtOAc : CH2Cl2 = 1:2 + 5% MeOH) and recrystallized from acetonitrile to give 8b as a colorless solid. Rf = 0.91 (MeOH : CH2Cl2 = 5:95), mp 153-155 °C , yield 86 mg (56 %). C29H32N2O (424.6 g/mol). Purity (HPLC): 99 %, tr = 21.33 min. HRMS (EI): m/z = calcd. for C29H33N2O [MH+H] 425.2587, found 425.2608. 1H NMR (CDCl3): δ (ppm) = 1.15 (t, J = 7.2 Hz, 6H, N(CH2CH3)2), 2.15 (quint, J = 6.3 Hz, 2H, 6-Ch2), 2.40 (s, 3H, CH3tolyl), 2.71 (t, J = 6.6 Hz, 2H, 7-Ch2), 2.81-2.92 (m, 2H, 5-Ch2), 3.34 (q, J = 7.0 Hz, 4H, N(CH2CH3)2), 6.68 (d, J = 9.0 Hz, 2H, 3-Chphenyl, 5-Chphenyl), 7.22 (d, J = 7.8 Hz, 1H, 4-Ch), 7.25 (d, J = 8.4 Hz, 2H, 3-Chtolyl, 5-Chtolyl), 7.38-7.44 (m, 4H, 3-Ch, 9-Ch, 2-Chphenyl, 6-Chphenyl), 7.47-7.50 (m, 3H, 2-Chtolyl, 6-Chtolyl, 1-Ch), 7.51 (s, 1H, NH). 13C
NMR (CDCl₃): δ (ppm) = 13.0 (N(CH₂CH₃)₂), 21.6 (CH₃tolyl), 28.5 (C-6), 30.9 (C-7), 35.0 (C-5), 45.0 (N(CH₂CH₃)₂), 112.9 (C-3phenyl, C-5phenyl), 122.8 (C-2phenyl, C-6phenyl), 127.1 (C-3), 127.2 (C-1), 129.9 (C-2tolyl, C-6tolyl), 130.2 (C-3tolyl, C-5tolyl), 131.1 (C-4), 134.2 (C-9) 135.4 (C-8), 137.5 (C-9a), 138.1 (C-1tolyl), 138.6 (C-4tolyl), 139.6 (C-2), 141.6 (C-4a), 145.7 (C-4phenyl), 164.9 (O=C-NH). A signal for the atom C-1phenyl is not visible. FT-IR ( neat): ν (cm⁻¹) = 3344 (N-H), 2785 (C-Halkyl), 1627 (C=O).

2-(4-Methylphenyl)-N-[4-[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (8c)

4-[4-(Tetrahydro-2H-pyran-4-yl)piperazin-1-yl]aniline (78 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 6 (100 mg, 0.36 mmol), triethylamine (110 mg, 1.08 mmol, 3 eq.) and COMU™ (232 mg, 0.54 mmol, 1.5 eq.) in acetonitrile (5 mL). The mixture was stirred overnight at rt, during which a precipitate was formed. The solid was filtered off, washed with acetonitrile and water, dried and recrystallized from acetonitrile to afford 8c as a colorless solid. Rf = 0.34 (MeOH : CH₂Cl₂ = 5:95), mp 248-250 °C (dec.), yield 107 mg (53 %). C₃₄H₃₉N₃O₂ (521.7 g/mol). Purity (HPLC): >97 %, tᵣ = 21.05 min. HRMS (APCI): m/z = calcd. for C₃₄H₄₀N₃O₂ [MH⁺] 522.3115, found 522.3092. ¹H NMR (CDCl₃): δ (ppm) = 1.62 (qd, J = 12.0/4.3 Hz, 2H, 3-CH₂pyran-axial, 5-CH₂pyran-axial), 1.76-1.86 (m, 2H, 3-CH₂pyran-equat, 5-CH₂pyran-equat), 2.15 (quint. m, J = 6.3 Hz, 2H, 6-CH₂), 2.40 (s, 3H, CH₃tolyl), 2.48 (tt, J = 10.0/2.9 Hz, 1H, 4-Hpyran), 2.67-2.78 (m, 6H, 7-CH₂, 3-CH₂piperazin, 5-CH₂piperazin), 2.82-2.92 (m, 2H, 5-CH₂), 3.13-3.28 (m, 4H, 2-CH₂piperazin, 6-CH₂piperazin), 3.41 (td, J = 11.9/1.9 Hz, 2H, CH₂axial-O-CH₂axial), 4.05 (dd, J = 11.5/3.9 Hz, 2H, CH₂equat.-O-CH₂equat.), 6.93 (d, J = 8.9 Hz, 2H, 3-CHphenyl, 5-CHphenyl), 7.18-7.25 (m, 3H, 4-CH, 3-CHtolyl, 5-CHtolyl), 7.40 (s, 1H, 9-CH), 7.43 (dd, J = 7.8/1.9 Hz, 1H, 3-CH), 7.45-7.52 (m, 5H, 1-CH, 2-CHphenyl, 6-CHphenyl, 2-CHtolyl, 6-CHtolyl), 7.53 (s, 1H, NH). ¹³C NMR (CDCl₃): δ (ppm) = 21.6 (CH₃tolyl), 28.4 (C-6), 30.0 (C-3pyran, C-5pyran), 30.9 (C-5), 35.0 (C-7), 49.5 (C-2piper., C-6piper.), 50.3 (C-3piper, C-5piper), 61.4 (C-4pyran), 67.9 (C-2pyran, C-6pyran), 117.1 (C-3phenyl, C-5phenyl), 121.9 (C-2phenyl, C-6phenyl), 127.2 (C-2tolyl, C-6tolyl), 129.1 (C-1phenyl), 130.0 (C-3tolyl, C-5tolyl), 130.3 (C-3), 131.0 (C-1), 131.1 (C-4), 134.5 (C-9), 135.2 (C-8), 137.6 (C-9a), 138.0 (C-1tolyl), 138.4 (C-4tolyl), 139.6 (C-2), 141.7 (C-4a), 148.8 (C-4phenyl), 168.6 (O=C-NH). FT-IR ( neat): ν (cm⁻¹) = 3290 (N-H), 2831, 2769 (C-Halkyl), 1635 (C=O).
2-(4-Methylphenyl)-N-(4-[N-(thiazol-2-yl)sulfamoyl]phenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (8d)

4-Amino-N-(1,3-thiazol-2-yl)benzenesulfonamide (Sulfathiazole) (92 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 6 (100 mg, 0.36 mmol), triethylamine (75 mg, 0.72 mmol, 2 eq.) and COMU™ (171 mg, 0.4 mmol. 1.1 eq.) in acetonitrile (15 mL). The mixture was stirred overnight at rt, during which a precipitate was formed. The solid was filtered off, washed with acetonitrile and water, dried and recrystallized from acetonitrile to afford 8d as a colorless solid. Rf = 0.28 (MeOH : CH₂Cl₂ = 5:95), mp 222-224 °C (dec.), yield 45 mg (25 %). C₂₈H₂₅N₃O₃S₂ (515.6 g/mol). Purity (HPLC): >95 %, tR = 21.48 min. HRMS (APCI): m/z = calcd. for C₂₈H₂₆N₃O₃S₂ [MH⁺] 516.1410, found 516.1448. ¹H NMR (DMSO-d₆): δ (ppm) = 1.95-2.05 (m, 2H, 6-CH₂), 2.34 (s, 3H, CH₃tolyl), 2.62 (t, J = 6.5 Hz, 2H, 7-CH₂), 2.79-2.89 (m, 2H, 5-CH₂), 6.82 (d, J = 4.6 Hz, 1H, 5-CHthiazol), 7.23-7.31 (m, 4H, 4-CHthiazol, 4-CH, 3-CHtolyl, 5-CHtolyl), 7.39 (s, 1H, 9-CH), 7.52 (dd, J = 7.8/2.0 Hz, 1H, 3-CH), 7.58 (d, J = 8.2 Hz, 2H, 2-CHtolyl, 6-CHtolyl), 7.68 (d, J = 2.0 Hz, 1H, 1-CH), 7.76 (d, J = 8.8 Hz, 2H, 2-CHphenyl, 6-CHphenyl), 7.87 (d, J = 8.9 Hz, 2H, 3-CHphenyl, 5-CHphenyl), 10.30 (s, 1H, NH), 12.69 (s, 1H, SO₂NH). ¹³C NMR (DMSO-d₆): δ (ppm) = 20.5 (CH₃tolyl), 27.2 (C-6), 29.9 (C-5), 33.8 (C-7), 107.7 (C-5thiazol), 119.3 (C-2phenyl, C-6phenyl), 126.1 (C-2tolyl, C-6tolyl), 126.2 (C-3), 126.6 (C-3phenyl, C-5phenyl), 129.4 (C-3tolyl, C-5tolyl), 129.7 (C-4thiazol), 129.8 (C-4, C-1), 133.8 (C-9), 134.5 (C-9a), 136.4 (C-4phenyl), 136.5 (C-4a), 136.9 (C-8), 137.8 (C-1tolyl), 137.9 (C-4tolyl), 140.9 (C-2), 142.4 (C-1phenyl), 168.5 (O=C-NH), 179.6 (C-2thiazol). FT-IR (neat): ν (cm⁻¹) = 3348 (N-H), 2773 (C-Halkyl), 1647 (C=O) 1350, 1184 (SO₂-N).

2-(4-Methylphenyl)-N-(thiazol-2-yl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (8e)

2-Aminothiazole (100 mg, 1.0 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 6 (280 mg, 1.0 mmol), triethylamine (203 mg, 2.0 mmol, 2 eq.) and COMU™ (471 mg, 1.1 mmol. 1.1 eq.) in acetonitrile (15 mL). The mixture was stirred overnight at rt, during which a precipitate was formed. The solid was filtered off, washed with acetonitrile and water, dried and recrystallized from acetonitrile to afford 8e as a beige solid. Rf = 0.37 (MeOH : CH₂Cl₂ = 5:95), mp 200-202 °C (dec.), yield 297 mg (82 %). C₂₂H₂₀N₂OS (360.5 g/mol). Purity (HPLC): 97 %, tR = 22.70 min. HRMS (APCI): m/z = calcd. for C₂₂H₂₁N₃O₃ [MH⁺] 361.1369, found 361.1383. ¹H NMR (CDCl₃): δ (ppm) = 2.11-2.27 (m, 2H, 6-CH₂), 2.39 (s, 3H, CH₃tolyl), 2.81 (t, J = 6.6 Hz, 2H, 7-CH₂), 2.89-3.00
(m, 2H, 5-CH$_2$), 6.83-6.91 (m, 1H, 5-CH$_{thiazol}$), 7.19-7.30 (m, 3H, 3-CH$_{toly}$, 5-CH$_{toly}$, 4-CH), 7.29-7.37 (m, 1H, 4-CH$_{thiazol}$), 7.37 (s, 1H, 9-CH), 7.42 (d, J = 7.8, 2H, 2-CH$_{toly}$, 6-CH$_{toly}$), 7.47 (dd, J = 7.8/2.0 Hz, 1H, 3-CH), 7.55 (broad, 1H, 1-CH), 12.06 (s, 1H, NH). $^{13}$C NMR (CDCl$_3$): δ (ppm) = 21.6 (CH$_{3toly}$), 28.2 (C-6), 30.9 (C-5), 35.3 (C-7), 113.9 (C-5$_{thiazol}$), 127.1 (C-2$_{toly}$, C-6$_{toly}$), 127.7 (C-3), 130.0 (C-3$_{toly}$, C-5$_{toly}$), 130.5 (C-4), 131.6 (C-1), 134.6 (C-9), 137.3 (C-9a), 137.3 (C-8), 137.7 (C-1$_{toly}$), 137.8 (C-4$_{toly}$), 137.8 (C-4a), 139.6 (C-2), 141.9 (C-4$_{thiazol}$), 160.5 (C-2$_{thiazol}$), 168.5 (O=C-NH). FT-IR (neat): $\tilde{\nu}$ (cm$^{-1}$) = 3205 (N-H), 2773 (C=H$_{alkyl}$), 1647 (C=O).

2-[(4-Methyl)phenyl]-N-{4-[(piperidin-1-yl)methyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (8f)

1-(4-Aminobenzyl)piperidine dihydrochloride (95 mg, 0.36 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 6 (100 mg, 0.36 mmol), triethylamine (110 mg, 1.08 mmol, 3 eq.) and HATU™ (153 mg, 0.39 mmol, 1.1 eq.) in acetonitrile (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo and the residue was purified by fc (EtOAc : cyclohexane = 8:2 → EtOAc : CH$_2$Cl$_2$ = 1:2 + 5% MeOH) and recrystallization from acetonitrile afforded 8f as a colorless solid. R$_f$ = 0.14 (CH$_2$Cl$_2$ : MeOH = 95:5), mp 194-196 °C, yield 140 mg (86%). C$_{31}$H$_{34}$N$_2$O (450.6 g/mol). Purity (HPLC): >95 %, t$_r$ = 21.44 min. HRMS (APCI): m/z = calcld. for C$_{31}$H$_{33}$N$_2$O [MH$^+$] 451.2744, found 451.2741. $^1$H NMR (CDCl$_3$): δ (ppm) = 1.34-1.48 (m, 2H, 4-CH$_2$piperidin), 1.57 (m, Hz, 4H, 3-CH$_2$piperidin, 5-CH$_2$piperidin), 2.10-2.25 (m, 2H, 6-CH$_2$), 2.30-2.43 (m, 7H, 2-CH$_2$piperidin, 6-CH$_2$piperidin, CH$_3$toly), 2.72 (t, J = 6.5 Hz, 2H, 2H, 7-CH$_2$), 2.83-2.97 (m, 1H, 5-CH$_2$), 3.46 (s, 2H, Ph-CH$_2$-N), 7.20-7.25 (m, 3H, 4-CH, 3-CH$_{toly}$, 5-CH$_{toly}$), 7.31 (d, J = 8.5 Hz, 2H, 3-CH$_{phenyl}$, 5-CH$_{phenyl}$), 7.41 (s, 1H, 9-CH), 7.44 (dd, J = 7.9/1.9 Hz, 1H, 3-CH), 7.48 (d, J = 8.1 Hz, 2H, 2-CH$_{toly}$, 6-CH$_{toly}$), 7.51 (d, J = 1.8 Hz, 1H, 1-CH), 7.55 (d, J = 8.5 Hz, 2H, 2-CH$_{phenyl}$, 6-CH$_{phenyl}$), 7.62 (s, 1H, NH). $^{13}$C NMR (CDCl$_3$): δ (ppm) = 21.6 (C-4$_{piper}$), 24.8 (C-6), 26.4 (C-3$_{piper}$, C-5$_{piper}$), 30.9 (C-7), 32.0 (C-5), 54.8 (C-2$_{piper}$, C-6$_{piper}$), 63.8 (Ph-CH$_2$-N), 120.3 (C-2$_{phenyl}$, C-6$_{phenyl}$), 127.2 (C-2$_{toly}$, C-6$_{toly}$), 127.3 (C-3), 130.0 (C-3$_{phenyl}$, C-5$_{phenyl}$), 130.3 (C-9), 130.4 (C-3$_{toly}$, C-5$_{toly}$), 131.1 (C-1), 134.7 (C-4), 135.1 (C-4$_{phenyl}$), 137.3 (C-1$_{toly}$), 137.6 (C-4$_{toly}$), 137.9 (C-9a), 138.4 (C-4a), 139.6 (C-2), 141.7 (C-4a), 146.3 (C-1$_{phenyl}$), 168.4 (O=C-NH). FT-IR (neat): $\tilde{\nu}$ (cm$^{-1}$) = 3325 (N-H), 2931 (C-H$_{alkyl}$), 1643 (C=O), 1041, 1018 (C-O).
**N-[4-\{N-Methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl\}phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9a)**

