Chemistry

*5-chloro-3-iodo-2-aminobenzensulfonamide (**4b**)*

To a stirring solution of 5-chloro-2-aminobenzensulfonamide (1.2 g, 5.81 mmol) in DMF (8ml), a solution of ICl (8.71 mmol) in AcOH (4.23ml) was added dropwise. The reaction was stirred overnight at room temperature and then water was added. The reaction mixture was neutralized with a solution of NaOH (5M) and extracted with ethyl acetate. Combined organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum. Column chromatography (ethyl acetate/ petroleum ether, 1/1) provides 1.2 g of the pure compound as a yellow solid

Yield 63%;

m.p.: 184-186 °C from petroleum ether.

IR (Nujol): 3401, 3363, 3267, 2725, 1598, 1612, 1300, 1147 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ= 5.89 (s, broad, 2H), 7.60 (d, J= 2.4 Hz, 1H), 7.65 (s, broad, 2H), 7.90 (d, J= 2.4 Hz, 1H).

GC-MS (70eV): m/z 332 (100)[M+], 315 (70), 251 (75), 124 (35).HRMS-ESI: calculated for $C_6H_7ClIN_2O_2S$ $[M+H]^+$ 332.8956; found 332.8957.

*General procedure for the preparation of 5-chloro-3-aryl-2-aminobenzensulfonamide(**4c**) (general procedure A)*

To a stirring solution of 5-chloro-3-iodo-2-aminobenzensulfonamide (120mg, 0.36 mmol) and 3-arylboronic acid (0.43 mmol) in water/dioxane (1/1 v/v), tetrakis(triphenylphosphine)palladium (5% mol.) and Na_2CO_3 (383 mg, 3.6 mmol) were added. The reaction mixture was heated at 100°C for 3 hours and then cooled down to room temperature. The mixture was then neutralized with a 1M solution of HCl and extracted with ethyl acetate. Combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. Column chromatography (ethyl acetate/ petroleum ether, 1:3) yield the pure compound.

*5-chloro-3-(3-furanyl)-2-aminobenzensulfonamide (**16**) (general procedure A)*

The compound was obtained from 3-furanylboronic acid and 5-chloro-3-iodo-2-aminobenzensulfonamide by the general procedure A.

Yield 91%;

m.p.: 81-83 °C from petroleum ether.

IR (Nujol): 3393, 3283, 2348,1633, 1303, 1322, 1113, 1073 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.10 (s, broad, 2H), 5.12 (s, broad, 2H), 6.56 (s, 1H), 7.32 (d, J= 2.5 Hz, 1H), 7.57 (t, J= 1.5 Hz, 1.6 Hz, 1H), 7.63 (s, 1H), 7.75 (d, J= 2.5 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 110.6, 120.8, 122.5, 123.0, 126.0, 127.0, 134.4, 140.6, 141.1, 144.3.

GC-MS (70eV): *m/z* 272 (84)[M+], 191 (67), 163 (60), 128 (100), 101 (30).

HRMS-ESI: calculated for $C_{10}H_{10}ClN_2O_3S$ $[M+H]^+$ 273.0095; found 273.0097.

5-chloro-3-(3-thiophenyl)-2-aminobenzensulfonamide (general procedure A)

The compound was obtained from 3-thiophenylboronic acid and 5-chloro-3-iodo-2-aminobenzensulfonamide by the general procedure A.

Yield 89%;

m.p.: 174-176 °C from petroleum ether.

IR (Nujol): 3365, 3288, 2723, 2359,1619, 1559, 1300, 1143 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.97 (s, broad, 2H), 5.03 (s, broad, 2H), 7.17 (d, J= 4.8 Hz, 1H), 7.34 (d, J= 2.3 Hz, 1H), 7.36-7.40 (m, 1H), 7.51 (dd, J= 4.8 Hz, 2.9 Hz, 1H), 7.78 (d, J= 2.3 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 122.6, 124.3, 126.3, 127.0, 127.5, 127.8, 134.6, 136.5, 136.9, 141.0.

GC-MS (70eV): *m/z* 288 (62)[M+], 283 (57), 207 (70), 172 (100), 145 (15).

HRMS-ESI: calculated for $C_{10}H_{10}ClN_2O_2S_2$ $[M+H]^+$ 288.9867; found 288.9869.

