Synthesis and QSAR of quinazoline sulfonamides as highly potent human histamine H_4 receptor inverse agonists.

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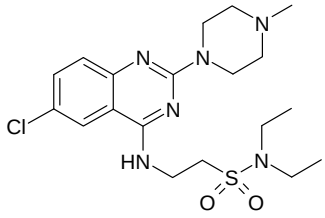
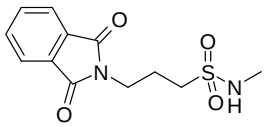
Contents

Experimental details for compounds **3**, **7b**, **8**, **11**, **12**, **13a**, **13b**, **14**, **15**, **17**, **18**, **33-36**, **38**, **39**, **41-44**, **46**, **47-61**, **82**, **89-104**.



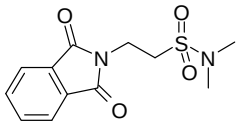
2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N,N*-diethylethanesulfonamide (3)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethane-*N,N*-diethylsulfonamide oxalate (240 mg, 0.88 mmol). Yield: 154 mg (44%). Mp 154.0-156.4°C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.41-7.27 (m, 3H), 6.32 (m, 1H), 4.01 (q, *J*= 5.8 Hz, 2H), 3.85 (t, *J*= 4.9 Hz, 4H), 3.31-3.17 (m, 6H), 2.41 (t, *J*= 4.9 Hz, 4H), 2.28 (s, 3H), 1.15 (t, *J*= 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 158.53, 150.69, 133.10, 127.24, 125.81, 120.23, 110.79, 54.97, 50.61, 46.11, 43.63, 41.41, 35.53, 14.24; MS (ESI) m/z 441 $(M+H)^+$.



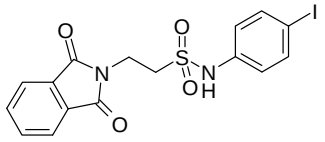
3-phtalimidopropane-*N*-methylsulfonamide (7b)

Prepared according to general method A from 3-phtalimidopropanesulfonylchloride (2.50 g, 8.69 mmol). Yield: 854 mg (35%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.82-7.76 (m, 2H), 7.72-7.64 (m, 2H), 4.13 (br s, 1H), 3.78 (t, *J*= 6.8 Hz, 2H), 3.07-2.99 (m, 2H), 2.74 (d, *J*= 5.2 Hz, 3H), 2.21-1.18 (m, 2H).



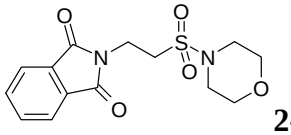
2-phtalimidoethane-*N,N*-dimethylsulfonamide (8)

2-Phtalimidoethanesulfonylchloride (2.0 g, 7.31 mmol) was used in a procedure identical to the one used for **7a**. Yield: 1.03 g (50%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.87-7.79 (m, 2H), 7.75-7.66 (m, 2H), 4.11 (t, *J*= 7.1 , 2H), 3.30 (t, *J*= 7.1 Hz, 2H), 2.87 (s, 6H).



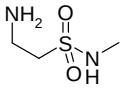
2-phtalimidoethane-*N*-(4-iodophenyl)sulfonamide (11)

Prepared according to general method A from 2-phtalimidoethanesulfonylchloride (1.50 g, 5.48 mmol) and 4-iodoaniline (2.70 g, 12.3 mmol). Yield: 1.56 g (62%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 10.14 (s, 1H), 7.83 (s, 4H), 7.63 (d, *J*= 8.7 Hz, 2H), 7.00 (d, *J*= 8.8 Hz, 2H), 3.94 (t, *J*=7.1 Hz, 2H), 3.94-3.44 (m, 2H).



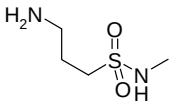
2-(2-(morpholinosulfonyl)ethyl)isoindole-1,3-dione (12)

Prepared according to general method A from 2-phtalimidoethanesulfonylchloride (2.0 g, 7.31 mmol) and morpholine (2.14 ml, 24.6 mmol). Yield: 1.28 g (54%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.94-7.84 (m, 4H), 3.99 (t, *J*= 6.8 Hz, 2 H), 3.62 (t, *J*= 4.7 Hz, 4H), 3.45 (t, *J*= 6.8 Hz, 4H), 3.15 (t, *J*= 4.6 Hz, 4H),.



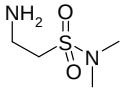
2-aminoethane-*N*-methylsulfonamide hydrochloride (13a)

Prepared according to general method B from 3-phtalimidoethane-*N*-methylsulfonamide (1.03 g, 3.84 mmol). Yield: 415 mg (72%). ^{1}H-NMR (D_2O) δ (ppm) 3.53-3.46 (m, 2H), 3.43-3.40 (m, 2H), 2.73 (s, 3H).



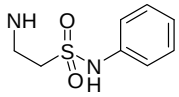
3-aminopropane-*N*-methylsulfonamide hydrochloride (13b)

Prepared according to general method B from 3-phtalimidopropane-*N*-methylsulfonamide (847 mg, 3.00 mmol). Yield: 500 mg (88%). ^{1}H-NMR (D_2O) δ (ppm) 3.31 (t, *J*= 7.5 Hz, 2H), 3.15 (t, *J*= 7.7 Hz, 2H), 2.72 (s, 3H), 2.13 (p, *J*= 7.5 Hz, 2H).



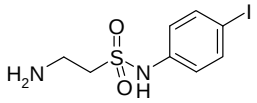
2-aminoethane-*N*,*N*-dimethylsulfonamide hydrochloride (14)

Prepared according to general method B from 3-phtalimidopropane-*N*,*N*-dimethylsulfonamide (1.03 g , 3.65 mmol). Yield: 602 mg (87%). ^{1}H-NMR (D_2O) δ (ppm) 3.49 (s, 4H), 2.89 (s, 6H); ^{13}C NMR (D_2O) δ (ppm) 45.61, 38.31, 35.36.



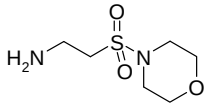
2-aminoethane-*N*-phenylsulfonamide (15)

Prepared according to general method B from 2-phtalimidoethane-*N*-phenylsulfonamide (1.60 g, 4.84 mmol). The filtrate that was evaporated to dryness was not added to water but was sufficiently pure to be used in the next step without further purification. Yield: 386 mg (40%) of a light yellow solid. ^{1}H-NMR (DMSO-δ_6) δ (ppm) 7.36-7.04 (m, 5H), 3.14 (t, *J*=7.0 Hz, 2H), 2.88 (t, *J*= 6.7 Hz, 2H).