According to general procedure A amide 7 (83 mg, 0.17 mmol), PdCl$_2$(dpff) (16 mg, 0.02 mmol, 10 mol %), NaOCH$_3$ (20 mg, 0.35 mmol, 2 eq.) and phenylboronic acid (24 mg, 0.2 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9a as a colorless solid. Rt = 0.17 (CH$_2$Cl$_2$ : MeOH= 95:5), mp 165-167 °C, yield 74 mg (90 %). C$_{31}$H$_{34}$N$_2$O$_2$ (466.6 g/mol). Purity (HPLC): 95 %, t$_R$ = 20.83 min. HRMS (APCI): m/z = calcd. for C$_{31}$H$_{35}$N$_2$O$_2$ [MH$^+$] 467.2693, found 467.2690. $^1$H NMR (CDCl$_3$): δ (ppm) = 1.63-1.88 (m, 4H, 3-CH$_2$pyran, 5-CH$_2$pyran), 2.11-2.22 (m, 2H, 6-CH$_2$), 2.23 (s, 3H, N-CH$_3$), 2.58-2.69 (m, 1H, 4-HPyran), 2.72 (t, $J$ = 6.6 Hz, 2H, 7-CH$_2$), 2.84-2.96 (m, 2H, 5-CH$_2$), 3.37 (td, $J$ = 11.7/2.3 Hz, 2H, CH$_2$axial=O-CH$_2$axial), 3.60 (s, 2H, Ph-CH$_2$-N), 4.04 (dd, $J$ = 11.4/2.5 Hz, 2H, CH$_2$equat.-O-CH$_2$equat.), 7.25 (d, $J$ = 7.7 Hz, 1H, 4-CH$_1$), 7.30-7.38 (m, 4H, 3-CH$_2$phenyl, 5-CH$_2$phenyl, 3-CH, 9-CH$_1$), 7.37-7.47 (m, 3H, 4-CH$_2$phenyl, 3CH$_2$phenyl, 5-CH$_2$phenyl), 7.46 (d, $J$ = 2.1 Hz, 1H, 1-CH$_2$), 7.54 (m, 2H, 2-CH$_2$phenyl, 6-CH$_2$phenyl), 7.57-7.60 (m, 2H, 2-CH$_2$phenyl, 6-CH$_2$phenyl), 7.65 (s, 1H, N-H). $^{13}$C NMR (CDCl$_3$): δ (ppm) = 28.4 (C-6), 29.4 (C-7), 30.9 (C-3pyran, C-5pyran), 35.1 (C-5), 37.7 (N-CH$_3$), 57.7 (Ph-CH$_2$-N), 60.0 (C-4pyran), 68.0 (C-2pyran, C-6pyran), 120.5 (C-2N-phenyl, C-6N-phenyl), 127.4 (C-2phenyl, C-6phenyl), 127.6 (C-3), 127.8 (C-3phenyl, C-5phenyl), 129.3 (C-3N-phenyl, C-5N-phenyl), 130.2 (C-4phenyl), 130.4 (C-4), 131.3 (C-1), 134.8 (C-9), 135.1 (C-4a), 138.4 (C-2), 139.7 (C-1N-phenyl), 140.9 (C-9a), 142.0 (C-8), 146.4 (C-1phenyl), 168.5 (O=O-C-NH). A Signal for the quaternary carbon atom C-4-phenyl is not visible. FT-IR (neat): $\tilde{\nu}$ (cm$^{-1}$) = 3302 (N-H), 2939, 2843 (C-Halkyl), 1643 (C=O), 1049, 1010 (C-O).

**2-(3-Methylphenyl)-N-[\{N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl\}phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9b)**

According to general procedure A amide 7 (100 mg, 0.21 mmol), PdCl$_2$(dpff) (10 mg, 0.01 mmol, 5 mol%), K$_2$CO$_3$ (60 mg, 0.42 mmol, 2 eq.) and 3-methylphenylboronic acid (45 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9b as a colorless solid. Rt = 0.24 (CH$_2$Cl$_2$ : MeOH = 95:5), mp 183-184 °C, yield 92 mg (92 %). C$_{32}$H$_{36}$N$_2$O$_2$ (480.6 g/mol). Purity (HPLC): 95 %, t$_R$ = 20.89 min. HRMS (APCI): m/z = calcd. for C$_{32}$H$_{37}$N$_2$O$_2$ [MH$^+$] 481.2850, found 481.2827. $^1$H NMR (CDCl$_3$): δ (ppm) = 1.63-1.88 (m, 4H, 3-CH$_2$pyran, 5-CH$_2$pyran), 2.13-2.21 (m, 2H, 6-CH$_2$), 2.21 (s,

According to general procedure A amide 7 (100 mg, 0.21 mmol), PdCl₂(dppf) (10 mg, 0.01 mmol, 5 mol%), K₂CO₃ (60 mg, 0.42 mmol, 2 eq.) and 2-methylphenylboronic acid (45 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH+3 % triethylamine = 95:5) and recrystallized from acetonitrile to give 9c as a colorless solid. Rᵣ = 0.24 (CH₂Cl₂ : MeOH = 95:5), mp 144-145 °C, yield 69 mg (68 %). C₃₂H₃₈N₂O₂ (480.6 g/mol). Purity (HPLC): 99 %, tᵣ = 21.34 min. HRMS (APCI): m/z = calcd. for C₃₂H₃₈N₂O₂ [MH⁺] 481.2850, found 481.2869.

¹H NMR (CDCl₃): δ (ppm) = 1.63-1.88 (m, 4H, 3-Ch₂pyran, 5-Ch₂pyran), 2.13-2.21 (m, 2H, 6-Ch₂), 2.21 (s, 3H, N-Ch₃), 2.28 (s, 3H, CH₃tolyl), 2.65 (tt, J = 11.2/3.9 Hz, 1H, 4-Hpyran), 2.73 (t, J = 6.3 Hz, 2H, 7-Ch₂), 2.89 (t, J = 5.7 Hz, 2H, 5-Ch₂), 3.36 (td, J = 11.6/2.3 Hz, 2H, CH₂axial-O-CH₂axial), 3.57 (s, 2H, Ph-Ch₂-N), 4.04 (dd, J = 10.7/4.1 Hz, 2H, CH₂equat.-O-CH₂equat.), 7.18 (dd, J = 7.7/1.7 Hz, 1H, 3-ChF), 7.20 (d, J = 7.0 Hz, 1H, 4-ChF), 7.22 (d, J = 1.9 Hz, 1H, 1-ChF), 7.23-7.30 (m, 4H, 2-, 3-, 4-, 5-Chtolyl), 7.30 (d, 2H, J = 8.5 Hz, 3-Chphenyl, 5-Chphenyl), 7.35 (s, 9-ChF), 7.55 (d, J = 8.5 Hz, 2H, 2-Hphenyl, 6-Hphenyl), 7.67 (s, 1H, N-H). ¹³C NMR (CDCl₃): δ (ppm) = 21.0 (CH₃tolyl), 28.3 (C-6), 29.6 (C-3pyran, C-5pyran), 31.0 (C-7), 35.2 (C-5), 38.0 (N-Ch₃), 57.7 (Ph-Ch₂-N), 60.0 (C-4pyran), 68.2 (C-2pyran, C-6pyran), 120.4 (C-2phenyl, C-6phenyl), 126.3 (C-3), 127.8 (C-4), 129.4 (C-5tolyl), 129.7 (C-6tolyl), 129.7 (C-4tolyl), 129.9 (C-3phenyl, C-5phenyl), 130.2 (C-3tolyl), 130.1 (C-1), 133.4 (C-9), 136.4 (C₄pyran, C-5pyran), 30.9 (C-7), 35.1 (C-5), 38.0 (N-Ch₃), 57.7 (Ph-Ch₂-N), 60.0 (C-4pyran), 68.2 (C-2pyran, C-6pyran), 120.5 (C-2phenyl, C-6phenyl), 124.5 (C-2tolyl), 127.5 (C-3), 128.2 (C-4tolyl), 128.5 (C-4), 129.2 (C-5tolyl), 129.9 (C-3phenyl, C-5phenyl), 130.3 (C-6tolyl), 131.3 (C-1), 134.7 (C-9), 135.1 (C-4a), 136.4 (C-3tolyl), 137.2 (C-4phenyl), 138.4 (C-2), 138.9 (C-1tolyl), 139.8 (C-1phenyl), 140.8 (C-9a), 141.9 (C-8), 168.5 (O=C-NH). FT-IR (neat): ν (cm⁻¹) = 3344 (N-H), 2924, 2866 (C-Halkyl), 1647 (C=O), 1095, 1010 (C-O).
134.6 (C-2_{tolyl}), 135.8 (C-4a), 137.2 (C-4_{phenyl}), 137.8 (C-2), 139.1 (C-1_{phenyl}), 140.5 (C-9a), 141.5 (C-8), 142.3 (C-1_{tolyl}). A signal for the carbon atom O=C-NH is not visible. FT-IR (neat): $\tilde{\nu}$ (cm$^{-1}$) = 3302 (N-H), 2966, 2862 (C-H$_{alkyl}$), 1651 (C=O), 1095, 1014 (C-O).

2-(4-Ethylphenyl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9d)

According to general procedure A amide 7 (100 mg, 0.21 mmol), PdCl$_2$(dpff) (8 mg, 0.01 mmol, 5 mol%), KOAc (42 mg, 0.42 mmol, 2 eq.) and 4-ethylphenylboronic acid (50 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9d as a colorless solid. R$_f$ = 0.20 (CH$_2$Cl$_2$ : MeOH= 95:5), mp 154-156 °C, yield 100 mg (96 %). C$_{33}$H$_{38}$N$_2$O$_2$ (494.6 g/mol). Purity (HPLC): 98 %, t$_{R}$ = 21.61 min. HRMS (APCI): m/z = calcd. for C$_{33}$H$_{38}$N$_2$O$_2$ [MH$^+$] 495.3006, found 495.3004. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) = 1.28 (t, J = 7.6 Hz, 3H, CH$_2$CH$_3$), 1.62-1.83 (m, 4H, 3-CH$_2$pyran, 5-CH$_2$pyran), 2.10-2.19 (m, 2H, 6-CH$_2$), 2.21 (s, 3H, N-CH$_3$), 2.54-2.70 (m, 1H, 4-CH$_2$pyran), 2.68-2.76 (m, 4H, 7-CH$_2$, CH$_2$CH$_3$), 2.82-2.95 (m, 2H, 5-CH$_2$), 3.37 (td, J = 11.6/2.4 Hz, 2H, CH$_{2\text{axial}}$-O-CH$_{2\text{axial}}$), 3.57 (s, 2H, Ph-CH$_2$-N), 4.04 (dd, J = 10.9/3.4 Hz, 2H, CH$_{2\text{equat}}$-O-CH$_{2\text{equat}}$), 7.23 (d, J = 7.9 Hz, 1H, 4-CH$_2$), 7.28 (d, J = 8.5 Hz, 2H, 3-CH$_{ethylphenyl}$, 5-CH$_{ethylphenyl}$), 7.32 (d, J = 8.3 Hz, 2H, 3-CH$_{phenyl}$, 5-CH$_{phenyl}$), 7.42 (s, 1H, 9-CH$_2$), 7.44 (dd, J = 7.8/1.9 Hz, 1H, 3-CH$_2$), 7.51 (m, 3H, 1-CH, 2-CH$_{ethylphenyl}$ 6-CH$_{ethylphenyl}$), 7.56 (d, J = 8.5 Hz, 2H, 2-CH$_{phenyl}$, 6-CH$_{phenyl}$), 7.61 (s, 1H, N-H). $^{13}$C NMR (CDCl$_3$): $\delta$ (ppm) = 16.04 (CH$_3$), 28.4 (C-6), 28.9 (CH$_2$CH$_3$), 29.6 (C-3$_{pyran}$, 5$_{pyran}$), 30.9 (C-7), 35.1 (C-5), 38.0 (N-CH$_3$), 57.8 (Ph-CH$_2$), 60.0 (C-4$_{pyran}$), 68.2 (C-2$_{pyran}$, C-6$_{pyran}$), 120.5 (C-2$_{phenyl}$, C-6$_{phenyl}$), 127.3 (C-2$_{ethylphenyl}$, C-6$_{ethylphenyl}$), 127.3 (C-3), 128.8 (C-3$_{ethylphenyl}$, C-5$_{ethylphenyl}$), 129.9 (C-3$_{phenyl}$, C-5$_{phenyl}$), 130.3 (C-4), 131.2 (C-1), 134.8 (C-9), 135.1 (C-4a), 137.3 (C-4$_{phenyl}$), 138.2 (C-4$_{ethylphenyl}$), 138.4 (C-1$_{phenyl}$), 139.7 (C-2), 139.7 (C-9a), 141.7 (C-8), 143.9 (C-1$_{ethylphenyl}$), 161.5 (O=C-NH). FT-IR (neat): $\tilde{\nu}$ (cm$^{-1}$) = 3332 (N-H), 2951, 2835 (C-H$_{alkyl}$), 1643 (C=O), 1087 (C-O).

2-(4-Butylphenyl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9e)

According to general procedure A amide 7 (100 mg, 0.21 mmol), PdCl$_2$(dpff) (10 mg, 0.01 mmol, 5 mol%), NaOCH$_3$ (23 mg, 0.42 mmol, 2 eq.) and 4-butylphenylboronic acid (41 mg, 0.23 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (6 mL). The crude
product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9e as a colorless solid. Rf = 0.32 (CH2Cl2 : MeOH= 95:5), mp 134-135 °C, yield 83 mg (76%). C38H42N2O2 (522.7 g/mol). Purity (HPLC): 99 %, tR = 22.95 min. HRMS (APCI): m/z = calcld. for C38H42N2O2 [MH+] 523.3319, found 523.3335. 1H NMR (CDCl3): δ (ppm) = 0.95 (t, J = 7.3 Hz, 3H, 4-CH3butyl), 1.39 (h, 2H, 3-CH2butyl), 1.55-1.81 (m, 6H, 3-CH2pyran, 5-CH2pyran, 2-CH2butyl), 2.07-2.19 (m, 2H, 6-CH2), 2.21 (s, 3H, N-CH3), 2.58-2.70 (m, 3H, 4-CH2pyran, 1-CH2butyl), 2.71 (t, J = 6.5 Hz, 2H, 7-CH2), 2.82-2.92 (m, 2H, 5-CH2), 3.37 (td, J = 11.3/2.3 Hz, 2H, CH2axial-O-CH2axial), 3.57 (s, 2H, Ph-CH2-N), 4.04 (dd, J = 11.3/4.0 Hz, 2H, CH2equat-O-CH2equat), 7.19-7.27 (m, 3H, 4-CH, 3-CHbutylphenyl, 5-CHbutylphenyl), 7.31 (d, J = 8.3 Hz, 2H, 3-CHphenyl, 5-CHphenyl), 7.41 (s, 1H, 9-CH), 7.44 (dd, J = 7.8/2.0 Hz, 1H, 3-CH), 7.46-7.53 (m, 3H, 1-CH, 2-CHbutylphenyl 6-CHbutylphenyl), 7.56 (d, J = 8.4 Hz, 2H, 2-Hphenyl, 6-Hphenyl), 7.67 (s, 1H, N-H). 13C NMR (CDCl3): δ (ppm) = 14.4 (C-4butyl), 22.9 (C-3butyl), 28.4 (C-6), 29.6 (C-3pyran, C-5pyran), 30.9 (C-7), 34.1 (C-2butyl), 35.1 (C-5), 35.7 (C-1butyl), 38.0 (N-CH3), 57.8 (Ph-CH2-N), 60.0 (C-4pyran), 68.2 (C-2pyran, C-6pyran), 120.5 (C-2phenyl, C-6phenyl), 127.2 (C-2butylphenyl, C-6butylphenyl), 127.3 (C-3butylphenyl, C-5butylphenyl), 129.4 (C-3), 129.9 (C-3phenyl, C-5phenyl), 130.3 (C-4), 131.2 (C-1), 134.8 (C-9), 135.1 (C-4a), 136.3 (C-1butylphenyl), 137.3 (C-4phenyl), 138.1 (C-1phenyl), 138.3 (C-2), 139.6 (C-9a), 141.7 (C-8), 142.6 (C-4butylphenyl), 168.5 (O=C-NH). FT-IR (neat): ν (cm⁻¹) = 3352 (N-H), 2951, 2927 (C-Halkyl), 1643 (C=O), 1087 (C-O).