5-chloro-3-(2-thiophenyl)-2-aminobenzensulfonamide (general procedure A)

The compound was obtained from 2-thiophenylboronic acid and 5-chloro-3-iodo-2-aminobenzensulfonamide by the general procedure A.

Yield 87%;

m.p.: 80-82 °C from hexane.

IR (KBr): 3368, 3268, 2920, 2851, 2371, 1720, 1615, 1458, 1319, 1144 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.16 (s, broad, 2H), 5.2 (s, broad, 2H), 7.21-7.23 (m, 2H), 7.39 (d, J= 2.4 Hz, 1H), 7.45 (dd, J= 1.8 Hz, 3.5 Hz, 1H), 7.77 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 122.3, 124.3, 126.2, 127.1, 127.5, 127.6, 127.9, 135.3, 136.9, 141.3.

GC-MS (70eV): *m/z* 288 (67)[M+], 207 (100), 172 (95), 145 (17).

HRMS-ESI: calculated for $C_{10}H_{10}ClN_2O_2S_2$ $[M+H]^+$ 288.9867; found 288.9869.

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5-chloro-3-(2-furanyl)-2aminobenzensulfonamide (general procedure A)

The compound was obtained from 2-furanylboronic acid and 5-chloro-3-iodo-2-aminobenzensulfonamide by the general procedure A.

Yield 90%;

m.p.: 146-148 °C from hexane.

IR (Nujol): 3393, 3353, 3253, 2723, 2359, 1626, 1330, 1157, 1136 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.04 (s, broad, 2H), 5.62 (s, broad, 2H), 6.56 (dd, J= 1.8 Hz, 3.3 Hz, 1H), 6.65 (d, J= 3.3 Hz, 1H), 7.50 (d, J= 2.4 Hz, 1H), 7.55 (d, J= 1.8 Hz, 1H), 7.59 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 108.9, 111.8, 120.3, 122.6, 127.0, 127.3, 132.2, 140.2, 142.7, 150.4.

GC-MS (70eV): *m/z* 272 (84)[M+], 191 (30), 163 (32), 128 (100), 101 (23).

HRMS-ESI: calculated for $C_{10}H_{10}ClN_2O_3S$ $[M+H]^+$ 273.0095; found 273.0097.

2'-amino-3'-(aminosulfonyl)-5'-chloro-1,1'-biphenyl-4-carboxylic acid (general procedure A)

The compound was obtained from 4-carboxyphenylboronic acid and 5-chloro-3-iodo-2-aminobenzensulfonamide by the general procedure A.

Yield 88%;

m.p.: 216-218 °C from petroleum ether.

IR (KBr): 3485 (broad), 3373, 3275, 2359,1691, 1609, 1307, 1148 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ= 4.97 (s, broad, 4H), 7.22 (d, J= 2.4 Hz, 1H), 7.52 (d, J= 8.1 Hz, 2H), 7.73 (d, J= 2.4 Hz, 1H), 8.01 (d, J= 8.1 Hz, 2H).

^{13}C NMR (400 MHz, CD_3OD): δ= 122.1, 128.1, 128.7, 130.2, 130.5, 131.8, 134.2, 134.8, 142.5, 143.3, 169.4.

HRMS-ESI: calculated for $C_{13}H_{12}ClN_2O_4S$ $[M+H]^+$ 327.0201; found 327.0201.

General procedure for the preparation of 7-chloro-5-aryl-3-alkyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (general procedure B)

To a stirring solution of 5-chloro-3-aryl-2aminobenzensulfonamide (0.37mmol) in isopropanol, aldehyde (1.47mmol) and ethyl acetate saturated with HCl were added. The reaction solution was heated to 65°C for 2h. Subsequently water was added and the mixture was extracted with ethyl acetate. Combined organic layer was dried over anhydrous Na_2SO_4 and removed under reduce pressure to give the pure compound.

*7-chloro-5-(2-furanyl)-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (**5**) (general procedure B)*

The compound was obtained from 5-chloro-3-(2-furanyl)-2aminobenzensulfonamide and acetaldehyde by general procedure B

Yield 99%;

m.p.: 195-197 °C from petroleum ether.