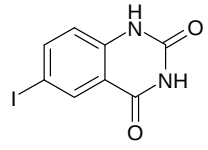
2-aminoethane-*N*-(4-iodophenyl)sulfonamide hydrochloride (17)

Prepared according to general method B from 2-phtalimidoethane-*N*-(4-iodophenyl)sulfonamide (1.47 g, 3.22 mmol). The title compound was obtained after recrystallisation of the crude hydrochloride salt from water. Yield: 704 mg (60%). ^{1}H-NMR (DMSO-δ_6) δ (ppm) 8.17 (br m, 3H), 7.70 (d, *J*= 8.5 Hz, 2H), 7.07 (d, *J*= 8.6 Hz, 2H), 3.49-3.42 (m, 2H), 3.10 (m, 2H).



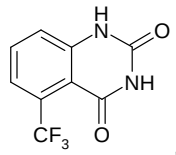
2-(morpholinosulfonyl)ethanamine hydrochloride (18)

Prepared according to general method B from 2-(2-(morpholinosulfonyl)ethyl)isoindole-1,3-dione (1.23 g, 3.87 mmol). Yield: 429 mg (57%). ^{1}H-NMR (D_2O) δ (ppm) 4.90-4.75 (m, 2H), 2.79 (t, *J*= 4.7 Hz, 4H), 3.59-3.46 (m, 2H), 3.34 (t, *J*= 4.7 Hz, 4H).



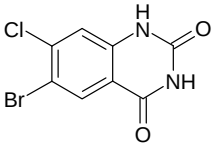
6-iodoquinazolin-2,4(1*H*,3*H*)-dione (33)

Prepared according to general method B from 2-amino-5-iodobenzoic acid (5.0 g, 19.0 mmol) and urea (11.4 g, 190 mmol). Yield: 5.34 g (98%) of a yellow powder. ^{1}H-NMR (DMSO-δ_6) δ (ppm) 8.04 (d, *J*= 2.0 Hz, 1H), 7.77 (dd, *J*= 2.1 Hz, *J*= 8.6 Hz, 1H), 6.90 (d, *J*= 8.6 Hz, 1H).



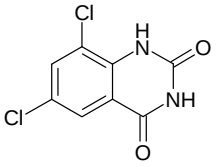
5-trifluoromethylquinazolin-2,4(1*H*,3*H*)-dione (34)

Prepared according to general method C from 2-amino-6-trifluoromethylbenzoic acid (1.0 g, 4.87 mmol) and urea (2.92 g, 48.7 mmol). Yield: 948 mg (85%) of a white solid. ^{1}H-NMR (DMSO-δ_6) δ (ppm) 11.43 (br s, 2H), 7.78 (t, *J*= 7.9 Hz, 1H), 7.58 (d, *J*= 7.4 Hz, 1H), 7.48 (d, *J*= 8.2 Hz, 1H).



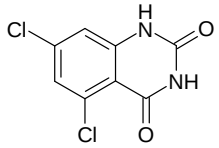
6-bromo-7-chloroquinazolin-2,4(1*H*,3*H*)-dione (35)

Prepared according to general method C from 2-amino-5-bromo-4-chlorobenzoic acid (987 mg, 3.94 mmol) and urea (2.36 g, 39.4 mmol). Yield: 1.00 g (92%) of a white solid. ^{1}H-NMR (DMSO-δ_6) δ (ppm) 8.01 (s, 1H), 7.36 (s, 1H).



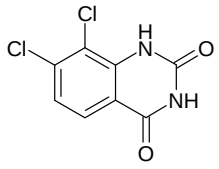
6,8-dichloroquinazolin-2,4(1*H*,3*H*)-dione (36)

Prepared according to general method C from 2-amino-3,5-dichlorobenzoic acid (3.0 g, 14.6 mmol) and urea (8.8 g, 146 mmol). Yield: 3.20 g (95%) of a grey powder. Although it contained a small amount of an impurity it was used in the next step without further purification. ^{1}H-NMR (DMSO-δ_6) δ (ppm) 10.13 (br s,1H), 7.58 (d, *J*=2.5 Hz, 1H), 7.50 (d, *J*=2.6 Hz, 1H).



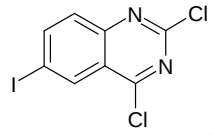
5,7-dichloroquinazolin-2,4(1*H*,3*H*)-dione (38)

Prepared according to general method C from 6-amino-2,4-dichlorobenzoic acid (2.0 g, 9.71 mmol) and urea (5.83 g, 97.1 mmol). Yield 1.72 g (77%) of a grey solid. ^{1}H-NMR (DMSO-δ_6) δ (ppm) 11.39 (br s, 2H), 7.32 (d, *J*=2.0 Hz, 1H), 7.15 (d, *J*=2.0 Hz, 1H).



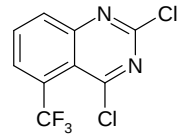
7,8-dichloroquinazolin-2,4(1*H*,3*H*)-dione (39)

Prepared according to general method C from 2-amino-3,4-dichlorobenzoic acid (2.23 g, 10.81 mmol) and urea (6.49 g, 108.1 mmol). Yield 2.18 g (87%) of a light yellow solid. ^{1}H-NMR (DMSO-δ_6) δ (ppm) 11.64 (br s, 1H), 10.87 (br s, 1H), 7.86 (d, *J*=8.5 Hz, 1H), 7.43 (d, *J*=8.5 Hz, 1H).



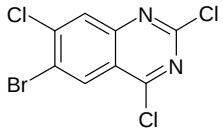
2,4-dichloro-6-iodoquinazoline (41)

Prepared according to general method D from 6-iodoquinazolin-2,4(1*H*,3*H*)-dione (2.0 g, 6.15 mmol). Yield: 1.73 g (87%); ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.59 (d, *J*= 1.9 Hz, 1H), 8.19 (dd, *J*= 1.9 Hz, *J*= 8.9 Hz, 1H), 7.69 (d, *J*= 8.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 162.25, 155.27, 151.16, 144.80, 134.53, 129.18, 123.46, 94.52.



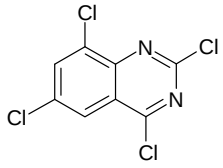
2,4-dichloro-5-trifluoromethylquinazoline (42)

Prepared according to general method D from 5-trifluoromethylquinazolin-2,4(1*H*,3*H*)-dione (814 mg, 3.54 mmol). Yield: 756 mg (80%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.23-8.17 (m, 2H), 8.00 (t, *J*=7.9 Hz, 1H).