2-(4-tert-Butylphenyl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9f)

According to general procedure A amide 7 (100 mg, 0.21 mmol), PdCl2(dpff) (8 mg, 0.01 mmol, 5 mol%), KOAc (42 mg, 0.42 mmol, 2 eq.) and 4-tert-butylphenylboronic acid (45 mg, 0.25 mmol, 1.2 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9f as a colorless solid. (Rf = 0.22, CH2Cl2 : MeOH= 95:5), mp 164-165 °C, yield 88 mg (79 %). C38H42N2O2 (522.7 g/mol). Purity (HPLC): 99 %, tR = 22.9 min. HRMS (APCI): m/z = calcld. for C38H42N2O2 [MH+] 523.3319, found 523.3335. 1H NMR (CDCl3): δ (ppm) = 1.36 (s, 9H, 2-CH3butyl, 3-CH3butyl, 4-CH3butyl), 1.62-1.84 (m, 4H, 3-CH2pyran, 5-CH2pyran), 2.17 (t, J = 5.9 Hz, 2H, 6-CH2), 2.21 (s, 3H, N-CH3), 2.51-2.69 (m, 1H, 4-CH2pyran), 2.72 (t, J = 6.6 Hz, 2H, 7-CH2), 2.84-2.94 (m, 2H, 5-CH2), 3.37 (td, J = 11.5/2.3 Hz, 2H, CH2axial-O-CH2axial), 3.57 (s, 2H, Ph-CH2-N), 4.04 (dd, J = 10.9/4.1 Hz, 2H, CH2equat-O-CH2equat), 7.23 (d, J = 7.8, 1H, 4-CH), 7.31 (d, J = 8.4 Hz, 2H, 3-CHphenyl, 5-
2-[(1,1'-Biphenyl]-4-yl]-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4yl)-aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9g)

According to general procedure A amide 7 (200 mg, 0.42 mmol), PdCl₂(dppf) (16 mg, 0.02 mmol, 5 mol%), KOAc (84 mg, 0.84 mmol, 2 eq.) and 1,1'-biphenylboronic acid (130 mg, 0.64 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (10 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9g as a colorless solid. Rt = 0.15 (CH₂Cl₂ : MeOH= 95:5), mp 203 °C, yield 205 mg (90 %). C₃₇H₃₈N₂O₂ (542.7 g/mol). Purity (HPLC): >99 %, tₚ = 25.01 min. HRMS (APCI): m/z = calcd. for C₃₇H₃₈N₂O₂ [MH⁺] 543.3006, found 543.3017. ¹H NMR (CDCl₃): δ (ppm) = 1.62-1.82 (m, 4H, 3-CH₂pyran, 5-CH₂pyran), 2.13-2.18 (m, 2H, 6-CH₂), 2.21 (s, 3H, N-CH₃), 2.56-2.69 (s, 1H, 4-CH₂pyran), 2.74 (t, J = 6.6 Hz, 2H, 7-CH₂), 2.85-3.08 (m, 2H, 5-CH₂), 3.37 (td, J = 11.6/2.4 Hz, 2H, CH₂axial-O-CH₂axial), 3.57 (s, 2H, Ph-CH₂-N), 4.04 (dd, J = 10.6/4.1 Hz, 2H, CH₂equat-O-CH₂equat), 7.27 (d, J = 8.1 Hz, 1H, 4-CH), 7.31 (d, J = 8.4 Hz, 2H, 3-CH₂phenyl, 5-CH₂phenyl), 7.34-7.39 (m, 1H, 4’-CH₂biphenyl), 7.43-7.49 (m, 3H, 9-CH, 3-CH₂phenyl, 5-CH₂phenyl), 7.51 (dd, J = 7.8/2.0 Hz, 1H, 1-CH, 7.53-7.61 (m, 3H, 1-CH, 2-CH₂biphenyl, 6-CH₂biphenyl), 7.62-7.65 (m, 3H, 2-H phenyl, 6-H phenyl, N-H), 7.65-7.69 (m, 4H, 2’, 3’, 5’, 6’-CH₂biphenyl). ¹³C NMR (CDCl₃): δ (ppm) = 28.4 (C-6), 29.6 (C-3pyran, C-5pyran), 30.9 (C-7), 35.1 (C-5), 38.0 (N-CH₃), 57.8 (Ph-CH₂-N), 60.0 (C-4pyran), 68.2 (C-2pyran, C-6pyran), 120.5 (C-2phenyl, C-6phenyl), 127.4 (C-3’biphenyl, C-5’biphenyl), 127.7 (C-3biphenyl, C-5biphenyl), 127.84 (C-3), 128.0 (C-2’biphenyl, C-6’biphenyl), 129.3 (C-2biphenyl, C-6biphenyl), 129.9 (C-3phenyl, C-5phenyl), 130.5 (C-4), 131.2 (C-1), 134.7 (C-9), 135.2 (C-4a), 137.3 (C-4phenyl), 137.9 (C-1phenyl), 138.6 (C-8), 139.2 (C-9a), 139.8 (C-4biphenyl), 140.6 (C-1’biphenyl), 141.1 (C-1biphenyl), 142.1 (C-8), 168.3 (O=C-H).
N-[4-[N-Methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-2-(naphtalen-2-yl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9h)

According to general procedure A amide 7 (100 mg, 0.21 mmol), PdCl₂(dppf) (8 mg, 0.01 mmol, 5 mol%), KOAc (40 mg, 0.42 mmol, 2 eq.) and 2-naphthylboronic acid (40 mg, 0.23 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (5 mL). (APCI): m/z = calcd. for C₃₅H₃₈N₂O₂ (516.6 g/mol). Purity (HPLC): 96 %, tₚ = 21.57 min. HRMS (APCI): m/z = calcd. for C₃₅H₃₈N₂O₂ [MH⁺] 517.2850, found 517.2880. ¹H NMR (CDCl₃): δ (ppm) = 1.63-1.88 (m, 4H, 3-CH₂pyran, 5-CH₂pyran), 2.15-2.20 (m, 2H, 6-CH₂), 2.21 (s, 3H, N-CH₃), 2.64 (tt, J = 11.1/4.1 Hz, 1H, 4-CH₂pyran), 2.75 (t, J = 6.6 Hz, 2H, 7-CH₂), 2.87-2.97 (m, 2H, 5-CH₂), 3.37 (td, J = 11.6/2.4 Hz, 2H, CH₂axial-O-CH₂axial), 3.57 (s, 2H, Ph-CH₂-N), 4.04 (dd, J = 10.8/4.3 Hz, 2H, CH₂equat-O-CH₂equat), 7.28-7.37 (m, 3H, 4-CH, 3-CH(phenyl), 5-CH(phenyl)), 7.45-7.54 (m, 3H, 9-CH, 6,7-CH(naphthyl), 7.55-7.61 (m, 3H, 3-CH, 2-CH(phenyl), 6-CH(phenyl)), 7.63 (s, 1H, N-H), 7.68 (d, J = 2.0 Hz, 1H, 1-CH), 7.74 (dd, J = 8.5/1.9 Hz, 1H, 3-CH(naphthyl), 7.82-7.98 (m, 3H, 1-CH(naphthyl), 5,8-CH(naphthyl), 8.04 (d, J = 1.8 Hz, 1H, 4-CH(naphthyl)). ¹³C NMR (CDCl₃): δ (ppm) = 28.4 (C-6), 29.6 (C-3pyran, C-5pyran), 30.9 (C-7), 35.1 (C-5), 38.0 (N-CH₃), 57.7 (Ph-CH₂-N), 60.0 (C-4pyran), 68.2 (C-2pyran, C-6pyran), 120.5 (C-2phenyl, C-6phenyl), 125.8 (C-3naphthyl), 126.0 (C-4naphthyl), 126.4 (C-7naphthyl), 126.8 (C-3), 127.8 (C-1naphthyl), 128.1 (C-5naphthyl), 128.6 (C-8naphthyl), 128.9 (C-6naphthyl), 129.9 (C-3phenyl, C-5phenyl), 130.5 (C-3), 131.6 (C-1), 133.1 (C-4anaphthyl), 134.1 (C-8anaphthyl), 134.7 (C-9), 135.3 (C-4a), 136.4 (C-2naphthyl), 137.3 (C-4phenyl), 138.2 (C-1phenyl), 138.6 (C-2), 139.6 (C-9a), 142.1 (C-8), 168.5 (O=C-NH). FT-IR (neat): ν (cm⁻¹) = 3298 (N-H), 2970, 2940 (C-H₃), 1645 (C=O), 1099, 1010 (C-O).

2-(2-Fluoropyridin-3-yl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9j)

According to general procedure A amide 7 (150 mg, 0.32 mmol), PdCl₂(dppf) (12 mg, 0.016 mmol, 5 mol%), KOAc (40 mg, 0.64 mmol, 2 eq.) and 2-fluoropyridine-3-ylboronic acid (68 mg, 0.48 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (8 mL). The crude product was purified by fc (CH₂Cl₂: EtOAc + 5 % MeOH = 2:1) and recrystallized
from acetonitrile to give 9j as a pale yellow solid. Rf = 0.17 (CH₂Cl₂ : MeOH= 95:5), mp 154-156 °C, yield 59 mg (60 %). C₃₀H₃₂FN₃O₂ (485.6 g/mol). Purity (HPLC): 98 %, tᵣ = 18.35 min. HRMS (APCI): m/z = calcd. for C₃₀H₃₂FN₃O₂ [MH⁺] 486.2551, found 486.2524. ¹H NMR (CDCl₃): δ (ppm) = 1.63-1.85 (m, 4H, 3-CH₂pyran, 5-CH₂pyran), 2.12-2.20 (m, 2H, 6-CH₂), 2.24 (s, 3H, N-CH₃), 2.64-2.81 (m, 3H, 4-CH₂pyran, 7-CH₂), 2.84-2.96 (m, 2H, 5-CH₂), 3.37 (td, J = 11.7/2.2 Hz, 2H, CH₂axial-O-CH₂axial), 3.61 (s, 2H, Ph-CH₂-N), 4.04 (dd, J = 11.2/4.4 Hz, 2H, CH₂equat-O-CH₂equat), 7.26 (m, 1H, 4-CH), 7.27-7.32 (m, 2H, 9-CH, 5-CH₂pyridine), 7.34 (d, J = 7.9 Hz, 2H, 3-CH₂phenyl, 5-CH₂phenyl), 7.43 (d, J = 7.8 Hz, 1H, 3-CH₂), 7.50 (s, 1H, 1-CH), 7.57 (d, J = 8.4 Hz, 2H, 2-CH₂phenyl, 6-CH₂phenyl), 7.69 (s, 1H, N-H), 7.87 (ddd, J = 9.7/7.4/2.0 Hz, 1H, 4-CH₂pyridine), 8.20 (d, J = 4.6 Hz, 1H, 6-CH₂pyridine). ¹³C NMR (CDCl₃): δ (ppm) = 28.3 (C-6), 29.5 (C-3pyran, C-5pyran), 30.9 (C-7), 35.2 (C-5), 37.8 (N-CH₃), 57.7 (Ph-CH₂-N), 60.0 (C-4pyran), 68.0 (C-2pyran, C-6pyran), 120.5 (C-2phenyl, C-6phenyl), 122.3 (d, J = 4.3 Hz, C-3pyridine), 123.5 (C-3), 129.1 (d, J = 2.6 Hz, C-5pyridine), 130.1 (C-3phenyl, C-5phenyl), 130.4 (C-4), 132.4 (C-2), 132.7 (C-4phenyl), 132.8 (C-1), 134.1 (C-9), 135.3 (C-4a), 139.0 (C-1phenyl), 140.9 (C-9a), 140.9 (d, J = 10.7 Hz, C-4pyridine), 143.3 (C-8), 146.8 (d, J = 14.6 Hz, C-6pyridine), 162.1 (d, J = 238.1 Hz, C-2pyridine), 168.4 (O=C-NH). FT-IR (neat): ν (cm⁻¹) = 3294 (N-H), 2943, 2924 (C-H), 2913, 2846 (N-H), 1687 (C=O), 1141, 1010 (C-O), 759, 725 (out of plane).

2-(6-Isopropoxypyridin-3-yl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-y1)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9k)

According to general procedure A amide 7 (172 mg, 0.37 mmol), PdCl₂(dppf) (15 mg, 0.02 mmol, 5 mol%), KOAc (73 mg, 0.74 mmol, 2 eq.) and 6-isopropoxypyridine-3-y1boronic acid (100 mg, 0.55 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (10 mL). The crude product was purified by fc (CH₂Cl₂: EtOAC + 5 % MeOH = 2:1) and recrystallized from acetonitrile to give 9k as a colorless solid. Rf = 0.06 (CH₂Cl₂: EtOAC + 5 % MeOH = 2:1), mp 173-175 °C, yield 132 mg (67 %). C₃₃H₃₉N₃O₃ (525.7 g/mol). Purity (HPLC): 99 %, tᵣ = 19.75 min. HRMS (APCI): m/z = calcd. for C₃₃H₄₀N₃O₃ [MH⁺] 526.3064, found 526.3077. ¹H NMR (CDCl₃): δ (ppm) = 1.38 (d, J = 6.2 Hz, 6H, CH(CH₃)₂), 1.52-1.87 (m, 4H, 3-CH₂pyran, 5-CH₂pyran), 2.07-2.20 (m, 2H, 6-CH₂), 2.21 (s, 3H, N-CH₃), 2.58-2.69 (m, 1H, 4-CH₂pyran), 2.72 (t, J = 6.6 Hz, 2H, 7-CH₂), 2.81-2.98 (m, 2H, 5-CH₂), 3.37 (td, J = 11.6/2.3 Hz, 2H, CH₂axial-O-CH₂axial), 3.57 (s, 2H, Ph-CH₂-N), 4.04 (dd, J = 11.5/4.3 Hz, 2H, CH₂equat-O-CH₂equat), 5.34 (sept., J = 6.2 Hz, 1H, CH(CH₃)₂), 6.75 (d, J = 8.6 Hz, 1H, 5-CH₂pyridine), 7.24 (d, J = 8.1 Hz, 1H, 4-CH), 7.31 (d, J = 8.2 Hz, 2H, 3-
CH₆phenyl, 5-CH₆phenyl), 7.37 (dd, J = 7.9/1.8 Hz, 1H, 3-CH), 7.40 (s, 1H, 9-CH), 7.44 (s, 1H, 1-CH), 7.56 (d, J = 8.4 Hz, 2H, 2-Hphenyl, 6-Hphenyl), 7.64 (s, 1H, N-H), 7.75 (dd, J = 8.6/2.6 Hz, 1H, 4-CHpyridine), 8.35 (d, J = 2.6 Hz, 1H, 2-CHpyridine). ¹³C NMR (CDCl₃): δ (ppm) = 22.6 (CH(CH₃)₂), 28.5 (C-6), 29.7 (C-3pyran, C-5pyran), 30.9 (C-7), 35.0 (C-5), 37.9 (N-CH₃), 57.7 (Ph-CH₂-N), 60.0 (C-4pyran), 68.2 (C-2pyran, C-6pyran), 68.6 (CH(CH₃)₂), 111.9 (C-5pyridine), 120.5 (C-2phenyl, C-6phenyl), 126.9 (C-3), 129.3 (C-2), 129.9 (C-3phenyl, C-5phenyl), 130.5 (C-4), 130.7 (C-1), 134.5 (C-9), 135.4 (C-4a), 136.6 (C-4phenyl), 137.2 (C-4pyridine), 137.7 (C-9a, C-3pyridine), 138.7 (C-1phenyl), 141.9 (C-8), 145.3 (C-2pyridine), 163.4 (C-6pyridine), 168.3 (O=C-NH). FT-IR (neat): ʋ (cm⁻¹) = 3321 (N-H), 2924, 2835 (C-Halkyl), 1643 (C=O), 1114, 1049 (C-O), 709, 686 (out of plane bending).