IR (Nujol): 3385, 3262, 2359, 1619, 1585, 1559, 1330, 1300, 1143 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 1.62 (d, J= 6.1 Hz, 3H), 4.51 (d, J= 13 Hz, 1H), 5.10-5.13 (m, 1H), 5.87 (s, 1H, broad), 6.56 (dd, J= 1.8 Hz, 3.3 Hz, 1H), 6.65 (d, J= 3.3 Hz, 1H), 7.50 (d, J= 2.4 Hz, 1H), 7.55 (d, J= 1.3 Hz, 1H), 7.59 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 21.1, 62.4, 108.9, 111.9, 118.9, 123.2, 123.9, 124.0, 131.1, 137.6, 142.7, 150.5.

GC-MS (70eV): *m/z* 298 (100)[M+], 283 (67), 255 (17), 192 (52), 164 (35), 128 (68).

HRMS-ESI: calculated for $C_{12}H_{12}ClN_2O_3S$ $[M+H]^+$ 299.0252; found 299.0253.

*7-chloro-5-(2-furanyl)-3-ethyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (**6**) (general procedure B)*

The compound was obtained from 5-chloro-3-(2-furanyl)-2aminobenzensulfonamide and propionaldehyde by the general procedure B.

Yield 99%;

m.p.: 148-150 °C from petroleum ether.

IR (KBr): 3404, 3300, 2924, 2853, 1735,1588, 1489, 1333, 1168 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 1.14 (t, J= 7.5 Hz, 3H), 1.88-1.92 (m, 2H), 4.51 (s, broad, 1H), 4.90-4.93 (m, 1H), 5.93 (s, broad, 1H), 6.56 (dd, J= 1.8 Hz, 3.3 Hz, 1H), 6.65 (d, J= 3.3 Hz, 1H), 7.50 (d, J= 2.4 Hz, 1H), 7.55 (d, J= 1.8 Hz, 1H), 7.59 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 8.8, 28.1, 67.1, 108.9, 111.9, 118.9, 123.0, 123.9, 124.1, 131.1, 137.7, 142.6, 150.6.

GC-MS (70eV): *m/z* 312 (30)[M+], 283 (100), 192 (20), 156 (15), 128 (25).

HRMS-ESI: calculated for $C_{13}H_{14}ClN_2O_3S$ $[M+H]^+$ 313.0408; found 313.0410.

*7-chloro-5-(2-furanyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (**7**) (general procedure B)*

The compound was obtained from 5-chloro-3-(2-furanyl)-2aminobenzensulfonamide and formaldehyde by the general procedure B.

Yield 40%;

m.p.: 204-206 °C from petroleum ether.

IR (KBr): 3439, 3325, 2926, 2853, 2354, 1724, 1496, 1462, 1344, 1165 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.71 (s, broad, 1H), 4.90 (s, 2H), 6.06 (s, broad, 1H), 6.56 (dd, J= 1.8 Hz, 3.3 Hz, 1H), 6.65 (d, J= 3.3 Hz, 1H), 7.50 (d, J= 2.4 Hz, 1H), 7.55 (d, J= 1.8 Hz, 1H), 7.59 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 55.4, 109.0, 111.9, 119.1, 123.2, 124.2, 124.9, 131.2, 137.6, 142.7, 150.5.

GC-MS (70eV): *m/z* 284 (100)[M+], 255 (30), 207 (76), 192 (74), 156 (34), 128 (64).

HRMS-ESI: calculated for $C_{11}H_{10}ClN_2O_3S$ $[M+H]^+$ 285.0095; found 285.0096.

*7-chloro-5-(2-thiophenyl)-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (**8**) (general procedure B)*

The compound was obtained from 5-chloro-3-(2-thiophenyl)-2-aminobenzensulfonamide and acetaldehyde by the general procedure B.

Yield 96%;

m.p.: 171-173 °C from hexane.

IR (KBr): 3405, 3314, 3031, 2927, 2359,1580, 1485, 1340, 1171, 1142 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.51 (d, J= 6.1 Hz, 3H), 4.69 (d, J= 12.8 Hz, 1H), 4.97 (s, broad, 1H), 4.99-5.02 (m, 1H), 7.15-7.17 (m, 2H), 7.32 (d, J= 2.4 Hz, 1H), 7.45 (dd, J= 1.8 Hz, 3.5 Hz, 1H), 7.58 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 29.6, 62.4, 123.0, 123.2, 124.0, 127.3, 127.4, 127.5, 128.0, 134.5, 136.6, 138.9.