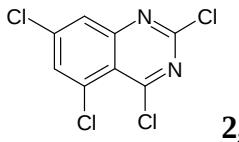
2,4,7-trichloro-6-bromoquinazoline (43)

Prepared according to general method D from 6-bromo-7-chloroquinazolin-2,4(1*H*,3*H*)-dione (950 mg, 3.45 mmol). Yield: 431 mg (40%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.52 (s, 1H), 8.10 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 162.50, 156.26, 151.00, 143.34, 130.23, 128.57, 124.18, 121.45.



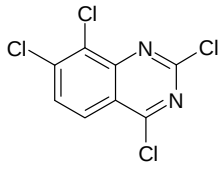
2,4,6,8-tetrachloroquinazoline (44)

Prepared according to general method D from 6,8-dichloroquinazolin-2,4(1*H*,3*H*)-dione (1.544 g, 6.68 mmol). Yield: 992 mg (55%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.15 (d, *J*= 2.2 Hz, 1H), 8.02 (d, *J*= 2.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 160.31, 144.80, 143.20, 134.25, 131.16, 130.88, 124.24, 123.34.



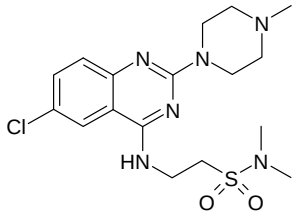
2,4,5,7-tetrachloroquinazoline (46)

Prepared according to general method D from 5,7-dichloroquinazolin-2,4(1*H*,3*H*)-dione (1.0 g, 4.33 mmol). Yield: 1.00 g (87%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 87.86 (d, *J*=2.1 Hz, 1H), 7.70 (d, *J*=2.1 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 162.09, 156.06, 154.54, 141.29, 132.48, 132.44, 126.78, 118.71.



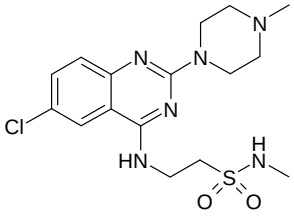
2,4,7,8-tetrachloroquinazoline (47)

Prepared according to general method D from 7,8-dichloroquinazolin-2,4(1*H*,3*H*)-dione (1.0 g, 4.33 mmol). Yield: 1.03 g (87%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.11 (d, *J*=9.0 Hz, 1H), 7.75 (d, *J*=9.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 164.16, 156.83, 149.78, 141.15, 130.94, 130.44, 124.53, 121.61.



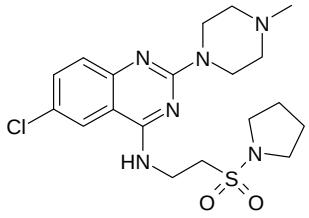
2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N,N*-dimethylethanesulfonamide (48)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethane-*N*,*N*-dimethylsulfonamide hydrochloride (162 mg, 0.86 mmol). Yield: 117 mg (33%). Mp 172.4-173.6°C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.45-7.32 (m, 3H), 6.34 (m, 1H), 4.09 (q, *J*= 5.8 Hz, 2H), 3.89 (t, *J*= 5.0 Hz, 4H), 3.25 (t, *J*= 6.0 Hz, 2H), 2.89 (s, 6H), 2.46 (t, *J*= 5.0 Hz, 4H), 2.32 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 158.52, 150.73, 133.19, 127.33, 125.91, 120.15, 110.74, 54.96, 46.43, 46.10, 43.63, 37.28, 35.24; MS (ESI) m/z 413 $(M+H)^+$.



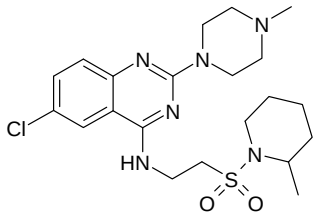
2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-methylethanesulfonamide (49)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethane-*N*-methylsulfonamide hydrochloride (131 mg, 0.86 mmol). Yield: 117 mg (34%). Mp 187.0-189.2°C; ^{1}H-NMR (MeOD) δ (ppm) 7.85 (d, *J*= 2.3 Hz, 1H), 7.49 (dd, *J*= 2.3 Hz, *J*= 9.0 Hz, 1H), 7.35 (d, *J*= 9.0 Hz, 1H), 3.99-3.89 (m, 6H), 3.46-3.31 (m, 2H), 2.71 (s, 3H), 2.52 (t, *J*= 5.0 Hz, 4H), 2.34 (s, 3H); ^{13}C-NMR (MeOD) δ (ppm) 160.73, 160.28, 151.72, 134.17, 127.66, 127.28, 122.69, 112.71, 55.96, 46.20, 44.69, 36.96, 29.18; MS (ESI) m/z 399 $(M+H)^+$.



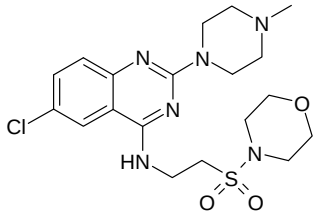
6-chloro-2-(4-methylpiperazin-1-yl)-*N*-(1-(pyrrolidine-1-ylsulfonyl)ethyl)quinazolin-4-amine (50)

Prepared according to general method E from 2,4,6-trichloroquinazoline (100 mg, 0.43 mmol) and 2-(pyrrolidin-1-ylsulfonyl)ethanamine (83 mg, 0.47 mmol). Yield 154 mg (82%). Mp 183.3-185.3^{o}C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.45 (s, 1H), 7.41-7.32 (m, 2H), 6.33 (br s, 1H), 4.08 (q, *J*= 5.8 Hz, 2H), 3.89 (t, *J*= 5.0 Hz, 4H), 3.39-3.27 (m, 6H), 2.47 (t, *J*= 5.0 Hz, 4H), 2.33 (s, 3H), 1.95-1.88 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 158.56, 158.52, 150.69, 133.15, 127.29, 125.89, 120.20, 110.79, 54.97, 47.64, 46.10, 43.63, 35.41, 30.80, 25.71; MS (ESI) m/z 439 $(M+H)^+$.