2-(4-Fluorophenyl)-N-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9l)

According to general procedure A amide 7 (57 mg, 0.12 mmol), PdCl₂(dpdpf) (10 mg, 0.01 mmol, 10 mol%), NaOCH₃ (14 mg, 0.24 mmol, 2 eq.) and 4-fluorophenylboronic acid (19 mg, 0.13 mmol, 1 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9l as a colorless solid. Rt = 0.25 (CH₂Cl₂ : MeOH = 95:5), mp 192 °C, yield 38 mg (65 %). C₃₁H₃₃FN₂O₂ (484.6 g/mol). Purity (HPLC): 97 %, tᵣ = 20.78 min. HRMS (APCI): m/z = calcd. for C₃₁H₃₄FN₂O₂ [M⁺] 485.2599, found 485.2598. ¹H NMR (CDCl₃): δ (ppm) = 1.59-1.84 (m, 4H, 3-CH₂pyran, 5-CH₂pyran), 2.10-2.22 (m, 2H, 6-CH₂), 2.24 (s, 3H, N-CH₃), 2.64-2.77 (m, 3H, 4-CHpyran,7-CH₂), 2.82-2.95 (m, 2H, 5-CH₂), 3.37 (td, J = 11.7/2.1 Hz, 2H, CH₂axial=O-CH₂axial), 3.61 (s, 2H, Ph-CH₂-N), 4.04 (dd, J = 11.0/3.9 Hz, 2H, CH₂equat=O-CH₂equat), 7.09 (m, 2H, 3-CH₆phen, 5-CH₆phen), 7.24 (d, J = 7.8 Hz, 1H, 4-CH), 7.34 (d, J = 8.1 Hz, 2H, 3-CH₆phenyl, 5-CH₆phenyl), 7.40 (dd, J = 7.8/2.0 Hz, 1H, 3-CH₆), 7.42 (s, 1H, 9-CH), 7.48 (d, J = 1.8 Hz, 1H, 1-CH₃), 7.51-7.55 (m, 2H, 2-CH₆phen, 6-CH₆phen), 7.57 (d, J = 8.4 Hz, 2H, 2-CH₆phenyl, 6-CH₆phenyl), 7.64 (s, 1H, N-H). ¹³C NMR (CDCl₃): δ (ppm) = 27.7 (C-6), 28.9 (C-3pyran, C-5pyran), 30.3 (C-7), 34.4 (C-5), 37.2 (N-CH₃), 57.1 (Ph-CH₂-N), 59.4 (C-4pyran), 67.4 (C-2pyran, C-6pyran), 115.5 (d, J = 21.5 Hz, C-3F-phen, C-5F-phen), 119.8 (C-2phenyl, C-6phenyl), 126.7 (C-3), 128.3 (d, J = 8.0 Hz, C-2F-phen, C-6F-phen), 129.4 (C-3phenyl, C-5phenyl), 129.8 (C-4), 130.5 (C-1), 134.0 (C-9a), 134.6 (C-4phenyl), 135.5 (C-9), 135.9 (C-4a), 136.3 (d, J = 3.1 Hz, C-1F-phen), 137.9 (C-2), 138.1 (C-1phenyl), 141.3 (C-8), 162.3 (d, J = 248.6 Hz, C-4F-phen), 167.7 (O=C-NH).
2-(4-Fluoro-3-methylphenyl)-N-(4-\{N-methyl-\{tetrahydro-2H-pyran-4-yl\}\}aminomethyl\{phenyl\})-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9m)

According to general procedure A amide 7 (65 mg, 0.14 mmol), PdCl₂(dppf) (12 mg, 0.017 mmol, 10 mol%), K₂CO₃ (59 mg, 0.42 mmol, 3 eq.) and 4-fluoro-3-methylphenylboronic acid (24 mg, 0.15 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9m as a colorless solid. Rₐ = 0.33, CH₂Cl₂ : MeOH = 95:5, mp 161-162 °C (dec.) yield 48 mg (70 %). C₃₂H₃₅FN₅O₂ (498.6 g/mol). Purity (HPLC): 98 %, tₙ = 21.48 min. HRMS (APCI): m/z = calcd. for C₃₂H₃₅FN₅O₂ [MH⁺] 499.2755, found 499.2773. ¹H NMR (CDCl₃): δ (ppm) = 1.61-1.90 (m, 4H, 3-CH₂pyran, 5-CH₂pyran), 2.10-2.22 (m, 2H, 6-CH₂), 2.28 (s, 3H, N-CH₃), 2.34 (s, 3H, CH₃F-phenyl), 2.72 (t, J = 6.2 Hz, 2H, 7-CH₂), 2.74-2.81 (m, 1H, 4-CH₃pyran), 2.84-2.93 (m, 2H, 5-CH₂), 3.37 (td, J = 11.7/2.0 Hz, 2H, CH₂axial-O-CH₂axial), 3.67 (s, 2H, Ph-CH₂-N), 4.05 (dd, J = 11.2/3.9 Hz, 2H, CH₂equat-O-CH₂equat), 7.06 (m, 5-CHF-phenyl), 7.23 (d, J = 7.7 Hz, 1H, 4-CH), 7.30-7.37 (m, 2H, 2-CHF-phenyl, 3-CH₃), 7.36 (d, J = 8.6 Hz, 2H, 3-CH₃phenyl, 5-CH₃phenyl), 7.40 (m, 1H, 6-CHF-phenyl), 7.42 (s, 1H, 9-CH), 7.48 (d, J = 1.8 Hz, 1H, 1-CH), 7.58 (d, J = 8.4 Hz, 2H, 2-CH₃phenyl, 6-CH₃phenyl), 7.66 (s, 1H, N-H). ¹³C NMR (CDCl₃): δ (ppm) = 14.56 (d, J = 3.2 Hz, CH₃F-phenyl), 27.7 (C-6), 28.3 (C-3pyran, C-5pyran), 30.3 (C-7), 34.4 (C-5), 36.5 (N-CH₃), 56.7 (Ph-CH₂-N), 59.8 (C-4pyran), 67.1 (C-2pyran, C-6pyran), 115.1 (d, J = 21.5 Hz, C-5F-phenyl), 120.0 (C-2phenyl, C-6phenyl), 125.5 (d, J = 8.2 Hz, C-6F-phenyl), 126.7 (C-3), 129.8 (C-4 ), 129.8 (d, J = 5.2 Hz, C-2F-phenyl), 130.0 (C-3phenyl, C-5phenyl), 130.5 (C-1), 134.4 (d, J = 18.8 Hz, C-3F-phenyl), 134.0 (C-9a), 134.6 (C-4phenyl), 135.9 (C-9), 136.0 (d, J = 3.7 Hz, C-1F-phenyl), 136.3 (C-4a), 137.7 (C-2), 138.3 (C-1phenyl), 141.2 (C-8), 160.9 (d, J = 245.2 Hz, C-4F-phenyl), 167.8 (O=C-NH). FT-IR (neat): ν (cm⁻¹) = 3286 (N-H), 2924, 2843 (C-H₉alkyl), 1651 (C=O), 1138, 1006 (C=O).

2-(4-Hydroxy-3-methylphenyl)-N-\{4-\{N-methyl-\{tetrahydro-2H-pyran-4-yl\}\}aminomethyl\{phenyl\}\}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9o)

According to general procedure A amide 7 (162 mg, 0.34 mmol), PdCl₂(dppf) (14 mg, 0.017 mmol, 5 mol%), NaOCH₃ (38 mg, 0.68 mmol, 2 eq.) and 4-hydroxy-3-methylphenylboronic acid (90 mg, 0.38 mmol, 1.1 eq.) were suspended in dry
dimethoxyethane (7 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9o as a colorless solid. Rf = 0.11 (CH2Cl2 : EtOAc + 5 % MeOH= 2:1), mp 192 °C , yield 128 mg (76 %).

C32H36N2O3 (496.6 g/mol). Purity (HPLC): 96 %, tr = 19.32 min. HRMS (APCI): m/z = calcd. for C32H37N2O3 [MH⁺] 497.2799, found 497.2778. 1H NMR (CDCl3): δ (ppm) = 1.55-1.73 (m, 4H, 3-CH2pyran, 5-CH2pyran), 2.03-2.12 (m, 2H, 6-CH2), 2.14 (s, 3H, CH3hydroxyphen.), 2.25 (s, 3H, N-C=H), 2.51-2.62 (m, 1H, 4-CHpyran.), 2.65 (t, J = 6.5 Hz, 2H, 7-CH2), 2.76-2.86 (m, 2H, 5-CH2), 3.37 (td, J = 11.6/2.4 Hz, 2H, CH2axial-O-CH2axial), 3.50 (s, 2H, Ph-CH2-N), 3.97 (dd, J = 10.9/4.3 Hz, 2H, CH2equat-O-CH2equat), 6.76 (d, J = 8.2 Hz, 1H, 5-CHhydroxyphen.), 7.13 (d, J = 7.9 Hz, 1H, 4-CH), 7.22 (d, J = 2.2 Hz, 1H, 2-CHhydroxyphen), 7.24 (d, J = 8.3 Hz, 2H, 3-CHphenyl, 5-CHphenyl), 7.29 (m, 1H, 6-CHhydroxyphen), 7.30-7.36 (m, 2H, 9-CH, 3-CH3), 7.40 (d, J = 2.0 Hz, 1H, 1-CH), 7.49 (d, J = 8.4 Hz, 2H, 2-CHphenyl, 6-CHphenyl), 7.56 (s, 1H, N-H). 13C NMR (DMSO-d6): δ (ppm) = 16.2 (CH3HO-phen), 27.5 (C-6), 28.9 (C-3pyran, C-5pyran), 30.2 (C-7), 34.0 (C-5), 37.1 (N-CH3), 56.7 (Ph-CH2-N), 58.9 (C-4pyran), 66.7 (C-2pyran, C-6pyran), 109.3 (C-5HO-phen), 115.0 (C-6HO-phen), 119.9 (C-2phenyl, C-6phenyl), 124.3 (C-3), 124.7 (C-3HO-phen), 125.5 (C-2HO-phen), 128.7 (C-3phenyl, C-5phenyl), 129.5 (C-4), 129.8 (C-1), 130.2 (C-9a), 131.4, 133.4 (C-4phenyl), 134.7 (C-9), 134.9 (C-4a), 137.9 (C-2), 138.1 (C-1HO-phen), 138.2 (C-1phenyl), 140.0 (C-8), 155.2 (C-4HO-phen), 168.3 (O=C-NH). FT-IR (neat): ν (cm⁻¹) = 3352 (N-H), 2927, 2846 (C-Halkyl), 1647 (C=O), 1161, 1083 (C-O), 810, 671 (out of plane bending).

2-[4-(Hydroxymethyl)phenyl]-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9p)

According to general procedure A amide 7 (100 mg, 0.21 mmol), PdCl2(dppe) (15 mg, 0.02 mmol, 10 mol%), NaOCH3 (23 mg, 0.42 mmol, 2 eq.) and 4-(hydroxymethyl)phenylboronic acid (35 mg, 0.23 mmol, 1.1 eq.) were suspended in dry dimethoxyethane (6 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9p as a colorless solid. Rf = 0.08 (CH2Cl2 : MeOH = 95:5), mp 210 °C (dec.), yield 53 mg (51 %).

C32H36N2O3 (496.6 g/mol). Purity (HPLC): 96 %, tr = 18.37 min. HRMS (APCI): m/z = calcd. for C32H37N2O3 [MH⁺] 497.2799, found 497.2798. 1H NMR (CDCl3): δ (ppm) = 1.57-1.86 (m, 4H, 3-CH2pyran, 5-CH2pyran), 2.10-2.22 (m, 2H, 6-CH2), 2.23 (s, 3H, N-C=H), 2.62-2.71 (m, 1H, 4-CHpyran), 2.71-2.77 (m, 2H, 7-CH2), 2.84-2.93 (m, 2H, 5-CH2), 3.37 (td, J = 11.7/4.4 Hz, 2H, CH2axial-O-CH2axial), 3.60 (s, 2H, Ph-CH2-N), 4.04 (dd, J =
11.0/3.9 Hz, 2H, CH2equat-O-CH2equat), 4.75 (s, 2H, CH2OH), 7.25 (d, J = 7.8 Hz, 1H, 4-CH), 7.33 (d, J = 8.0 Hz, 2H, 3-CHphenyl, 5-CHphenyl), 7.42 (s, 1H, 9-CH), 7.43-7.47 (m, 3H, 3-CH, 3-CHhydroxymethylphenyl, 5-CHhydroxymethylphenyl), 7.53 (d, J = 2.0 Hz, 1H, 1-CH) 7.56 (d, J 7.5 Hz, 2H, 2-CHhydroxymethylphenyl, 6-CHhydroxymethylphenyl), 7.58 (d, J = 8.1 Hz, 2H, 2-Chphenyl, 6-Chphenyl), 7.66 (s, 1H, N-H). 13C NMR (CDCl3): δ (ppm) = 28.1 (C-6), 29.3 (C-3pyran, C-5pyran), 30.6 (C-7), 34.7 (C-5), 37.7 (N-Ch3), 57.4 (Ph-Ch2-N), 59.7 (C-4pyran), 65.2 (CH2OH), 67.8 (C-2pyran, C-6pyran), 120.2 (C-2phenyl, C-6phenyl), 127.1 (C-3), 127.2 (C-2hydroxymethylphenyl, C-6hydroxymethylphenyl), 127.6 (C-3hydroxymethylphenyl, C-5hydroxymethylphenyl), 129.6 (C-3phenyl, C-5phenyl), 130.1 (C-4), 130.9 (C-1), 134.4 (C-9a), 134.8 (C-4phenyl), 135.8 (C-9), 138.2 (C-2), 138.9 (C-1phenyl), 139.9 (C-8), 141.7 (C-4hydroxymethylphenyl), 148.8 (C-1hydroxymethylphenyl). Signals for quaternary carbon atoms O=C-NH and C-4a are not visible.

2-(5-Formylthiophen-2-yl)-N-[4-[(methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9v)

According to general procedure A amide 7 (60 mg, 0.13 mmol), PdCl2(dpdpf) (10 mg, 0.01 mmol, 10 mol%), NaOCH3 (14 mg, 0.25 mmol, 2 eq.) and 5-formylthiophen-2-ylboronic acid (50 mg, 0.32 mmol, 1.5 eq.) were suspended in dry dimethoxyethane (5 mL). The crude product was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 9v as an orange solid. Rf = 0.23 (CH2Cl2 : MeOH= 95:5), mp 168-169 °C, yield 43 mg (86 %). C30H32N2O3S (500.6 g/mol). Purity (HPLC): 98 %, tr = 19.66 min. HRMS (APCI): m/z = calcld. for C30H32N2O3S [MH+] 501.2206, found 501.2223. 1H NMR (CDCl3): δ (ppm) = 1.63-1.85 (m, 4H, 3-Chpyran, 5-Chpyran), 2.09-2.22 (m, 2H, 6-Ch2), 2.25 (s, 3H, N-Ch3), 2.63-2.81 (m, 3H, 4-Chpyran, 7-Ch2), 2.82-2.95 (m, 2H, 5-Ch2), 3.37 (td, J = 11.7/2.2 Hz, 2H, Ch2axial-O-Ch2axial), 3.63 (s, 2H, Ph-Ch2-N), 4.05 (dd, J = 11.6/4.1 Hz, 2H, CH2equat-O-CH2equat), 7.23-7.26 (m, 1H, 4-CH), 7.26 (s, 1H, 9-CH), 7.36 (d, J = 7.4 Hz, 2H, 3-Chphenyl, 5-Chphenyl), 7.39 (d, J = 4.1 Hz, 1H, 4-Chthioph), 7.52 (dd, J = 7.8/2.0 Hz, 1H, 3-CH), 7.58 (d, J = 8.6 Hz, 2H, 2-Hphenyl, 6-Hphenyl), 7.61 (d, J = 1.9 Hz, 1H, 1-CH), 7.67 (s, 1H, N-H), 7.74 (d, J = 3.9 Hz, 1H, 3-Chthioph), 9.89 (s, 1H, CHO). 13C NMR (CDCl3): δ (ppm) = 28.3 (C-6), 29.2 (C-3pyran, C-5pyran), 30.9 (C-7), 35.2 (C-5), 37.5 (N-Ch3), 57.5 (Ph-Ch2-N), 60.1 (C-4pyran), 67.9 (C-2pyran, C-6pyran), 120.6 (C-2phenyl, C-6phenyl), 126.6 (C-3), 130.3 (C-3phenyl, C-5phenyl), 130.3 (C-4), 130.7 (C-3thioph.), 131.6 (C-1), 133.8 (C-9), 135.4 (C-4a), 138.0 (C-4thioph., C-4phenyl), 139.4 (C-1phenyl), 138.0 (C-2), 139.4 (C-9a), 142.7 (C-8), 144.4 (C-2thioph), 154.1 (C-5thioph), 168.3 (O=C-NH), 183.2 (HC=O). FT-IR (neat): ν (cm⁻¹) = 3290 (N-H), 2924, 2843 (C-Halkyl),
2789 (H-CO), 1647 (HC=O), 1593 (C=Caryl), 1141, 1010 (C-O), 767, 667 out of plane bending.