GC-MS (70eV): *m/z* 314 (100)[M+], 299 (65), 207 (67), 172 (90), 145 (21), 128 (16).

HRMS-ESI: calculated for $C_{12}H_{12}ClN_2O_2S_2$ $[M+H]^+$ 315.0023; found 315.0025.

*7-chloro-5-(3-furanyl)-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (**9**) (general procedure B)*

The compound was obtained from 5-chloro-3-(3-furanyl)-2aminobenzensulfonamide and acetaldehyde by the general procedure B.

Yield 99%;

m.p.: 183-185 °C from hexane.

IR (Nujol): 3337, 3283, 2730, 2358,1571, 1328, 1296, 1167, 1085 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.54 (d, J= 6.1 Hz, 3H), 4.65 (s, broad, 1H), 4.69 (s, 1H), 5.02-5.04 (m, 1H), 6.55 (s, 1H), 7.25 (d, J= 2.5 Hz, 1H), 7.53 (d, J= 2.5 Hz, 1H), 7.58 (t, J= 1.5 Hz, 1.6 Hz, 1H), 7.63 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 20.9, 62.5,110.3, 120.6, 121.7, 123.3, 133.5, 136.5, 137.8, 138.9, 140.6, 144.4.

GC-MS (70eV): *m/z* 298 (100)[M+], 283 (57), 192 (98), 163 (55), 128 (77), 101 (35).

HRMS-ESI: calculated for $C_{12}H_{12}ClN_2O_3S$ $[M+H]^+$ 299.0252; found 299.0253.

*7-chloro-5-(3-thiophenyl)-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (**10**) (general procedure B)*

The compound was obtained from *5*-chloro-3-(3-thiophenyl)-2-aminobenzensulfonamide and acetaldehyde by the general procedure B

Yield 99%;

m.p.: 140-142 °C from hexane.

IR (Nujol): 3391, 3196, 2359,1593, 1318, 1305, 1161, 1134 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.50 (d, J= 6.1 Hz, 3H), 4.63 (d, J= 12.9 Hz, 1H), 4.69 (s, broad, 1H), 5.03-5.06 (m, 1H), 7.15 (dd, J= 4.9 Hz, 1.3 Hz, 1H), 7.25 (d, J= 2.4 Hz, 1H), 7.39 (dd, J= 1.3 Hz, 2.9 Hz, 1H), 7.50 (dd, J= 2.9 Hz, 4.9 Hz, 1H), 7.59 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 21.0, 62.1, 123.0, 123.2, 123.4, 124.5, 125.6, 127.5, 127.8, 133.8, 136.1, 138.8.

GC-MS (70eV): *m/z* 314 (76)[M+], 299 (45), 207 (57), 173 (100), 145 (25).

HRMS-ESI: calculated for $C_{12}H_{12}ClN_2O_2S_2$ $[M+H]^+$ 315.0023; found 315.0025.

*3-(7-chloro-3-methyl-1,1-dioxide-3,4-dihydro-2H-1,2,4-benzothiadiazin-5-yl)benzoic acid (**13**) (general procedure B)*

The compound was obtained from 2'-amino-3'-(aminosulfonyl)-5'-chloro-1,1'-biphenyl-4-carboxylic acid and acetaldehyde by the general procedure B.

Yield 97%;

m.p.: 264-266 °C from hexane.

IR (KBr): 3456 (broad), 3420, 2960, 2924, 1702, 1595, 1488, 1261, 1097, 1018 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ= 1.30 (d, J= 6.0 Hz, 3H), 4.82 (s, broad, 1H), 5.08-5.12 (m, 1H), 5.33 (s, broad, 1H), 6.9 (d, J= 2.3 Hz, 1H), 7.17 (d, J= 7.8 Hz, 2H), 7.37 (d, J= 2.3 Hz, 1H), 8.00 (d, J= 7.8 Hz, 2H).

^{13}C NMR (400 MHz, CD_3OD): δ= 32.7, 63.7, 122.4, 124.0, 124.9, 129.7, 129.8, 131.5, 133.9, 134.1, 140.1, 140.4, 170.4.

HRMS-ESI: calculated for $C_{15}H_{14}ClN_2O_4S$ $[M+H]^+$ 353.0357; found 353.0360.