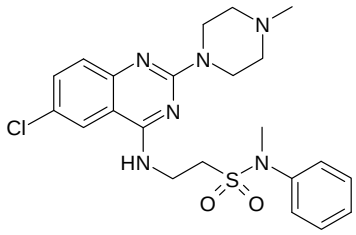
6-chloro-2-(4-methylpiperazin-1-yl)-*N*-(2-(2-methylpiperidin-1-ylsulfonyl)ethyl)quinazolin-4-amine (51)

Prepared according to general method E from 2,4,6-trichloroquinazoline (100 mg, 0.43 mmol) and 2-(2-methylpiperidin-1-ylsulfonyl)ethanamine oxalate (127 mg, 0.43 mmol). Yield 171 mg (85%) of a glassy white solid. ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.45-7.33 (m, 3H), 6.35 (br s, 1H), 4.18 (m, 1H), 4.05 (q, *J*=5.8 Hz, 2H), 3.89 (t, *J*= 5.0 Hz, 4H), 3.63-3.57 (m, 1H), 3.28-3.27 (m, 2H), 3.25-3.00 (m, 1H), 2.46 (t, *J*= 5.0 Hz, 4H), 2.33 (s, 3H), 1.95-1.52 (m, 6H), 1.26 (d, *J*= 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 158.55, 150.70, 133.14, 127.27, 125.87, 120.24, 110.82, 54.98, 51.21, 48. 53, 46.11, 43.64, 40.23, 35.64, 30.68, 25.72, 18.01, 16.26; MS (ESI) m/z 467 $(M+H)^+$.



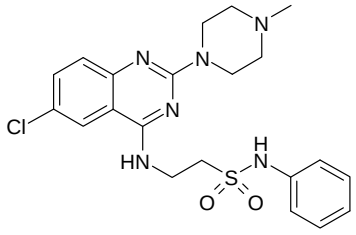
6-chloro-2-(4-methylpiperazin-1-yl)-*N*-(2-(morpholino4-ylsulfonyl)ethyl)quinazolin-4-amine (52)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 4-(2-aminoethylsulfonyl)-morpholine hydrochloride (218 mg, 0.95 mmol). Yield 303 mg (77%). Mp 172.3-174.3^{o}C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.46 (s, 1H), 7.41-7.34 (m, 2H), 6.27 (m, 1H), 4.15-4.06 (m, 2H), 3.93 (t, *J*= 4.4 Hz, 4H), 3.74 (t, *J*= 4.7 Hz, 4H), 3.28-3.23 (m, 6H), 2.52 (t, *J*= 5.0 Hz, 4H), 2.36 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 158.52, 158.31, 150.58, 133.27, 127.33, 126.05, 120.16, 110.72, 66.27, 54.84, 47.02, 45.91, 45.57, 43.46, 35.13; MS (ESI) m/z 455 $(M+H)^+$.



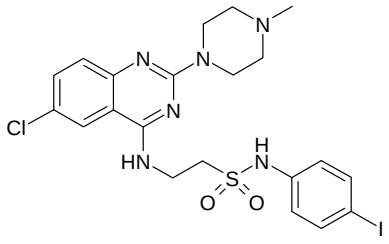
2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-methyl-*N*-phenylethanesulfonamide (53)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethane-*N*-methyl-*N*-phenylsulfonamide. Yield: 231 mg (57%). Mp 150.0-153.3°C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.43-7.23 (m, 8H), 6.12 (m, 1H), 4.03 (q, *J*= 6.0 Hz, 2H), 3.85 (t, *J*= 5.0 Hz, 4H), 3.39-3.22 (m, 7H), 2.45 (t, *J*= 5.0 Hz, 4H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.45, 150.72, 140.67, 133.16, 129.29, 127.47, 127.29, 126.16, 125.81, 120.18, 110.68, 54.96, 47.74, 46.13, 43.63, 38.24, 35.39; MS (ESI) m/z 475 $(M+H)^+$.



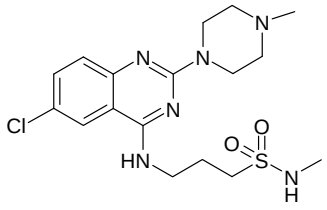
2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (54)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethane-*N*-phenylsulfonamide (172 mg, 0.86 mmol). Yield: 312 mg (79%). Mp 165.7-166.7°C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.41-7.07 (m, 8H), 6.20 (m, 1H), 4.00 (m, 2H), 3.80 (m, 4H), 3.52 (t, *J*= 5.7 Hz, 2H), 2.41 (t, *J*= 5.0 Hz, 4H), 2.30 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 158.57, 158.29, 150.63, 136.07, 133.20, 129.59, 127.26, 125.83, 125.32, 120.25, 110.62, 54.87, 49.89, 46.04, 43.56, 35.89; MS (ESI) m/z 385 $(M+H)^+$.



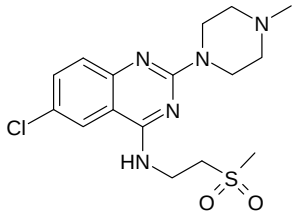
2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-(4-iodophenyl)ethanesulfonamide (55)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethane-*N*-(4-iodophenyl)sulfonamide (343 mg, 0.95 mmol). Mp 202.4-206.0°C; Yield: 441 mg (87%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 9.69 (br s, 1H), 8.01-7.98 (m, 1H), 7.95 (d, *J*=2.4 Hz, 1H), 7.61-7.57 (m, 2H), 7.48 (dd, *J*=2.4 Hz, *J*=8.8 Hz, 1H), 7.27 (d, *J*=8.8 Hz, 1H), 7.04-7.01 (m, 2H), 3.85-3.80 (m, 2H), 3.69 (t, *J*=5.0 Hz, 4H), 3.53-3.50 (m, 2H), 2.31 (t, *J*=5.0 Hz, 4H), 2.24 (s, 3H); ^{13}C-NMR (DMSO-δ_6) δ 158.62, 158.01, 150.14, 137.77, 137.68, 132.51, 126.79, 123.94, 121.78, 120.89, 110.87, 87.49, 54.10, 48.71, 45.35, 42.77, 35.22; MS (ESI) m/z 587 $(M+H)^+$.



3-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-methylpropanesulfonamide (56)

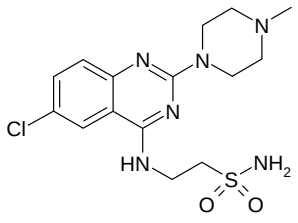
2,4,6-Trichloroquinazoline (200 mg) was added to a solution of DIPEA (0.46 ml) and 3-aminopropane-*N*-methylsulfonamide hydrochloride (162 mg) in THF (3.0 ml) and the mixture was stirred overnight at room temperature. The solution was diluted with EtOAc and washed with water and brine. Drying over Na_2SO_4 and removal of the solvent gave a solid that was purified over SiO_2 (EtOAc: Hex, 1:1) to yield the 3-(2,6-dichloro-quinazoline-4-amino)-*N*-methylpropanesulfonamide intermediate. This intermediate was added to a microwave tube containing *N*-methylpiperazine (1.0 ml) and THF (3.0 ml) and this solution was heated at 130^{o}C. After 15 minutes the obtained mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and evaporated to give the crude product as a yellow solid. Purification over SiO_2 (EtOAc:MeOH:Et_3N, 90:5:5) gave the title compound as a white solid. Yield: 104 mg (30%). Mp 213.6-214.5^{o}C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.48-7.32 (m, 3H), 5.91 (m, 1H), 5.91 (m, 1H), 3.88 (t, *J*= 5.0 Hz, 4H), 3.78 (q, *J*=6.2 Hz, 2H), 3.12 (t, *J*= 7.2 Hz, 2H), 2.78 (s, 3H), 2.45 (t, *J*= 5.1 Hz, 4H), 2.32 (s, 3H), 2.22 (p, *J*= 7.1 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm); 158.88, 158.39, 150.28, 132.30, 126.76, 123.78, 121.81, 111.00, 54.39, 47.14, 45.64, 43.08, 28.34, 22.61; MS (ESI) m/z 413 $(M+H)^{+}$.