2-(4-Methylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-y1)aminomethyl]-phenyl}-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14a)

N-(4-Aminophenyl)-N-methyltetrahydro-2H-pyran-4-amin (78 mg, 0.35 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 13a (100 mg, 0.35 mmol), triethylamine (71 mg, 0.70 mmol, 2 eq.) and HATU™ (150 mg, 0.38 mmol, 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo and the residue was purified by fc (EtOAc : CH2Cl2 = 1:2 + 5% MeOH) and recrystallized from acetonitrile to give 14a as a yellow solid. Rf = 0.13 (MeOH : CH2Cl2 = 5:95), mp 201 °C, yield 136 mg (80%).

HRMS (APCI): m/z = calcd. for C30H34N2O2S [MH+] 487.2414, found 487.2381. 1H NMR (CDCl3): δ (ppm) = 1.55-1.83 (m, 4H, 3-CH2pyran, 5-CH2pyran), 2.13 (quint, J = 5.1 Hz, 2H, 7-CH2), 2.21 (s, 3H, N-CH3), 2.36 (s, 3H, CH3tolyl), 2.64 (tt, J = 10.9/3.5 Hz, 1H, 4-Hpyran), 2.84 (t, J = 5.8 Hz, 2H, 6-CH2), 3.11 (t, J = 5.6 Hz, 2H, 8-CH2), 3.37 (td, J = 11.6/2.3 Hz, 2H, CH2axial-O-CH2axial), 3.57 (s, 2H, Ph-CH2-N), 4.04 (dd, J = 11.4/4.4 Hz, 2H, CH2equat-O-CH2equat), 7.07 (s, 1H, 3-CH), 7.14-7.24 (m, 3H, 3-CHtolyl, 5-CHtolyl, 4-CH), 7.30 (d, J = 8.2 Hz, 2H, 3-CHphenyl, 5-CHphenyl), 7.42 (d, J = 8.1 Hz, 2H, 2-CHtolyl, 6-CHtolyl), 7.49-7.57 (m, 3H, 2-CHphenyl, 6-CHphenyl, NH). 13C NMR (CDCl3): δ (ppm) = 21.6 (CH3tolyl), 24.6 (C-7), 29.6 (C-3pyran, C-5pyran), 31.1 (C-8, C-6), 37.9 (N-CH3), 57.7 (C-4pyran), 59.9 (Ph-CH2-N), 68.2 (C-2pyran, C-6pyran), 120.4 (C-2phenyl, C-6phenyl), 125.8 (C-2tolyl, C-6tolyl), 127.1 (C-3), 127.7 (C-4), 129.9 (C-3phenyl, C-5phenyl), 130.0 (C-3tolyl, C-5tolyl), 131.5 (C-1tolyl), 133.8 (C-4phenyl), 136.4 (C-1phenyl), 137.7 (C-2), 137.8 (C-3a), 140.8 (C-5), 143.7 (C-8a), 146.3 (C-4tolyl), 168.7 (O=C-NH). FT-IR (neat): ν (cm-1) = 3309 (N-H), 2839 (C-Halkyl), 1627 (C=O).

2-(4-Methylphenyl)-N-[2-(tetrahydro-2H-pyran-4-y1)-1,2,3,4-tetrahydroisoquinolin-7-y1]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14b)

2-(Tetrahydro-2H-pyran-4-y1)-1,2,3,4-tetrahydroisoquinolin-7-amine (82 mg, 0.35 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 13a (100 mg, 0.35 mmol), triethylamine (71 mg, 0.70 mmol, 2 eq.) and HATU™ (150 mg, 0.38 mmol, 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo and the residue was purified by fc (EtOAc : CH2Cl2 = 1:2 + 5 % MeOH) and recrystallized from acetonitrile to give 14b as a yellow solid. Rf = 0.13 (MeOH : CH2Cl2 = 5:95), mp 201 °C, yield 136 mg (80%).
recrystallized from acetonitrile to give 14b as a yellow solid. \(R_t = 0.34\) (MeOH : \(\text{CH}_2\text{Cl}_2 = 5:95\)), mp 215°C (dec.), yield 120 mg (69 %). \(\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2\text{S}\) (498.6 g/mol). Purity (HPLC): 95 %, \(t_R = 20.90\) min. HRMS (APCI): m/z = calcld. for \(\text{C}_{31}\text{H}_{35}\text{N}_2\text{O}_2\text{S} [\text{MH}^+]\) 499.2414, found 499.2389. \(^1\)H NMR (CDCl3): δ (ppm) = 1.69 (dq, \(J = 12.1/4.2\) Hz, 2H, 3-\(\text{CH}_2\)pyran-axial, 5-\(\text{CH}_2\)pyran-axial), 1.81-1.90 (m, 2H, 3-\(\text{CH}_2\)pyran-axial, 5-\(\text{CH}_2\)pyran-axial), 2.11 (quint., \(J = 5.9\) Hz, 2H, 7-\(\text{CH}_2\)), 2.36 (s, 3H, \(\text{CH}_3\text{tolyl}\)), 2.65 (tt, \(J = 11.1/3.8\) Hz, 1H, 4-\(\text{H}_\text{pyran}\)), 2.77-2.90 (m, 6H, 6-\(\text{CH}_2\), 3-\(\text{CH}_2\)isoqu., 4-\(\text{CH}_2\) isoqu.), 3.09 (t, \(J = 5.3\) Hz, 2H, 8-\(\text{CH}_2\)), 3.42 (t, \(J = 12.1\) Hz, 2H, CH2axial-O-CH2axial), 3.77 (s, 2H, 1-\(\text{CH}_2\) isoqu.), 4.06 (dd, \(J = 11.8/4.0\) Hz, 2H, CH2equat-O-CH2equat), 7.05-7.08 (m, 2H, 3-\(\text{CH}\), 5-\(\text{CH}_\text{tolyl}\), 4-\(\text{CH}\)), 7.21 (dd, \(J = 8.2/2.2\) Hz, 1H, 6-\(\text{CH}_\text{isoqu.}\)), 7.41 (d, \(J = 7.7\) Hz, 2H, 2-\(\text{CH}_\text{tolyl}\), 6-\(\text{CH}_\text{tolyl}\)), 7.43 (d, \(J = 2.2\) Hz, 1H, 8-\(\text{CH}_\text{isoqu.}\)), 7.55 (s, 1H, NH). \(^{13}\)C NMR (CDCl3): δ (ppm) = 21.7 (\(\text{CH}_3\text{tolyl}\)), 24.6 (C-7), 29.4 (C-4 isoqu.), 30.0 (C-3 pyran, C-5 pyran), 31.1 (C-8, C-6), 47.0 (C-3 isoqu.), 52.5 (C-1 isoqu.), 60.7 (C-4 pyran), 67.9 (C-2 pyran, C-6 pyran), 118.6 (C-8 isoqu.), 118.7 (C-6 isoqu.), 125.8 (C-2 tolyl, C-6 tolyl), 127.1 (C-3), 127.6 (C-4), 129.6 (C-5 isoqu.), 130.0 (C-3 tolyl, C-5 tolyl), 131.0 (C-1 tolyl), 131.5 (C-4 isoqu.), 133.9 (C-8 isoqu.), 136.2 (C-4 tolyl), 136.2 (C-2), 136.4 (C-5), 137.8 (C-3a), 140.5 (C-7 isoqu.), 143.7 (C-8a), 168.7 (O=C-NH). FT-IR (neat): ν (cm\(^{-1}\)) = 3290 (N-H), 2943 (C-H alkyl), 1627 (C=O).

\(N\{4-\{N\text{-Methyl}-N\text{-}(\text{tetrahydro-2H-pyran-4-yl})\text{aminomethyl}\text{phenyl}\}\}-2\{\text{3-methylphenyl}\}-7,8\text{-dihydro-6H\text{-}[7\text{-annuleno[b]}\text{thiophene-5-carboxamide (14d)}\}

\(N\{4\{\text{Aminophenyl}\}-\text{N-methyltetrahydro-2H-pyran-4-amin\}(78\text{mg, }0.35\text{mmol, }1\text{eq.})\}\text{ was added to a vigorously stirred mixture of acid 13b}(100\text{mg, }0.35\text{mmol}), \text{triethylamine}(71\text{mg, }0.70\text{mmol, }2\text{eq.) and HATU™ (150mg, }0.38\text{mmol, }1.1\text{eq.) in THF (5mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo and the residue was purified by fc (EtOAc : \(\text{CH}_2\text{Cl}_2 = 1.2 + 5\% \text{MeOH}) and recrystallized from acetonitrile to give 14d as a yellow solid. \(R_t = 0.17\) (EtOAc : \(\text{CH}_2\text{Cl}_2 + 5\% \text{MeOH} = 1:2\)), mp 189 °C, yield 128 mg (74 %). \(\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_2\text{S}\) (486.6 g/mol). Purity (HPLC): 97 %, \(t_R = 20.94\) min. HRMS (APCI): m/z = calcld. for \(\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_2\text{S} [\text{MH}^+]\) 487.2414, found 487.2395. \(^1\)H NMR (CDCl3): δ (ppm) = 1.60-1.82 (m, 4H, 3-\(\text{CH}_2\)pyran, 5-\(\text{CH}_2\)pyran), 2.14 (quint, \(J = 6.2\) Hz, 2H, 7-\(\text{CH}_2\)), 2.21 (s, 3H, N-\(\text{CH}_3\)), 2.38 (s, 3H, \(\text{CH}_3\text{tolyl}\)), 2.64 (tt, \(J = 11.2/4.0\) Hz, 1H, 4-\(\text{H}_\text{pyran}\)), 2.84 (t, \(J = 5.5\) Hz, 2H, 6-\(\text{CH}_2\)), 3.13 (t, \(J = 5.7\) Hz, 2H, 8-\(\text{CH}_2\)), 3.37 (td, \(J = 11.5/2.3\) Hz, 2H, \(\text{CH}_2\text{axial-O-CH}_2\text{axial}\)), 3.57 (s, 2H, Ph-\(\text{CH}_2\text{N})\), 4.04 (dd, \(J = 11.2/3.4\) Hz, 2H, \(\text{CH}_2\text{equat-O-CH}_2\text{equat}\)), 7.10 (d, \(J = 7.5\) Hz, 1H, 4-\(\text{CH}_\text{tolyl}\)), 7.11 (s, 1H, 3-\(\text{CH}\)), 7.20 (s, 1H, 4-\(\text{CH}\)), 7.27-7.28 (m, 1H, 5-\(\text{CH}_\text{tolyl}\)), 7.30 (d, \(J = 8.3\) Hz, 2H, 3-
CH_\text{phenyl}, 5-CH_\text{phenyl}), 7.34 (m, 2H, 2-CH_\text{tolyl}, 6-CH_\text{tolyl}), 7.48-7.57 (m, 3H, 2-CH_\text{phenyl}, 6-CH_\text{phenyl}, NH). 13C NMR (CDCl_3): δ (ppm) = 21.7 (CH_3tolyl), 24.4 (C-7), 29.4 (C-3pyran, C-5pyran), 30.9 (C-8, C-6), 37.7 (N-CH_3), 57.5 (C-4pyran), 59.7 (Ph-CH_2-N), 67.9 (C-2pyran, C-6pyran), 120.1 (C-2phenyl, C-6phenyl), 122.8 (C-2tolyl), 126.4 (C-6tolyl), 127.3 (C-3), 127.4 (C-4), 127.8 (C-1phenyl), 128.5 (C-4tolyl), 129.0 (C-5tolyl), 129.6 (C-3phenyl, C-5phenyl), 133.6 (C-3tolyl), 133.9 (C-1tolyl), 136.2 (C-2), 140.5 (C-3a), 144.7 (C-8a), 147.9 (C-5), 168.5 (O=C-NH). A signal for the carbon atom C-4phenyl is not visible. FT-IR (neat): ν (cm\(^{-1}\)) = 3305 (N-H), 2939, 2862 (C-Halcy), 1643 (C=O), 1053, 1010 (C-O).

2-(4-Butylphenyl)-N-[4-(piperidin-1-ylmethyl)phenyl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14g)

1-(4-Aminobenzyl)piperidine dihydrochloride (79 mg, 0.30 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 13c\(^{40}\) (100 mg, 0.30 mmol), triethylamine (61 mg, 0.60 mmol, 2 eq.) and HATU™ (130 mg, 0.33 mmol, 1.1 eq.) in acetonitrile (5 mL). The mixture was stirred overnight at rt. The mixture was stirred overnight at rt during which a precipitate was formed. The solid was filtered off, washed with acetonitrile and recrystallized from acetonitrile to give 14g as a colorless solid. R_t = 0.11 (CH_2Cl_2 : MeOH = 95:5), mp 185-188 °C, yield 132 mg (88 %). C_{32}H_{38}N_2OS (498.7 g/mol). Purity (HPLC): >97 %, tR = 23.67 min. HRMS (APCI): m/z = calcd. for C_{32}H_{38}N_2OS [MH\(^+\)] 499.2778, found 499.2803. \(^1\)H NMR (CDCl_3): δ (ppm) = 0.94 (t, J = 7.4 Hz, 3H, 4-CH_3n-butyl), 1.29-1.47 (m, 4H, 3-CH_2n-butyl, 4-CH_2piperidin), 1.50-1.71 (m, 6H, 3-CH_2piperidin, 5-CH_2piperidin, 2-CH_2n-butyl), 2.13 (quint, J = 5.4 Hz, 2H, 7-CH_2), 2.36 (m, 4H, 2-CH_2piperidin, 6-CH_2piperidin), 2.61 (t, J = 7.7 Hz, 2H, 1-CH_2n-butyl), 2.84 (t, J = 5.7 Hz, 2H, 6-CH_2), 3.11 (tt, J = 5.7 Hz, 2H, 8-CH_2), 3.45 (s, 2H, Ph-CH_2-N), 7.07 (s, 1H, 3-CH), 7.15-7.20 (m, 3H, 4-CH, 3-CHbutylphen, 5-CHbutylphen), 7.29 (d, J = 8.5 Hz, 2H, 3-CHphenyl, 5-CHphenyl), 7.43 (d, J = 8.2 Hz, 2H, 2-CHbutylphen, 6-CHbutylphen), 7.52 (d, J = 8.5 Hz, 2H, 2-CHphenyl, 6-CHphenyl), 7.54 (s, 1H, NH). 13C NMR (CDCl_3): δ (ppm) = 14.1 (C-4butyl), 22.5 (C-4piperidin), 24.3 (C-3butyl), 24.5 (C-7), 26.1 (C-3piperidin, C-5piperidin), 30.8 (C-8, C-6), 33.7 (C-2butyl), 35.5 (C-1butyl), 54.5 (C-2piperidin, C-6piperidin), 63.5 (Ph-CH_2-N), 119.9 (C-2phenyl, C-6phenyl), 125.5 (C-3butylphen, C-5butylphen), 126.8 (C-2butoxyphen, C-6butoxyphen), 127.4 (C-3), 129.1 (C-4), 130.0 (C-3phenyl, C-5phenyl), 131.3 (C-1butoxyphen), 133.5 (C-4phenyl), 134.7 (C-1phenyl), 136.1 (C-2), 137.0 (C-3a), 140.5 (C-5), 142.6 (C-8a), 143.4 (C-4butoxyphen), 168.4 (O=C-NH). FT-IR (neat): ν (cm\(^{-1}\)) = 3325 (N-H), 2931 (C-Halcy), 1643 (C=O), 1041, 1018 (C-O).
2-(4-tert-Butylphenyl)-N-4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14h)