*3-(7-chloro-3-ethyl-1,1-dioxide-3,4-dihydro-2H-1,2,4-benzothiadiazin-5-yl)benzoic acid (**14**) (general procedure B)*

The compound was obtained from 2'-amino-3'-(aminosulfonyl)-5'-chloro-1,1'-biphenyl-4-carboxylic acid and propionaldehyde by the general procedure B.

Yield 99%;

m.p.: 216-218 °C from petroleum ether.

IR (KBr): 3487 (broad), 3370, 3276, 2360,1693, 1617, 1307, 1148 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d6): δ= 0.99 (t, J= 7.4 Hz, 3H), 1.71-1.83 (m, 2H), 4.80-4.83 (m, 1H), 5.51 (s, broad, 1H), 6.43 (d, J= 12.4 Hz, 1H), 7.25 (d, J= 2.5 Hz, 1H), 7.56 (d, J= 2.5 Hz, 1H), 7.58 (d, J= 8.4 Hz, 2H), 8.09 (d, J= 8.4 Hz, 2H).

^{13}C NMR (400 MHz, acetone-d6): δ= 8.4, 26.9, 67.8, 122.6, 123.3, 124.5, 129.3, 129.4, 130.2, 130.4, 133.2, 139.6, 141.1, 170.1.

HRMS-ESI: calculated for $C_{16}H_{16}ClN_2O_4S$ $[M+H]^+$ 367.0514; found 367.0515.

*3-(7-chloro-1,1-dioxide-3,4-dihydro-2H-1,2,4-benzothiadiazin-5-yl)benzoic acid (**15**) (general procedure B)*

The compound was obtained from 2'-amino-3'-(aminosulfonyl)-5'-chloro-1,1'-biphenyl-4-carboxylic acid and formaldehyde by the general procedure B.

Yield 99%;

m.p.: 106-108 °C from petroleum ether.

IR (KBr): 3487 (broad), 3370, 2987, 2942, 2901, 1756, 1446, 1375, 1244, 1096, 1052 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d6): δ= 4.84 (s, 2H), 5.51 (s, broad, 1H), 5.97 (s, broad, 1H), 7.26 (d, J= 2.5 Hz, 1H), 7.53 (d, J= 8.1 Hz, 2H), 7.60 (d, J= 2.5 Hz, 2H), 8.11 (d, J= 8.1 Hz, 2H).
^{13}C NMR (400 MHz, acetone-d6): δ= 59.7, 121.0, 123.3, 124.2, 128.8, 129.1, 130.4, 133.1, 133.2, 139.7, 140.5, 170.1.
HRMS-ESI: calculated for $C_{14}H_{12}ClN_2O_4S$ $[M+H]^+$ 339.0201; found 339.0201.

General procedure for the preparation of 3-(7-chloro-3-alkyl-1,1-dioxide-3,4-dihydro-2H-1,2,4-benzothiadiazine-5-yl)aniline (general procedure C).
To a stirring solution of 7-chloro-5-iodo-3-alkyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (prepared by the general procedure B) and 3-aminoboronic acid (0.43 mmol) in water/dioxane (1/1 v/v), tetrakis(triphenylphosphine)palladium (5% mol.) and Na_2CO_3 (3.6 mmol) were added. The reaction mixture was heated at 100°C for 3 hours and then cooled down to room temperature. The mixture was then neutralized with a 1M solution of HCl and extracted with ethyl acetate. Combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum.

7-chloro-5-iodo-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (general procedure B)
The compound was obtained from 5-chloro-3-iodo-2-aminobenzensulfonamide and acetaldehyde by general procedure B
Yield 98%;
m.p. 230-232°C from hexane;
IR (KBr) 3379, 3267, 2966, 2878, 2846, 1580, 1460, 1376, 1340, 1307, 1214, 1171, 1138 cm^{-1};
^{1}H NMR (400MHz, $CDCl_3$) δ= 1.58 (d, J= 6.1Hz, 3H), 4.32 (s, broad, 1H), 4.84 (s, broad, 1H), 5.14 (q, J= 6.1Hz, 1H), 7.65 (d, J= 2.2Hz, 1H), 7.77 (d, J= 2.2Hz, 1H);
GC-MS (70eV) *m/z* =358 (77) [M+], 343 (100), 252 (80), 125 (35);
HRMS-ESI: calc. per $C_8H_9ClIN_2O_2S$ $[M+H]^+$ 358.9118; found: 359.9120