2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*S*-methylethanesulfone (57)

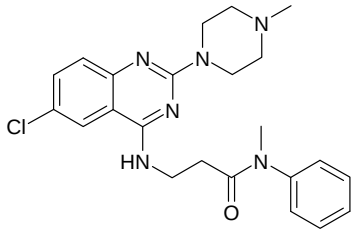
Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethylmethylsulfone hydrochloride (151 mg, 0.95 mmol). Yield 296 mg (90%). Mp 191.2-192.0^{o}C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.45 (s, 1H), 7.41-7.32 (m,

2H), 6.25 (m, 1H), 4.13 (q, *J*= 5.8 Hz, 2H), 3.88 (t, *J*=5.0 Hz, 4H), 3.43 (t, *J*= 5.8 Hz, 2H), 2.96 (s, 3H), 2.46 (t, *J*= 5.0 Hz, 4H), 2.32 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 158.61, 158.22, 150.30, 132.48, 126.83, 123.91, 121.75, 110.94, 54.38, 51.85, 45.65, 43.10, 34.34; MS (ESI) m/z 384 $(M+H)^+$.



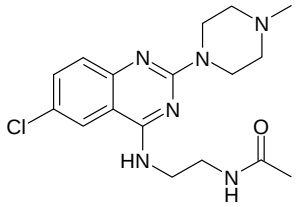
2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-ethanesulfonamide (58)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 2-aminoethanesulfonamide hydrochloride (130 mg, 0.86 mmol). Yield: 125 mg (38%). Mp 244.9-249.7°C; ^{1}H-NMR (DMSO-δ_6) δ (ppm) 8.23 (m, 1H), 8.04 (d, *J*= 2.3 Hz, 1H), 7.51 (dd, *J*= 2.3 Hz, *J*= 8.9 Hz, 1H), 7.27 (d, *J*= 8.9 Hz, 1H), 3.78 (m, 6H), 2.34 (m, 4H), 2.21 (s, 2H); ^{13}C-NMR (DMSO-δ_6) δ (ppm) 158.60, 158.27, 150.25, 132.45, 126.80, 123.86, 121.76, 110.95, 54.38, 52.49, 45.64, 43.09, 35.67; MS (ESI) m/z 461 $(M+H)^+$.



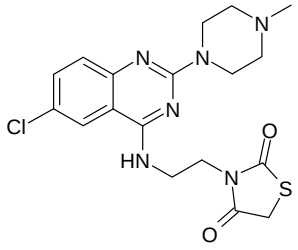
3-(6-chloro-2-(4-methylpiperazin-1-yl)quinazolin-4-ylamino)-*N*-methyl-*N*-phenylpropanamide (59)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 3-amino-*N*-methyl-*N*-phenyl-propionamide (154 mg, 0.86 mmol). Yield 154 mg (41%). Mp 134.4-137.7°C; ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.51 (d, *J*= 2.0 Hz, 1H), 7.43-7.30 (m, 5H), 7.09-7.04 (m, 2H), 6.65 (br s, 1H), 3.79-3.77 (m, 6H), 3.26 (s, 3H), 2.46-2.37 (m, 6H), 2.30 (s, 3H); ^{13}C-NMR (DMSO-δ_6) δ (ppm) 169.98, 158.66, 158.23, 150.20, 143.45, 132.22, 129.28, 127.28, 127.00, 126.71, 123.70, 121.79, 111.01, 54.32, 45.66, 42.98, 36.52, 35.23, 32.10; MS (ESI) m/z 439 $(M+H)^+$.



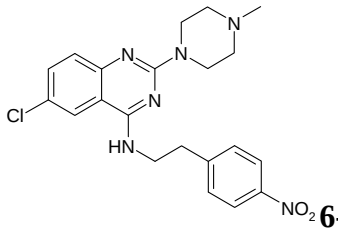
_N_-(2-(6-chloro-2-(4-methylpiperazin-1-yl)quinazolin-4-ylamino)ethyl)acetamide (60)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and *N*-(2-aminoethyl)-acetamide (88 mg, 0.86 mmol). Yield: 115 mg (37%). Mp 199.1-201.2°C; ^{1}H-NMR (DMSOδ_6) δ (ppm) 8.09-7.99 (m, 3H), 7.49 (dd, *J*= 2.3 Hz, *J*= 8.9 Hz, 1H), 7.26 (d, *J*= 8.9 Hz, 1H), 3.77 (m, 4H), 3.48-3.36 (m, 4H), 2.35 (m, 4H), 2.21 (s, 3H), 1.80 (s, 3H); ^{13}C-NMR (DMSO-δ_6) δ (ppm) 169.25, 158.94, 158.40, 150.25, 132.26, 126.73, 123.72, 123.72, 121.88, 111.07, 54.38, 45.60, 43.03, 37.31, 22.45; MS (ESI) m/z 363 $(M+H)^+$.



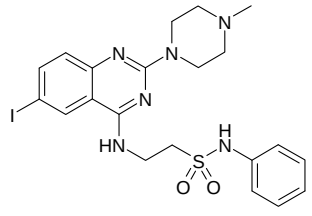
3-{2-[6-Chloro-2-(4-methylpiperazin-1-yl)-quinazolin-4-amino]-ethyl}-thiazolidine-2,4-dione (61)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 3-(2-aminoethyl)-1,3-thiazolidine-2,4-dione (169 mg, 0.86 mmol). Yield: 196 mg (54%). Mp 248.2-249.9°C. ^{1}H-NMR (DMSOδ_6) δ (ppm) 8.20 (m, 1H), 7.97 (d, *J*=2.3 Hz, 1H), 7.49 (dd, *J*=2.3 Hz, *J*=8.9 Hz, 1H), 7.26 (d, *J*=8.9 Hz, 1H), 4.07 (s, 2H), 3.77-3.36 (m, 8H), 2.35 (m, 4H), 2.20 (s, 3H); ^{13}C-NMR (DMSO-δ_6) δ 172.23, 171.86, 159.05, 158.36, 150.30, 132.36, 126.77, 123.78, 121.72, 110.92, 54.46, 45.67, 43.10, 37.18, 33.66; MS (ESI) m/z 421 $(M+H)^+$.