N-(4-Aminophenyl)-N-methyltetrahydro-2H-pyran-4-amin (66 mg, 0.30 mmol, 1 eq.) was added to a vigorously stirred mixture of acid 13d\(^{40}\) (100 mg, 0.30 mmol), triethylamine (61 mg, 0.60 mmol, 2 eq.) and HATU™ (128 mg, 0.33 mmol, 1.1 eq.) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo and the residue was purified by fc (EtOAc : MeOH = 95:5) and recrystallized from acetonitrile to give 14h as pale yellow solid. \(R_t = 0.28\) (MeOH : CH\(_2\)Cl\(_2\) = 5:95), mp 209 °C, yield 123 mg (77 %). C\(_{33}H\(_{40}\)N\(_2\)O\(_2\)S (528.7 g/mol). Purity (HPLC): 95 %, \(t_R = 22.66\) min. HRMS (APCI): \(m/z =\) calcd. for C\(_{33}H\(_{41}\)N\(_2\)O\(_2\)S [MH\(^+\)] 529.2883, found 529.2927. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) (ppm) = 1.34 (s, 9H, C(CH\(_3\))\(_3\)), 1.55-1.81 (m, 4H, 3-CH\(_{2}\)pyran, 5-CH\(_{2}\)pyran), 2.13 (quint., \(J = 5.3\) Hz, 2H, 7-CH\(_2\)), 2.20 (s, 3H, N-CH\(_3\)), 2.64 (tt, \(J = 11.2/4.1\) Hz, 1H, 4-H\(_{\text{pyran}}\)), 2.83 (t, \(J = 5.7\) Hz, 2H, 6-CH\(_{2}\)), 3.11 (t, \(J = 5.7\) Hz, 2H, 8-CH\(_2\)), 3.37 (td, \(J = 11.6/2.3\) Hz, 2H, CH\(_{2}\)axial-O-CH\(_{2}\)axial), 3.56 (s, 2H, Ph-CH\(_2\)-N), 4.04 (dd, \(J = 11.3/4.9\) Hz, 2H, CH\(_2\)equat-O-CH\(_2\)equat), 7.07 (s, 1H, 3-CH\(_3\)), 7.19 (s, 1H, 4-CH\(_3\)), 7.30 (d, \(J = 8.6\) Hz, 2H, 3-CH\(_{\text{phenyl}}\), 5-CH\(_{\text{phenyl}}\)), 7.39 (d, \(J = 8.3\) Hz, 2H, 3-CH\(_{\text{butylphen}}\), 5-CH\(_{\text{butylphen}}\)), 7.46 (d, \(J = 8.4\) Hz, 2H, 2-CH\(_{\text{butylphen}}\), 6-CH\(_{\text{butylphen}}\)), 7.53 (d, \(J = 8.5\) Hz, 2H, 2-CH\(_{\text{phenyl}}\), 6-CH\(_{\text{phenyl}}\)), 7.59 (s, 1H, NH). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) (ppm) = 24.6 (C-7), 29.7 (C-3\(_{\text{pyran}}\), C-5\(_{\text{pyran}}\)), 31.1 (C-8), 31.1 (C-6), 31.7 (C(CH\(_3\))\(_3\)), 35.0 (C(CH\(_3\))\(_3\)), 38.0 (N-CH\(_3\)), 57.8 (C-4\(_{\text{pyran}}\)), 60.0 (Ph-CH\(_2\)-N), 68.2 (C-2\(_{\text{pyran}}\), C-6\(_{\text{pyran}}\)), 120.4 (C-2\(_{\text{phenyl}}\), C-6\(_{\text{phenyl}}\)), 125.7 (C-3\(_{\text{butylphen}}\), C-5\(_{\text{butylphen}}\)), 126.3 (C-2\(_{\text{butylphen}}\), C-6\(_{\text{butylphen}}\)), 127.2 (C-3), 127.7 (C-4), 129.9 (C-3\(_{\text{phenyl}}\), C-5\(_{\text{phenyl}}\)), 131.5 (C-1\(_{\text{butylphen}}\)), 133.9 (C-4\(_{\text{phenyl}}\)), 136.2 (C-1\(_{\text{phenyl}}\)), 136.4 (C-2), 137.4 (C-3a), 140.7 (C-5), 143.8 (C-8a), 151.1 (C-4\(_{\text{butylphen}}\)), 168.8 (O=C-NH). FT-IR (neat): \(\tilde{\upsilon}\) (cm\(^{-1}\)) = 3251 (N-H), 2966 (C-H\(_{\text{alkyl}}\)), 1651 (C=O), 1597 (C=C), 1053, 1014 (C-O).

3. Experimental Pharmacology

\(\sigma\) receptor assays

Materials

The guinea pig brains and rat liver for the \(\sigma_1\) and \(\sigma_2\) receptor binding assays were commercially available (Harlan-Winkelmann, Borchen, Germany). Centrifuges: Cooling centrifuge model Rotina 35R (Hettich, Tutlingen, Germany) and High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96-well multiplates (Diagonal, Muenster, Germany).

Preparation of membrane homogenates from guinea pig brain
5 guinea pig brains were homogenized with the potter (500-800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 23,500 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23,500 x g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

Preparation of membrane homogenates from rat liver
Two rat livers were cut into small pieces and homogenized with the potter (500-800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1,200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 8.0) and incubated at room temperature for 30 min. After the incubation, the suspension was centrifuged again at 31,000 x g for 20 min at 4 °C. The final pellet was resuspended in 5-6 volumes of buffer and stored at −80 °C in 1.5 mL portions containing about 2 mg protein/mL.

Protein determination
The protein concentration was determined by the method of Bradford, modified by Stoscheck. The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95 %, v/v). 10 mL deionized water and 5 mL phosphoric acid (85%, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50.0 mL with deionized water. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8,
1.0, 1.5, 2.0 and 4.0 mg/mL). In a 96 well standard multiplate, 10 µL of the calibration solution or 10 µL of the membrane receptor preparation were mixed with 190 µL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at \( \lambda = 595 \) nm was measured with a platereader (Tecan Genios, Tecan, Crailsheim, Germany).

**General protocol for the binding assays**
The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2-4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in 96-well multiplates. The concentrations given are the final concentrations in the assay. Generally, the assays were performed by addition of 50 µL of the respective assay buffer, 50 µL test compound solution in various concentrations (10\(^{-5}\), 10\(^{-6}\), 10\(^{-7}\), 10\(^{-8}\), 10\(^{-9}\) and 10\(^{-10}\) mol/L), 50 µL of corresponding radioligand solution and 50 µL of the respective receptor preparation into each well of the multiplate (total volume 200 µL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500-600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration each well was washed five times with 300 µL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at room temperature, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the \([^{3}\text{H}]\)counting protocol. The overall counting efficiency was 20%. The IC\(_{50}\) values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC\(_{50}\) values were transformed into K\(_i\) values using the equation of Cheng and Prusoff.

**Protocol for the determination of \( \sigma_1 \) affinity**
The assay was performed with the radioligand \([^{3}\text{H}]\)(+)-Pentazocine (0.81 GBq/µmol (22.0 Ci/mmol); Perkin Elmer). The thawed membrane preparation of guinea pig brain
cortex (about 100 μg of protein) was incubated with various concentrations of test compounds, 2 nM [³H](+)-Pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 μM unlabeled (+)-Pentazocine. The Kᵰ value of (+)-pentazocine is 2.9 nM. The nonspecific binding was determined in the presence of a large excess of non-tritiated (+)-pentazocine. Kᵰ values of the reference compounds (+)-pentazocine, ditolylguanidine (DTG), haloperidol and rimcazol were determined and compared with literature data to verify the in-vitro assay.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ki ± SEM [nM] (literature)</th>
<th>Ki ± SEM [nM] (recorded)</th>
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<tbody>
<tr>
<td>(+)-pentazocine</td>
<td>2.1 ± 0.1⁵⁴</td>
<td>5.4 ± 0.5 (n = 17)</td>
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<td>ditolylguanidine</td>
<td>107 ± 21⁵⁵</td>
<td>71 ± 8 (n = 15)</td>
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<tr>
<td>haloperidol</td>
<td>1.8 ± 0.09⁵⁵</td>
<td>6.6 ± 0.9 (n = 14)</td>
</tr>
<tr>
<td>rimcazole</td>
<td>2380 ± 812⁵⁶</td>
<td>1746 ± 609 (n = 6)</td>
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σ₁ Affinities of reference compounds (literature and own data).

Protocol for the determination of σ₂ affinity

The assays were performed with the radioligand [³H]DTG (specific activity 1.85 GBq/μmol (50 Ci/mmol); ARC, St. Louis, MO, USA). The thawed membrane preparation of rat liver (about 100 μg of protein) was incubated with various concentrations of the test compound, 3 nM [³H]DTG and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in 50 mM TRIS, pH 8.0) at room temperature. The non-specific binding was determined with 10 μM non-labeled DTG. The Kᵰ value of [³H]DTG is 17.9 nM. Excess of unlabeled DTG (D) was used to determine the nonspecific binding. Kᵰ values of reference compounds haloperidol, ditolylguanidine (DTG), ifenprodil and rimcazol were determined and compared with literature data to verify the in vitro assay.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ki ± SEM [nM] (literature)</th>
<th>Ki ± SEM [nM] (recorded)</th>
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<tr>
<td>haloperidol</td>
<td>22 ± 8.5⁵⁵</td>
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<td>ditolylguanidine</td>
<td>40 ± 2.6⁵⁷</td>
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<td>ifenprodil</td>
<td>6.25 ± 0.38⁵⁸</td>
<td>60 ± 16 (n = 5)</td>
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σ₂ Affinities of reference compounds (literature and own data).
4. $^1$H and $^{13}$C and gHSQC NMR spectra, HPLC analysis and MS spectra

2-(4-Methylphenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxylic acid$^{37}$ (6)
HPLC

Sample Name: AJ82 acid
Injection from this vial: 1 of 1

Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Substr Sample Name: ACN
Column Type: 016
Solvent A: Wasser + 0.05% TFA
Solvent B: ACN + 0.05% TFA

Developed by: Jens

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Mass Spectrum SmartFormula Report

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Comment: Junker

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Operator: Melmers
Instrument / Ser#: microTOF-Q II 10252
Calibration: mit Fettsäureeinstelln

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err [ppm]
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Bruker Compass DataAnalysis 4.0
printed: 8/28/2012 1:41:15 PM
Page 1 of 1
2-(4-Methyphenyl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-
6,7-dihydro-5H-benzo[7]annulene-8-carboxamide\textsuperscript{39} (8a)
HPLC

Sample Name: AJ1106
Injection from this vial: 1 of 1

Chrom Type: HPLC Channel: 1

Retention Time (min)

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: G10
Solvent A: Wasser + 0.05%TFA
Solvent B: ACN + 0.05%TFA

Developed by: Jens

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HPLC

Sample Name: AJ452
Injection from this vial: 1 of 1

Acquisition Method: Chromatography
Blank Substr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0.05% TFA

Retention Time (min)

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Developed by: Jens
Solvent B: ACN + 0.05% TFA

Peak rejection level: 0
Mass Spectrum SmartFormula Report

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Comment: Junker

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Scan End: 1000 m/z

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Set Dry-Heater: 200 °C
Set Dry Gas: 9.0 L/min
Set Divert Valve: Waste

Intens. m/z

+MS, 6.6min #824

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549.5125

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err [mDa]: -0.1
err [ppm]: -4.2
mSigma: 10.7
nSigma: 14.5
e- Conf: 1.0
N-Rule: 1

Bruker Compass DataAnalysis 4.0
printed: 6/11/2012 8:38:31 AM
Page 1 of 1
2-(4-Methylphenyl)-N-[4-[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]phenyl]-6,7-dihydro-5H-benz[7]annulene-8-carboxamide (8c)
HPLC

Sample Name: AJ42201
Injection from this vial: 1 of 1
Chron Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0.05%TFA
Solvent B: ACN + 0.05%TFA

Developed by: Jens

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Reported: 02.08.12 15:02
Processed: 02.08.12 15:02

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Vial Type: UNK
Volume: 5.0 ul
Mass Spectrum SmartFormula Report

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- Comment: Juncker

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Braker Compass Data Analysis 4.0
- printed: 8/29/2012 9:45:25 AM
- Page 1 of 1
2-(4-Methylphenyl)-N-[4-[N-(thiazol-2-yl)sulfamoyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (8d)
### HPLC

**Acquired:** 02.08.12 14:52
**Processed:** 02.08.12 14:52
**Series:** 5040
**Vial Number:** 4
**Vial Type:** UNK
**Volume:** 5.0 μl

**Sample Name:** AJ450
**Injection from this vial:** 1 of 1

**Chromatographic Data:**
- **Retention Time (min):** 0 to 28
- **Intensity (mV):** 0 to 100

**Acquisition Method:** Chromni
**Blank Subcr Sample Name:** ACN
**Column Type:** 010
**Solvent A:** Wasser + 0.05% TFA
**Solvent B:** ACN + 0.05% TFA

**Developed by:** Jens

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**Peak rejection level:** 0

**Total Area:** 2970927
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Mass Spectrum SmartFormula Report

Analysis Info
- Date: 8/2/2012 11:16:38 AM
- Method: APCI_directprobe_positiv.m
- Sample Name: AJ45001
- Comment: Junger

Acquisition Parameter
- Source Type: APCI
- Ion Polarity: Positive
- Set Collision Cell RF: 1000.0 Vpp
- Set End Plate Offset: -200 V
- Set Nebulizer: 0.7 Bar
- Set Dry Gas: 3.0 L/min
- Set Dry Heater: 200 °C

Mass Spectra

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Bruker Compass DataAnalysis 4.0  
Printed: 8/2/2012 1:51:20 PM
2-(4-Methylphenyl)-N-(thiazol-2-yl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (8e)
**HPLC**

**Sample Name:** AJ451  
**Injection from this vial:** 1 of 1  
**Chrom Type:** HPLC Channel: 1

---

**Acquisition Method:** Chromni  
**Blank Substr Sample Name:** ACN  
**Column Type:** 010  
**Solvent A:** Wasser + 0.05%TFA  
**Developed by:** Jens  
**Solvent B:** ACN + 0.05%TFA  
**Peak rejection level:** 0

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**Integrated Area:** 13138375  
**Volume:** 5.0 ul
## Mass Spectrum SmartFormula Report

### Analysis Info
- **Analysis Name**: D:\Data\IPMC\PharmChem\Routine\APCI\12_08WJU_AJ45101.d
- **Method**: APCI direct probe, positive
- **Sample Name**: AJ45101
- **Comment**: Junker

### Acquisition Date
- **Date**: 8/2/2012 9:12:36 AM
- **Operator**: Meiners
- **Instrument / Ser#**: microTOF-Q II 11252

### Acquisition Parameter

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### Chart

- **MS, 1.6-1.9 min #1(187-188)**

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**Bruker Compass DataAnalysis 4.0**

- **Printed**: 8/2/2012 1:29:29 PM
2-[(4-Methyl)phenyl]-N-{4-[(piperidin-1-yl)methyl]phenyl}-6,7-dihydro-5H-benzof[7]annulene-8-carboxamide (8f)
HPLC

Data Path: D:\WIN32APF\ESM\Chromni\DATA\5056\  Reported: 25.01.13 10:18
Application: Chromni  Processed: 26.01.13 10:18
Sample Name: AJ84
Series: 5056
Injection from this vial: 1 cf 1  Vial Number: 15
Chrom Type: HPLC Channel: 1  Vial Type: UNK
Volume: 5.0 ul

Acquisition Method: Chromni
Developed by: Jens
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0.05%TFA
Solvent B: ACN + 0.05%TFA

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Peak rejection level: 0

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\[ 100.000 \]
$N$-{$N$-Methyl-$N$-(tetrahydro-$2H$-pyran-$4$-yl)aminomethyl}$N$-phenyl-$6,7$-dihydro-$5H$-benzo[7]annulene-$8$-carboxamide (9a)
**HPLC**

**Sample Name:** A75901

**Injection from this vial:** 1 of 1

**Chrom Type:** HPLC Channel 1

---

**Acquisition Method:** Chromni

**Blank Substr Sample Name:** ACN

**Column Type:** 010

**Solvent A:** Water + 0.05% TFA

**Solvent B:** ACN + 0.05% TFA

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**Peak rejection level:** 0
Generic Display Report

Analysis Info
Analysis Name: D:\Datei\PMCM\PharmChemie\Routine\2011_5\WJU_AJ5901.d
Method: APCI_directprobe_default.m
Sample Name: AJ5901
Comment: Junker

Acquisition Date: 5/2/2011 2:35:53 PM
Operator: Menners
Instrument: microTOF-Q II

Calibration: mit Fettsäureestern

Bruker Compass DataAnalysis 4.0  printed: 5/3/2011 2:40:41 PM  Page 1 of 1
2-(3-Methyphenyl)-N-[(N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl)phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9b)
### HPLC

**Application:** Chromni

**Sample Name:** Ao1201

**Injection from this vial:** 1 of 1

**Chrom Type:** HPLC Channel 1

---

**Acquisition Method:** Chromni

**Blank Subtr Sample Name:** ACN

**Column Type:** 010

**Solvent A:** Wasser + 0.05% TFA

**Solvent B:** ACN + 0.05% TFA

**Developed by:** Jens

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**Peak rejection level:** 3
Mass Spectrum SmartFormula Report

Analysis Info
Analysis Name: E:Weiners\12_06WJU_AJ\12\4
Method: APCI_directprobe_poslitin.m
Sample Name: AJ\12
Comment: Junker

Acquisition Info
Acquisition Date: 9/7/2012 9:16:48 AM
Operator: Senderker
Instrument / Ser#: microCTOF-Q II 10252

Acquisition Parameter
Source Type: APCI
IOn Polarity: Positive
Scan Begin: 100 m/z
Scan End: 1000 m/z
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Set Nebulizer: 0.7 Bar
Set Dry Heater: 200 °C
Set Dry Gas: 3.0 l/min
Set Divert Valve: Waste

Spectrum

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Bruker Compass DataAnalysis 4.0
printed: 9/7/2012 12:26:30 PM
Page 1 of 1
2-(2-Methyphenyl)-N-[4-[N-Methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-
6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9c)
HPLC

Analysis: 21.10.10 09:58
Reported: 21.10.10 13:45
Processed: 21.10.10 13:45

Data Path: D:\WIN\LAMP\HSI\Chromni\DATA\2286\ 
Application: Chromni
Series: 2286
Vial Number: 1
Vial Type: UNK
Volume: 5.0 µl

Sample Name: AO1301
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subr Sample Name: ACN
Column Type: 010
Solvent A: Water + 0.05% TFA
Solvent B: ACN + 0.05% TFA
Developed by: Jens

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Peak rejection level: 0

48630649 100.000
Mass Spectrum SmartFormula Report

Analysis Info
Acquisition Date: 9/10/2012 8:36:48 AM
Analysis Name: D:\Data\PMCI\PharmChemTe\Routine\APCN12_09\WU_JJ13_6
Method: APCI_directprobe_positiv.m
Sample Name: JJ13
Comment: Junker

Acquisition Parameter
Source Type: APCI
Focus: Ion source
Scan Begin: 100 m/z
Scan End: 1000 m/z
Ion Polarity: Positive
Capillary: 4000 V
Set End Plate Offset: -500 V
Collision Cell RF: 130.6 Vpp
Set Nebulizer: 0.7 Bar
Set Dry Heater: 203 °C
Set Dry Gas: 3.0 L/min
Set Divert Valve: Waste

---

Bruker Compass DataAnalysis 4.0
printed: 9/10/2012 2:31:35 PM
Page 1 of 1
2-(4-Ethylphenyl)-N-(4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9d)
HPLC

Data Path: D:\WINM2APP\HSM\Chromni\DATA\4971\ Application: Chromni
Sample Name: A07501
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subtr Sample Name: KG 97.1
Column Type: 010
Solvent A: Wasser + 0.05%TFA
Solvent B: ACN + 0.05%TFA

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12001733 100,000

Peak rejection level: 0
Generic Display Report

Analysis Info
Analysis Name: APCI_directprobe_positiv.m
Method: APCI_direct
Sample Name: AJ7501
Comment: Junker

Calibration with Fettäureeestern

Acquisition Date: 8/2/2012 9:37:48 AM
Operator: Menes
Instrument: microTOF-Q II

---

WJU_AJ7501.dat: TIC +AM

---

MS, 1.4-1.4 min @ 161-158

---

MS, 1.4-1.4 min @ 161-158

---

Buker Compass DataAnalysis 4.0

Printed: 6/2/2012 1:39:11 PM
### Mass Spectrum SmartFormula Report

**Analysis Info**
- **Analysis Name:** D:\Daten\PMCV\PharmChemie\Routine\APCI12_092011_AJ7501.d
- **Method:** APCI_dircoprobe_positiv.m
- **Sample Name:** AJ7501
- **Comment:** Junker
- **Acquisition Date:** 8/2/2012 9:37:48 AM
- **Operator:** 
- **Instruments:** microOTOF-Q II 10252

**Acquisition Parameter**
- **Source Type:** APCI
- **Scan Type:** NCE 99.99999
- **Scan Range:** 100-1000 m/z
- **Scan Time:** 0.2 s
- **Number of Scans:** 100
- **Accurate Mass:** Yes

**Peaks**

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**Figures**
- **MS:** 14.5 mm (161-165)

**Note:**
- Bruker Compass DataAnalysis 4.0
- Printed: 8/2/2012 1:39:18 PM
- Page 1 of 1
2-(4-Butylphenyl)-N-(4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl)-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9e)
HPLC

Sample Name: AJ9401
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0.05%TFA

Developed by: Jens
Solvent B: ACN + 0.05%TFA

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Peak rejection level: 0

Reported: 05.07.12 15:57
Processed: 05.07.12 15:57
## Mass Spectrum SmartFormula Report

### Analysis Info
- **Analysis Name**: epc-rs1PZPharmChemie/Routine\APCI:12_06WJU_A_B401.d
- **Method**: APCI_directprobe_positiv.m
- **Sample Name**: AJ401
- **Comment**: Junker
- **Acquisition Date**: 02.08.2012 11:40:36
- **Operator**: Meiners
- **Instrument / Ser#**: micrOTOF-Q II 10252
- **Calibration**: mit Fettsäureestern

### Acquisition Parameter
- **Source Type**: APCI
- **Ion Polarity**: Positive
- **Set Capillary**: 4000 V
- **Set End Plate Offset**: -100 V
- **Set Collision Cell RF**: 130.0 Vpp
- **Set Nebulizer**: 0.7 bar
- **Set Dry Heater**: 200 °C
- **Set Dry Gas**: 3.0 L/min
- **Set Divert Valve**: always

### Mass Spectrum

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Bruker Compass DataAnalysis 4.0  
**printed**: 02.08.2012 14:11:50  
Page 1 of 1
**HPLC**

**Sample Name:** AJ6902  
**Injection from this vial:** 1 of 1  
**Chrom Type:** HPLC  
**Channel:** 1

**Acquisition Method:** Chromni  
**Blank Subtr Sample Name:** ACN  
**Column Type:** C18  
**Solvent A:** Wasser + 0.05%TFA  
**Solvent B:** ACN + 0.05%TFA  
**Developed by:** Jens

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**Peak rejection level:** 0
Generic Display Report

Analysis Info
Analysis Name: E:Wieners112_09\WJU_AJ6902.d
Method: APCI_directprobe_positiv.m
Sample Name: AJ6902
Comment: Junker

Acquisition Date: 9/4/2012 11:32:37 AM
Operator: Sendker
Instrument: micrOTOF-Q II

Image of chromatograms and mass spectra with peaks at various m/z values and intensities.

Bruker Compass DataAnalysis 4.0
printed: 9/4/2012 2:25:44 PM
Mass Spectrum SmartFormula Report

Analysis Info
Analysis Name: E:Weinera12_09WJU_AJ6902.d
Method: APCL_directprobe_positiv.m
Sample Name: AJ6902
Comment: Jurker

Acquisition Parameter
Source Type: APCL
Focus: Neutral
Scan Begin: 100 m/z
Scan End: 1003 m/z

Intensities:

Mass m/z: 523.3335

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2-[[1,1'-Biphenyl]-4-yl]-N-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9g)
HPLC

Sample Name: AJ7602
Injection from this vial: 1 of 1

Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0.05%TFA

Developed by: Jens
Solvent B: ACN + 0.05%TFA

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Peak rejection level: 0

Series: 5233
Vial Number: 7
Vial Type: UNK
Volume: 5.0 ul

Reported: 13.09.12 10:00
Processed: 13.09.12 10:00

Data Path: D:\WIN32API\ESN\Chromni\DATA\5233\
# Mass Spectrum SmartFormula Report

**Analysis Info**
- Analysis Name: D:\Data\VPM\PharmChemie\Routines\LC-MIC192012_10_22A76_B46_D1_B46.d
- Method: tune_low_icms_routine_positiv_16min.m
- Sample Name: AJ76
- Comment: Junker
- Calibration: T-Formate

**Acquisition Parameter**
- Source Type: ESI
- Focuss: not active
- Scan Begin: 100 m/z
- Scan End: 1000 m/z

**Intensity**

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<td>428.1954</td>
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<th>e° Conf</th>
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Bruker Compass DataAnalysis 4.0
Printed: 03/23/2012 7:55:57 AM
Page 1 of 1
$N$-{4-$\{N$-Methyl-$N$-(tetrahydro-$2H$-pyran-$4$-yl)aminomethyl$\}$phenyl$}$-$2$-(naphtalen-$2$-yl)-$6,7$-dihydro-$5H$-benzo[7]annulene-$8$-carboxamide ($9h$)
HPLC

Sample Name: AJ7901
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel : 1

Acquisition Method: Chromni
Blank Substr Sample Name: ACN
Column Type: 010
Solvent A: Water : 0.05%TFA
Solvent B: ACN + 0.05%TFA

Developed by: Jens

<table>
<thead>
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<th>No.</th>
<th>RT</th>
<th>Area</th>
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22470786  100,000

Peak rejection level: 0
## Mass Spectrum SmartFormula Report

### Acquisition Information
- **Analysis Name**: lip2-ml2PharmChemie_Routine\APCI12_08\WJU\AJ7001.f
- **Method**: APCI_directprobe_positiv.m
- **Sample Name**: AJ7001
- **Comment**: Jurker
- **Acquisition Date**: 02.08.2012 10:53:37
- **Operator**: Meiners
- **Instrument/Server**: microOTOF-Q II 10252

### Acquisition Parameters
- **Source Type**: APCI
- **Ion Polarity**: Positive
- **Set Nebulizer**: 0.7 Bar
- **Scan Begin**: 100 m/z
- **Scan End**: 1000 m/z
- **Scan Capillary**: 4000 V
- **Set End Plate Offset**: -500 V
- **Set Dry Gas**: 3.0 L/min
- **Set Collison Cell RF**: 130.0 Vpp
- **Set Divert Valve**: Waste

### Mass Spectra

#### Spectrum 1
- M /z 297.1386: C21H17N2 (Score: 100.00), Error: 0.6 ppm, mSigma: 6.1, si: 145, sven/a: ok
- M /z 551.2864: C30H39N4O9 (Score: 76.07), Error: 1.9 ppm, mSigma: 18.7, sven/a: ok

#### Spectrum 2
- M /z 314.1502: C23H15N16O (Score: 160.00), Error: 2.3 ppm, mSigma: 11.9, sven/a: ok
- M /z 517.2867: C39H37N2O2 (Score: 151.00), Error: 3.3 ppm, mSigma: 3.5, sven/a: ok

---

**Bruker Compass DataAnalysis 4.3**

**Printed: 29.08.2012 14:18:15**

**Page 1 of 1**
2-(2-Fluoropyridin-3-yl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9j)
HPLC

Analyzed: 29.11.12 09:45
Data Path: D:\WINI2APP\HSM\Chromni\DATA\5605\Application: Chromni
Sample Name: AJ78
Injection from this vial: 1 of 1

Chrom Type: HPLC Channel: 1

Retention Time (min)

Intensity (A.U.)

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0,05%TFA

Developed by: Jens
Solvent B: ACN + 0,05%TFA

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34938465

100,000

Peak rejection level: 0

Series: 5605
Vial Number: 23
Vial Type: UNK
Volume: 5.0 ul

Reported: 30.11.12 09:18
Processed: 30.11.12 09:18
## Generic Display Report

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<td>mcrTOF-Q ii</td>
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<td>Sample Name</td>
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<td>Junker</td>
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### Intensity Graph

**WJIU_AJ78.d TIC +AI M+**

- **WJIU_AJ78.d**: 2D chromatogram showing retention time vs. intensity.
- **+AI M+**: Mass chromatogram focusing on ions at specific masses.

### Mass Spectra

- **M/z 149.082**: Mass spectrum highlighting a specific mass-to-charge ratio.
- **M/z 265.092**: Another mass spectrum with a different mass-to-charge ratio.

---

**Bruker Compass DataAnalysis 4.0**

**printed: 12/10/2012 1:17:52 PM**

**Page 1 of 1**
## Mass Spectrum SmartFormula Report

### Analysis info
- **Analysis Name:** E:\Meiners\12_12\WUJU_AJ78.d
- **Method:** APCI_directprobe_positiv.rts
- **Sample Name:** AJ78
- **Comment:** Junior
- **Acquisition Date:** 12/10/2012 8:55:51 AM
- **Operator:** Meiners
- **Instrument / Ser#:** mcrTOF-Q II 10252

### Acquisition Parameter
- **Source Type:** APCI
- **Focus:** II:active
- **Scan Begin:** 100 m/z
- **Scan End:** 1000 m/z

### Mass Spectra

**Infrastrucutre**

![Infrastrucutre Image]

**Integration**

![Integration Image]

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<th>rcb</th>
<th>e°</th>
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**Selected Formulae**

- C30H33F11O2
- C28H32F4N3
- C27H34F2N2O3
- C24H37F10H8
- C26H39F12
- C28H41F14
- C22H33F6N13
- C21H35F5N10
- C23H40F6N9
- C19H30F6N10
- C21H35F6N10
- C19H35F5N10
- C18H27F3N15
- C18H30F3N10
- C17H32F4N9O3
- C19H35F7N3O3
- C15H29F11O3
- C17H34F2N7O7
- C19H37F1N7O7
- C19H35F9N11O7

**References**

- Bruker Compass DataAnalysis 4.0
- printed: 12/10/2012 1:18:03 PM
- Page 1 of 2
2-(6-Isopropoxypyridin-3-yl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9k)
**HPLC**

**Sample Name:** AJ74  
**Injection from this vial:** 1 of 1  
**Chrom Type:** HPLC Channel 1

**Acquisition Method:** Chromni  
**Blank Subtr Sample Name:** ACN  
**Column Type:** 010  
**Solvent A:** Wasser + 0.05%TFA  
**Solvent B:** ACN + 0.05%TFA

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**Peak rejection level:** 0

---

**Data Path:** D:\WIN32APP\HSM\chromni\DATA\5629\  
**Application:** Chromni  
**Series:** 5629  
**Vial Number:** 7  
**Vial Type:** UNK  
**Volume:** 5.0 ml

**Reported:** 06.12.12 09:19  
**Processed:** 06.12.12 09:19
### Mass Spectrum SmartFormula Report

**Analysis Info**
- **Acquisition Date**: 12/18/2012 9:28:57 AM
- **Method**: APCI_directprobe_positiv.m
- **Sample Name**: AJ74
- **Comment**: Junke
- **Operator**: Meiners
- **Instrument / Set#**: micrOTOF-Q II 11252

**Acquisition Parameter**
- **Source type**: APCI
- **Ion Polarity**: Positive
- **Set Nebulizer**: 0.7 Bar
- **Scan Begin**: 100 m/z
- **Set End Plate Offset**: -200 V
- **Scan End**: 1000 m/z
- **Set Collision Cell RF**: 130.0 Vpp
- **Set Divert Valve**: Waste