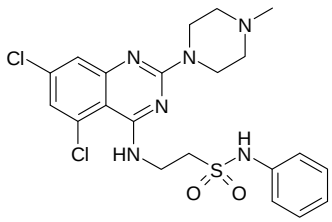
6-chloro-2-(4-methylpiperazin-1-yl)-*N*-(4-nitrophenethyl)quinazolin-4-amine (82)

Prepared according to general method E from 2,4,6-trichloroquinazoline (200 mg, 0.86 mmol) and 4-nitrophenylethylamine hydrochloride (191 mg, 0.95 mmol). Yield: 212 mg (58%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.16 (d, *J*= 8.7 Hz, 2H), 7.46-7.33 (m, 5H), 5.49 (br s, 1H), 3.94-3.81 (m, 6H), 3.12 (t, *J*= 7.0 Hz, 2H), 2.48 (t, *J*= 4.8 Hz, 4H), 2.34 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm). 158.68, 150.80, 146.81, 146.67, 133.04, 129.49, 127.51, 125.67, 123.77, 119.77, 110.64, 55.00, 46.15, 43.68, 41.90, 35.07, 30.80; MS (ESI) m/z 427 $(M+H)^+$.



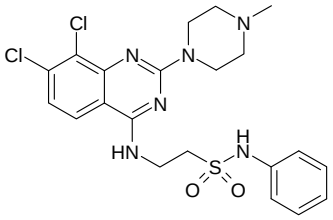
2-(6-iodo-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (98)

Prepared according to general method E from 2,4-dichloro-6-iodoquinazoline (200 mg, 0.62 mmol) and 2-aminoethane-*N*-phenylsulfonamide (134 mg, 0.67 mmol). Yield: 261 mg (76%). Mp 218.7-222.7^{o}C; ^{1}H-NMR (DMSO-δ_6) δ (ppm) 9.93 (br s, 1 H), 8.26-8.22 (m, 2H), 7.72 (dd, *J*=1.8 Hz, *J*= 8.8 Hz, 1H), 7.34-7.18 (m, 3H), 7.12-7.03 (m, 2H), 3.77-3.66 (m, 6H), 3.50-3.42 (m, 2H), 2.50-2.27 (m, 4H), 2.20 (s, 3H); MS (ESI) m/z 553 $(M+H)^+$.



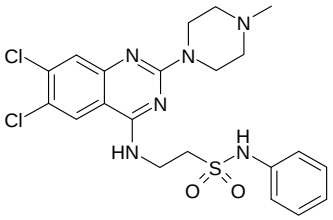
2-(5,7-dichloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (99)

Prepared according to general method E from 2,4,5,7-tetrachloroquinazoline (200 mg, 0.75 mmol) and 2-aminoethane-*N*-phenylsulfonamide (164 mg, 0.82 mmol). Yield: 296 mg (80%). Mp 171.6-173.5°C; ^{1}H-NMR (DMSO-δ_6) δ (ppm) 7.93 (m, 1H), 7.30-7.26 (m, 2H), 7.23-7.21 (m, 3H), 7.11 (d, *J*=2.1 Hz, 1H), 7.09-7.05 (m, 1H), 3.94 (q, *J*=6.4 Hz, 2H), 3.72 (t, *J*=5.0 Hz, 4H), 3.50 (t, *J*=6.8 Hz, 2H), 2.31 (t, *J*=5.0 Hz, 4H), 2.22 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 163.21, 162.74, 160.33, 143.13, 141.35, 135.00, 134,32, 128.78, 128.68, 127.10, 124.41, 111.74, 59.51, 53.95, 50.88, 48.17, 41.19; MS (ESI) m/z 495 $(M+H)^+$.



2-(7,8-dichloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (100)

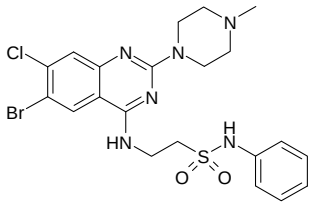
Prepared according to general method E from 2,4,7,8-tetrachloroquinazoline (200 mg, 0.75 mmol) and 2-aminoethane-*N*-phenylsulfonamide (164 mg, 0.82 mmol). Yield: 306 mg (82%). Mp 205.0-206.8°C; ^{1}H-NMR (DMSO-δ_6) δ (ppm) 8.15 (m, 1H), 7.82 (d, *J*=8.8 Hz, 1 H), 7.30-7.26 (m, 2H), 7.23-7.21 (m, 2H), 7.19 (d, *J*=8.8 Hz, 1H), 7.10-7.06 (m, 1H), 3.87-3.83 (m, 2H), 3.78 (t, *J*=5.0 Hz, 4H), 3.51-3.47 (m, 2H), 2.34 (t, *J*=5.0 Hz, 4H), 2.24 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 164.69, 163.67, 154.71, 143.09, 140.53, 134.35, 130.98, 128.88, 127.44, 125.76, 124.38, 114.86, 59.51, 53.93, 50.87, 48.21, 40.60; MS (ESI) m/z 495 $(M+H)^+$.



2-(6,7-dichloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (101)

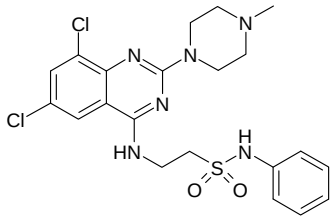
Prepared according to general method E from 2,4,6,7-tetrachloroquinazoline (200 mg, 0.75 mmol) and 2-aminoethane-*N*-phenylsulfonamide (164 mg, 0.82 mmol). Yield: 284

mg (75%). Mp 207.1-209.2°C; ^{1}H-NMR (DMSO-δ_6) δ (ppm) 8.15-8.13 (m, 2H), 7.42 (s, 1H), 7.30-7.26 (m, 2H), 7.23-7.20 (m, 2H), 7.09-7.06 (m, 1H), 3.86-3.81 (m, 2H), 3.71 (t, *J*=5.0 Hz, 4H), 3.50-3.47 (m, 2H), 2.31 (t, *J*=5.0 Hz, 4H), 2.22 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 158.44, 158.34, 151.12, 137.80, 134.90, 129.06, 125.57, 124.25, 123.60, 121.59, 119.08, 109.83, 54.23, 48.57, 45.58, 42.94, 35.23; MS (ESI) m/z 495 $(M+H)^+$.