**Mass, m/z**

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<th>err [ppm]</th>
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**Bruker Compass DataAnalysis 4.0**
- **printed**: 12/18/2012 12:31:54 PM
- **Page 1 of 1**
2-(4-Fluorophenyl)-N-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benz[7]annulene-8-carboxamide (9I)
HPLC

Analyzed: 08.04.11 08:01
Reported: 08.04.11 08:04
Processed: 08.04.11 08:04

Data Path: D:\WIN32APP\MSM\Chrommi\DATA\2932\Series: 2932
Application: Chrommi
Sample Name: A26001
Injection from this vial: 1 of 1
Vial Number: 8
Vial Type: UNK
Volume: 5.0 μl

Chrom Type: HPLC Channel: 1

Acquisition Method: Chrommi
Blank Subtr Sample Name: ACR
Column Type: 010
Solvent A: Wasser + 0.05%TFA
Solvent B: ACN + 0.05%TFA

Developed by: Jens

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<thead>
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<th>Area</th>
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17411193  100.000

Peak rejection level: 0
Mass Spectrum SmartFormula Report

Analysis Info
Analysis Name: D:\Data\IPMCPharmChemielRoutine2011_4W\U_A9061.d
Method: Kurz_pos_MS_low.m
Sample Name: AJ6001
Comment: Junker ESI-Direkt Calibration mit Li-Formate

Acquisition Info
Acquisition Date: 4/18/2011 7:46:36 AM
Operator: Meiners
Instrument / Ser#: micrOTOF-G II 10252

Acquisition Parameter
Source Type: ESI
Ion Polarity: Positive
Set Nebulizer: 3.0 Bar
Focus: not active
Set Capillary: 4500 V
Set Dry Heater: 220 °C
Scan Begin: 50 m/z
Set End Plate Offset: -300 V
Set Dry Gas: 9.0 l/min
Scan End: 1006 m/z
Set Collision Cell RF: 600.0 Vpp
Set Divert Valve: Waste

MS, 3.05-0.38min #(5-45)

485.2508
372.1992

Meas. m/z # Formula m/z err [mDa] err [pm] mSigma ndb e Conf N-Rule
455.2598 1 C31 H 34 F N 2 O 2 455.2599 0.1 0.2 9.9 15.5 ever ok 304884

Bruker Compass DataAnalysis 4.0
printed: 4/18/2011 7:53:23 AM
Page 1 of 1
2-(4-Fluoro-3-methylphenyl)-N-{4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl}-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9m)
HPLC

Sample Name: AJ6103
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Blank Substr Sample Name: ACN
Column Type: O10
Solvent A: Wasser + 0.05%TFA
Developed By: Jens
Solvent B: ACN + 0.05%TFA

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Peak rejection level: 0

Retention Time (min)

Intensity (mV)
2-(4-Hydroxy-3-methylphenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9o)
HPLC

Sample Name: AJ5101
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Water + 0.05% TFA
Developed by: Jens
Solvent B: ACN + 0.05% TFA

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41109245  100,000

Peak rejection level: 0

Data Path: D:\WIN\ZAPP\RSM\Chromni\DATA\3414\Reports: 3414
Vial Number: 12
Vial Type: UNK
Volume: 5,0 µl
Mass Spectrum SmartFormula Report

Analysis Info
Analysis Name: D:\Data\PMI\PharmChem\Routine\APCI\12_09\V1N\AJ51\d
Method: APCI directprobe positiv.m
Sample Name: AJ51
Comment: Junker

Acquisition Info
Acquisition Date: 9/11/2012 9:34:38 AM
Operator: Sender
Instrument / Ser#: microTOF-Q II 10252

Acquisition Parameters
Source Type: APCI
Focus: Not active
Scan Begin: 100 m/z
Scan End: 1000 m/z
Set Capillary: 4000 V
Set End Plate Offset: -500 V
Set Collission Cell RF: 130.0 Vpp
Set Nebulizer: 0.7 Bar
Set Dry Heater: 300 °C
Set Divent Valve: Waste

Peaks

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<th>rdis</th>
<th>e° Conf</th>
<th>N-Rule</th>
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Brucker Compass DataAnalysis 4.0
printed: 9/11/2012 12:46:20 PM
Page 1 of 1
2-[4-(Hydroxymethyl)phenyl]-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benzo[7]annulene-8-carboxamide (9p)
HPLC

Sample Name: AD15001
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0.05%TFA
Solvent B: ACN + 0.05%TFA

Developed by: Jens

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27390507  100,000

Peak rejection level: 0
Generic Display Report

Analysis Info
Analysis Name: D:\Data1\PMC\PharmChemie\Routine\APCI\12_09\WJU_AJ150.d
Method: APCI_directprobe_posllit.m
Sample Name: AJ150
Comment: Junker

Acquisition Date: 9/11/2012 9:41:50 AM
Operator: Sendker
Instrument: microOTOF-Q II

Kaliertion mit Ferseureaustern

Brucker Compass DataAnalysis 4.0  printed: 9/11/2012 12:46:56 PM  Page 1 of 1
Mass Spectrum SmartFormula Report

Acquisition Parameter

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+MS, 56-57min #(672-678)

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Baker Compass Data Analysis 4.0

printed: 9/12/2012 12:46:48 PM  Page 1 of 1
2-(5-Formylthiophen-2-yl)-N-[4-[(methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-6,7-dihydro-5H-benz[7]annulene-8-carboxamide (9v)
HPLC

Sample Name: AQ7301
Injection from this vial: 1 of 1

Chrom Type: HPLC Channel: 1

Retention Time (min)

Intensity (AU)

Acquisition Method: Chromni
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0.05%TFA

Developed by: Jens
Solvent B: ACN + 0.05%TFA

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27953484  100,000

Peak rejection level: 0
Mass Spectrum Smart Formula Report

Analysis Info
Analysis Name: D:\Data\WMC\PharmChem\Routine\2011_5\WJU_AJ7301.d
Method: APCI_directprobe_default.m
Sample Name: AJ7301
Comment: Junker

Acquisition Info
Acquisition Date: 5/3/2011 2:41:29 PM
Operator: Meiners
Instrument / Ser#: micrOTOF-Q II 10252

Preparation: Kellnierung mit Fettsaureestern

Acquisition Parameter
Source Type: APCI
Focus: not active
Scan Begin: 100 m/z
Scan End: 1000 m/z
Ion Polarity: Positive
Capillary: 4600 V
Q1/RF: 500 V
Q3/RF: 150.0 Vpp
Set Divert Valve: Waste
Set Nebulizer: 0.7 Bar
Set Dry Heater: 200 °C
Set Dry Gas: 3.0 l/min

[Graph showing mass spectrum with peaks at m/z 501.223 and 388.1358]

Mass m/z # Formula Score m/z err [mDa] err [ppm] mSigma db e Conf N-Rule
501.223 1 C35H13O5S 100.00 501.2247 4.0 4.7 192.9 19.5 even ok
2 C30H23Na2O2S 21.82 501.2206 1.7 3.3 215.9 10.5 even ok

Bruker Compass Data Analysis 4.0 printed: 5/3/2011 2:44:37 PM Page 1 of 1
2-(4-Methylphenyl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14a)
HPLC

Sample Name: AJ40
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Retention Time (min)

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Total: 6333472, 100,000

Peak rejection level: 0
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**Generic Display Report**

**Acquisition Date:** 8/29/2012 9:35:27 AM

**Operator:** Meiners

**Instrument:** micrOTOF-Q II

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**Intensity**

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x10^8
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**Time (min)**

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**+MS, 1.4-1.5 min m/z (169-177)**

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**+MS, 1.4-1.5 min m/z (169-177)**

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## Mass Spectrum SmartFormula Report

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- **Method**: APCI directprobe_positiv.m
- **Sample Name**: AJ43
- **Comment**: Junker
- **Acquisition Date**: 9/28/2012 9:35:27 AM
- **Operator**: Meiners
- **Instrument / Set#**: microTOF-Q II (2252)
- **Calibration**: mit Falszsaeurestern

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<td>Set Dry Heater</td>
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### Mass spectrum

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**Bruker Compass DataAnalysis 4.0**

**Printed**: 9/28/2012 9:40:27 AM

**Page 1 of 1**
2-(4-Methylphenyl)-N-[2-(tetrahydro-2H-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14b)
HPLC

Sample Name: AC4101
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel 1

Acquisition Method: Chromni
Blank Subcr Sample Name: ACN
Column Type: 010
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

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12665843 100.000

Peak rejection level: 0

Reported: 19.07.12 13:20
Processed: 19.07.12 13:20
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**Generic Display Report**

**Acquisition Date:** 8/29/2012 9:25:00 AM

**Operator:** Meiners

**Instrument:** microTOF-Q II

---

**Graph 1:**
- Intens x10^6
- Time (min)

**Graph 2:**
- Intens x10^6
- m/z

**Graph 3:**
- Intens x10^6
- m/z

**Bruker Compass DataAnalysis 4.0**

**Printed:** 8/29/2012 9:28:41 AM

Page 1 of 1
Mass Spectrum SmartFormula Report

Analysis Info
Analysis Name: D:\Data\VRMCI\PharmChemi\Routine\APCI\12_08\WUJH_A4J1.d
Method: APCI_directprobe_positiv.m
Sample Name: A4J1
Comment: Junker

Acquisition Parameter
Source Type: APCI
Ion Polarity: Positive
Scan Begin: 100 m/z
Scan End: 1000 m/z

Acquisition Date: 8/29/2012 9:25:00 AM
Operator: Meiners
Instrument / Set#: microTOF-Q II 10252
Kalibrierung mit Fettsaeureestern

Acquisition Parameter
Source Type: APCI
Ion Polarity: Positive
Scan Begin: 100 m/z
Scan End: 1000 m/z

Mass, m/z 499.2389

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**HPLC**

**Sample Name:** AJ4701

Injection from this vial: 1 of 1

Chrom Type: HPLC Channel: 1

---

**Acquisition Method:** Chromni

Blank Subtr: Sample Name: ACN

Column Type: 610

Solvent A: Meazer + 0.05%TFA

**Developed by:** Jens

Solvent B: ACN + 0.05%TFA

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**Retention:**

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**Peak rejection level:** 0

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**Data Path:** D:\WINAPP\HPLC\Chromni\DATA\5003\ 
**Application:** Chromni

**Series:** 5003

Vial Number: 7

Vial Type: UNK

Volume: 5.0 ul

**Reported:** 19.07.12 13:12

**Processed:** 19.07.12 13:12

---

**S137**
## Mass Spectrum SmartFormula Report

### Analysis Info
- **Analysis Name:** D:\Date\FMQ\PharmChemie\Routine\APCI12_08WJU_A47.d
- **Method:** APCI_directprobe_positiv.m
- **Sample Name:** A47
- **Comment:** Jurker

### Acquisition Parameter
- **Source Type:** APCI
- ** Ion Polarity:** Positive
- **Set Nebulizer:** 0.7 Bar
- **Set Dry Gas:** 3.0 l/min

### Acquisition Info
- **Scan Begin:** 100 m/z
- **Scan End:** 1500 m/z
- **Set Collision Cell RF:** 130.0 Vpp

### Mass Spectrum Data

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**N2O**

### Notes
- **Acquisition Date:** 8/28/2012 8:37:56 AM
- **Operator:** Meiners
- **Instrument / Ser#:** microTOF-Q II 12526
- **Kellibration:** mit Freiburger Sternen

---

Bauer Compass DataAnalysis 4.0 printed 8/28/2012 8:42:36 AM Page 1 of 1
2-(4-Butylphenyl)-N-[4-(piperidin-1-ylmethyl)phenyl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14g)
HPLC

Acquired: 10.01.13 03:21
Reported: 10.01.13 10:18
Processed: 10.01.13 10:17

Data Path: D:\WIN32APP\BHM\Chrommi\DATA\5799\nApplication: Chrommi

Sample Name: AJ 87
Injection from this vial: 1 of 1

Retention Time (min)

Acquisition Method: Chrommi
Blank Subtr Sample Name: ACN
Column Type: 010
Solvent A: Water + 0.05%TFA
Solvent B: ACN + 0.05%TFA

Developed by: Jens

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Peak rejection level: 3

→ NHR
Mass Spectrum SmartFormula Report

Analysis info
Analysis Name: E:\Meiners\2013_01_14\A187\BC4_01\9214.d
Method: tune_low_lcms_routine_positiv_13_min.n
Sample Name: A187
Comment: Junker

Acquisition info
Acquisition Date: 1/4/2013 5:59:35 PM
Operator: Meiners
Instrument / Ser#: microTOF-Q II 10252

Acquisition Parameter
Source Type: ESI
Ion Polarity: Positive
Set Nebulizer: 2.0 Bar
Set Dry Heater: 200 °C
Set Dry Case: 8.0 °C
Set Divert Valve: Waste

Scan Begin: 100 m/z
Scan End: 1000 m/z
Set Exit Plate Offset: -550 V
Set Collision Cell RF: 300.6 Vpp

Intensity [V]

+MS: 6.6-6.8 min #(810-614), <Spectral Bkgrnd>

Meas. m/z # Formula Score m/z err [mDa] err [ppm] mSigma rdb e⁻ Conf N-Rule
499.2803 1 C32H39N2O5S 44.52 -499.2778 -25 -51 4.3 14.5 even ok
499.2811 2 C29H43N2O5S 2 100.00 -499.2811 0.8 1.7 23.7 9.3 even ok

Bruker Compass DataAnalysis 4.0
printed: 1/17/2013 2:45:56 PM Page 1 of 1
2-(4-tert-Butylphenyl)-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]phenyl]-7,8-dihydro-6H-[7]annuleno[b]thiophene-5-carboxamide (14h)
HPLC

Sample Name: AJ7001
Injection from this vial: 1 of 1
Chrom Type: HPLC Channel: 1

Acquisition Method: Chromni
Blank Subtr: Sample Name: ACN
Column Type: 410
Solvent A: Wasser + 0.05%TFA

No. | RT  | Area     | Conc 1  | EC  
--- |-----|----------|---------|------
1   | 20.33| 75324    | 1.002   | BB   
2   | 21.44| 17628    | 0.234   | NC   
3   | 22.37| 240727   | 3.198   | NC   
4   | 22.65| 7173172  | 95.2811 | NC   
5   | 24.08| 21550    | 0.296   | NC   

7527401  160,000

Peak rejection level: 0
Mass Spectrum SmartFormula Report

Analysis Info
Analysis Name: tune_low_lcmsroutine_positiv_10min.n
Method: Junker
Sample Name: A170
Comment: LCMS-ESI+
Acquisition Date: 1/28/2013 3:27:49 PM
Operator: Meiners
Instrument / S/N: micrOTOF-Q II 19252

Acquisition Parameter
Source Type: ESI
Focus: Not active
Scan Begin: 100 m/z
Scan End: 1000 m/z
Ion Polarity: Positive
Set Collison Cell RF: 3000 V
Set Collision Cell Offset: -0.0 V
Set Neulzer: 2.0 Bar
Set Dry Heater: 200 °C
Set Dry Gas: 9.0 L/min
Set Divert Valve: Waste

Intensity

529.3855
309.1319
414.1482

+MS, 6.5-6.6min # (773-779), Spectral Bkgnd

Mass m/z: 529.2815

#  | Formula          | Score | m/z  | err [mDa] | err [ppm] | mSgrna | rdb | e' | Conf | N-Rule
--- | ---------------- | ----- |------ | ---------- | ---------- | ------ | --- | --- | ------ | ------
1   | C33H41N2O2S      | 100.00 | 529.2835 | -1.2       | -2.3       | 4.9   | 14.5 | even | ok      |      
2   | C26H37N6         | 8.60  | 529.2856 | -3.5       | -7.4       | 5.9   | 15.5 | even | ok      |      
3   | C30H45N2O2S      | 35.08 | 529.2917 | 2.2        | 4.1        | 23.0  | 9.5  | even | ok      |      
4   | C38H51S          | 10.48 | 529.2923 | 2.8        | 6.3        | 26.1  | 18.6 | even | ok      |      

Bruker Compass DataAnalysis 4.0
printed: 1/29/2013 154:10 PM
Page 1 of 1