2-(6-bromo-7-chloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (102)

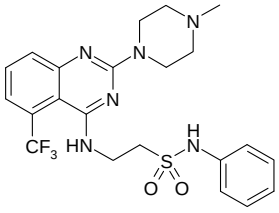
Prepared according to general method E from 6-bromo-2,4,7-trichloroquinazoline (200 mg, 0.64 mmol) and 2-aminoethane-*N*-phenylsulfonamide (140 mg, 0.70 mmol) Yield: 208 mg (60%). Mp 200.4-202.0°C; ^{1}H-NMR (DMSO-δ_6) δ (ppm) 9.68 (br s, 1H), 8.29 (s, 1H), 8.15 (m, 1H), 7.42 (s, 1H), 7.30-7.26 (m, 2H), 7.21 (d, *J*=7.2 Hz, 2H), 7.09-7.05 (m, 1H), 3.84-3.80 (m, 2H), 3.71 (t, *J*=5.2 Hz, 4H), 3.48 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=4.6 Hz, 4H), 2.22 (s, 3H) ; MS (ESI) m/z 451 $(M+H)^+$.



2-(6,7-dichloro-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (103)

Prepared according to general method E from 2,4,6,8-tetrachloroquinazoline (200 mg, 0.75 mmol) and 2-aminoethane-*N*-phenylsulfonamide (164 mg, 0.82 mmol). Yield: 305 mg (82%). Mp 196.2-197.5°C; ^{1}H-NMR (DMSO-δ_6) δ (ppm) 8.14 (t, *J*=5.2 Hz, 1H), 7.95 (d, *J*=2.4 Hz, 1H), 7.70 (d, *J*=2.4 Hz, 1H), 7.30-7.26 (m, 2H), 7.23-7.20 (m, 2H), 7.10-7.07 (m, 1H), 3.84-3.82 (m, 2H), 3.76 (t, *J*=5.0 Hz, 4H), 3.51-3.47 (m, 2H), 2.33 (t, *J*=5.0 Hz, 4H), 2.23 (s, 3H); ^{13}C-NMR (DMSO-δ_6) δ 158.75, 157.99, 146.96, 137.79, 131.76,

129.07, 123.61, 122.74, 121.05, 119.10, 111.55, 54.23, 48.56, 45.60, 42.93, 35.39; MS (ESI) m/z 495 $(M+H)^+$.



2-(5-trifluoromethyl-2-(4-methylpiperazin-1-yl)quinazoline-4-amino)-*N*-phenylethanesulfonamide (104)

Prepared according to general method E from 2,4-dichloro-5-trifluoromethylquinazoline (200 mg, 0.75 mmol) and 2-aminoethane-*N*-phenylsulfonamide (164 mg, 0.82 mmol) Yield: 308 mg (93%). ^{1}H-NMR (DMSO-δ_6) δ (ppm) 9.74 (br s, 1H), 7.64-7.57 (m, 2H), 7.50 (d, *J*=6.0 Hz, 1H), 7.32-7.28 (m, 2H), 7.24-7.21 (m, 2H), 7.11-7.06 (m, 1H), 6.56-6.55 (m, 1H), 3.98 (q, *J*=5.9 Hz, 2H), 3.74 (t, *J*=5.2 Hz, 4H), 3.47 (t, *J*=6.6 Hz, 2H), 2.32 (t, *J*=5.0 Hz, 4H), 2.23 (s, 3H); MS (ESI) m/z 495 $(M+H)^+$.

Purity data for compounds **3**, **48-61**, **82** and **98-104** as determined by LCMS.

Table 1: Purity and retention times of the synthesised compounds determined by analytical HPLC-MS.[a]

No.	Compound	Retention time (min)	Purity[b]	No.	Compound	Retention time (min)	Purity[b]
3	VUF10514	12.78	99%	**59**	VUF10518	12.32	99%
48	VUF10571	11.93	95%	**60**	VUF10557	10.75	96%
49	VUF10570	11.38	98%	**61**	VUF10554	11.87	97%
50	VUF10788	12.91	98%	**82**	VUF10506	14.58	98%
51	VUF10787	14.00	98%	**98**	VUF10659	13.67	98%
52	VUF10657	12.26	98%	**99**	VUF10782	14.77	99%
53	VUF10512	13.14	98%	**100**	VUF10781	14.37	99%
54	VUF10519	10.93	98%	**101**	VUF10660	14.21	99%
55	VUF10656	13.82	97%	**102**	VUF10776	14.34	99%
56	VUF10517	11.45	99%	**103**	VUF10658	14.62	99%
57	VUF10646	11.66	99%	**104**	VUF10775	13.81	96%
58	VUF10558	12.54	99%				

[a] The conditions can be found in the experimental section of the main article; [b] The purities were calculated as the percentage peak area of the analyzed compound by UV detection.

Value of the most influential descriptors for Eq. 1.

The value of the most influential descriptors, together with the observed, calculated and predicted affinity values of the training and test set.

No	a_ICM	PEOE_ VSA+5	SMR_ VSA1	PEOE_ VSA-3	GCUT_ PEOE_1	PEOE_VSA_ FPOS	obsd pK_i[a]	calc pK_i[b]	pred pK_i[c]
1	1.634	0.000	33.571	5.683	-0.383	0.708	8.12	7.41	7.35
3	1.723	0.000	35.090	5.683	-0.361	0.680	8.12	8.19	8.22
54	1.763	0.000	33.571	5.683	-0.394	0.609	8.31	8.21	8.18
59	1.634	0.000	48.531	5.683	-0.407	0.902	6.65	6.43	6.34
60	1.634	12.950	33.571	5.683	-0.395	0.813	6.31	6.41	6.43
61	1.830	27.875	36.695	5.683	-0.394	0.756	6.75	6.77	6.86
62	1.394	0.000	33.571	0.000	-0.368	0.952	5.12	5.28	5.36
63	1.471	0.000	44.571	5.683	-0.386	0.956	5.55	5.72	5.76
64	1.426	0.000	33.571	0.000	-0.366	0.880	5.76	5.61	5.54
65	1.368	0.000	33.571	5.683	-0.390	0.705	5.97	5.77	5.71
66	1.353	0.000	33.571	5.683	-0.390	0.718	5.83	5.67	5.60
67	1.490	0.000	33.571	5.683	-0.390	0.636	6.59	6.60	6.61
68	1.551	0.000	33.571	5.683	-0.371	0.835	7.10	6.85	6.83
69	1.524	0.000	33.571	0.000	-0.367	0.869	6.21	6.19	6.19
70	1.551	0.000	33.571	5.683	-0.382	0.835	6.02	6.73	6.79
71	1.385	0.000	33.571	5.683	-0.358	0.875	6.20	5.96	5.87
72	1.607	0.000	33.571	5.683	-0.394	0.853	6.73	6.90	6.93
73	1.575	0.000	33.571	5.683	-0.392	0.861	6.65	6.72	6.73
74	1.607	0.000	33.571	5.683	-0.396	0.860	6.87	6.86	6.86
75	1.634	0.000	33.571	5.683	-0.372	0.853	7.57	7.30	7.25
76	1.696	12.950	69.953	11.365	-0.384	0.800	6.43	6.42	6.41
77	1.607	0.000	33.571	5.683	-0.386	0.721	7.22	7.20	7.20
78	1.634	0.000	33.571	5.683	-0.397	0.708	7.45	7.26	7.24
79	1.682	0.000	50.357	5.683	-0.371	0.795	6.98	7.24	7.29
80	1.682	0.000	50.357	5.683	-0.371	0.835	6.97	7.17	7.21
82	1.590	0.000	33.571	5.683	-0.397	0.641	6.25	7.11	7.25
82	1.685	6.700	33.571	5.683	-0.404	0.791	7.30	6.98	6.92
83	1.516	0.000	33.571	5.683	-0.389	0.727	6.25	6.62	6.65
84	1.612	0.000	48.531	5.683	-0.397	0.741	6.98	6.67	6.62
85	1.690	0.000	63.491	5.683	-0.399	0.755	6.73	6.68	6.65
86	1.437	0.000	33.571	5.683	-0.361	0.867	6.23	6.24	6.25
2	1.634	0.000	33.571	5.683	-0.397	0.853	7.05	7.02	-
48	1.781	0.000	35.090	5.683	-0.365	0.802	7.90	8.29	-
49	1.813	0.000	33.571	5.683	-0.387	0.767	8.37	8.33	-
50	1.748	0.000	35.090	5.683	-0.375	0.726	7.75	8.11	-
51	1.696	0.000	35.090	5.683	-0.375	0.641	8.00	7.93	-
52	1.796	0.000	35.090	5.683	-0.358	0.805	8.03	8.45	-
53	1.737	0.000	33.571	5.683	-0.393	0.649	8.27	8.01	-
55	1.871	0.000	33.571	5.683	-0.391	0.639	7.15	8.83	-
56	1.781	0.000	33.571	5.683	-0.388	0.776	7.48	8.12	-
57	1.801	0.000	33.571	5.683	-0.387	0.762	7.57	8.27	-
58	1.848	0.000	33.571	5.683	-0.387	0.718	8.35	8.62	-
87	1.450	0.000	44.571	5.683	-0.389	0.721	5.39	5.94	-
88	1.384	0.000	33.571	0.000	-0.386	0.946	5.07	5.03	-
89	1.500	0.000	33.571	5.683	-0.365	0.852	6.12	6.59	-
90	1.581	0.000	33.571	0.000	-0.372	0.776	6.81	6.62	-
91	1.648	0.000	58.956	5.683	-0.393	0.803	6.36	6.54	-
92	1.686	14.708	33.571	5.683	-0.387	0.822	6.05	6.70	-
93	1.507	0.000	33.571	5.683	-0.395	0.938	6.22	6.16	-

94	1.607	0.000	33.571	5.683	-0.375	0.759	7.47	7.26	-
95	1.607	0.000	33.571	5.683	-0.358	0.759	7.41	7.45	-
96	1.578	0.000	44.571	5.683	-0.392	0.783	6.44	6.57	-
97	1.527	0.000	64.630	23.425	-0.393	0.738	6.89	7.32	-

[a] pK_i values taken from table 2 in the main article. [b] Calculated from equation 1.

[c] Determined by leave-one-out method.

Correlation matrix for descriptors of quinazolines as hH_4R ligands.

Correlation matrix for descriptors that influence the affinity of quinazoline derivatives for the human H_4R (pK_i hH_4R).

	pK_i hH_4R	**a_ICM**	**PEOE_ VSA+5**	**SMR_ VSA1**	**PEOE_ VSA-3**	**GCUT_ PEOE_1**	**PEOE_VSA_ FPOS**
pK_i hH_4R	1.000						
a_ICM	0.712	1.000					
PEOE_VSA+5	-0.017	0.464	1.000				
SMR_VSA1	-0.020	0.351	0.164	1.000			
PEOE_VSA-3	0.336	0.395	0.266	0.449	1.000		
GCUT_PEOE_1	-0.125	-0.341	-0.215	-0.136	-0.343	1.000	
PEOE_VSA_FPOS	-0.509	-0.302	-0.038	0.095	-0.323	0.326	1.000

HRMS data for compounds **3**, **48-61**, **82** and **98-104**.

Table 2: HRMS data for compounds **3**, **48-61**, **82** and **98-104**.[a]

No.	Compound	MF	MW Calc.	MW Found
3	VUF10514	C19H30ClN6O2S	441.1934	441.1840
48	VUF10571	C17H25ClN6O2S	413.1521	413.1507
49	VUF10570	C16H24ClN6O2S	399.1364	399.1370
50	VUF10788	C19H28ClN6O2S	439.1677	439.1678
51	VUF10787	C21H32ClN6O2S	467.1990	467.1986
52	VUF10657	C19H28ClN6O3S	455.1627	455.1633
53	VUF10512	C22H28ClN6O2S	475.1677	475.1676
54	VUF10519	C21H26ClN6O2S	461.1521	461.1532
55	VUF10656	C21H25ClIN6O2S	587.0487	587.0491
56	VUF10517	C17H26ClN6O2S	413.1521	413.1509
57	VUF10646	C16H22ClN5O2S	384.1255	384.1251
58	VUF10558	C15H22ClN6O2S	385.1208	385.1194
59	VUF10518	C23H28ClN6O	439.2008	439.2013
60	VUF10557	C17H24ClN6O	363.1695	363.1679
61	VUF10554	C18H22ClN6O2S	421.1208	421.1211
82	VUF10506	C21H24ClN6O2	427.1644	427.1654
98	VUF10659	C21H25IN6O2S	553.0877	553.0865
99	VUF10782	C21H25Cl2N6O2S	495.1131	495.1147
100	VUF10781	C21H25Cl2N6O2S	495.1131	495.1137
101	VUF10660	C21H25Cl2N6O2S	495.1131	495.1134
102	VUF10776	C21H25BrClN6O2S	539.0626	541.0607
103	VUF10658	C21H25Cl2N6O2S	495.1131	495.1140
104	VUF10775	C22H25F3N6O2S	495.1785	495.1766

[a] The conditions can be found in the experimental section of the main article.