7-chloro-5-iodo-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (general procedure B)
The compound was obtained from 5-chloro-3-iodo-2-aminobenzensulfonamide and formaldehyde by general procedure B
Yield 98%;
m.p. 220-222°C from hexane;
IR (KBr) 3382, 3271, 2970, 2879, 2849, 1582, 1462, 1377, 1341, 1308, 1216, 1175, 1140 cm^{-1};

^{1}H NMR (400MHz, $CDCl_3$) δ= 4.32 (s, broad, 1H), 4.84 (s, 2H), 4.88 (s, broad, 1H), 7.65 (d, J= 2.2Hz, 1H), 7.77 (d, J= 2.2Hz, 1H);

HRMS-ESI: calc. per $C_7H_7ClIN_2O_2S$ $[M+H]^+$ 344.8956; found: 344.8957.

*3-(7-chloro-3-methyl-1,1-dioxide-3,4-dihydro-2H-1,2,4-benzothiadiazine-5-yl)aniline (**11**) (general procedure C)*

The compound was obtained from 7-chloro-5-iodo-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide and 3-aminoboronic acid by general procedure C.

Yield 51%;

m.p.: 86-88 °C from petroleum ether.

IR (KBr): 3365, 3208, 2977, 2875, 2724, 1718, 1596, 1458, 1375, 1317, 1147 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.46 (d, J= 6.1 Hz, 3H), 3.80 (s, broad, 2H), 4.49 (s, broad, 1H), 4,67 (s, broad, 1H), 5.00-5.03 (m, 1H), 6.60 (s, 1H), 6.68 (d, J= 8.0 Hz, 1H), 6.72 (dd, J= 8.0 Hz, 1H), 7.18 (d, J= 2.4 Hz, 1H), 7.24 (t, J= 8.0 Hz, 1H), 7.69 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 20.9, 62.5, 115.1, 115.3, 118.4, 122.7, 123.1, 123.3, 130.4, 130.8, 133.7, 136.8, 138.5, 147.4.

GC-MS (70eV): *m/z* 323 (95)[M+], 280 (17), 216 (51), 181 (100), 154 (34).

HRMS-ESI: calculated for $C_{14}H_{15}ClN_3O_2S$ $[M+H]^+$ 324.0568; found 324.0569.

*3-(7-chloro-1,1-dioxide-3,4-dihydro-2H-1,2,4-benzothiadiazine-5-yl)aniline (**12**) (general procedure C)*

The compound was obtained from 7-chloro-5-iodo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide and 3-aminoboronic acid by general procedure C.

Yield 51%;

m.p.: 78-80 °C from petroleum ether.

IR (KBr): 3368, 3210, 2980, 2878, 2725, 1720, 1598, 1461, 1378, 1319, 1149, 1150 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 3.84 (s, broad, 2H), 4.50 (s, broad, 1H), 4,70 (s, broad, 1H), 4.84 (s, 2H), 6.65 (s, 1H), 6.70 (d, J= 8.0 Hz, 1H), 6.76 (dd, J= 8.0 Hz, 1H), 7.21 (d, J= 2.4 Hz, 1H), 7.26 (t, J= 8.0 Hz, 1H), 7.72 (d, J= 2.4 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ= 57.1, 115.4, 115.6, 118.7, 123.0, 123.4, 123.6, 130.7, 131.1, 134.0, 137.1, 138.8, 147.7.

HRMS-ESI: calculated for $C_{13}H_{13}ClN_3O_2S$ $[M+H]^+$ 310.0412; found 310.0414.

*Synthesis of 7-chloro-5-(3-furanyl)-3-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide (**17**)*

Step A Synthesis of 7-chloro-5-iodo-3-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide

5-chloro-3-iodo-2-aminobenzensulfonamide (1.0 mmol) was dissolved in 15 mL of acetic acid and subsequently 3-4 drops of sulfuric acid were added to the reaction mixture. The solution was heated to reflux during 3h. After cooling to room temperature, the title compound was collected by filtration, washed with diethyl ether, and dried.

Yield: 99%.

m.p.: 272-274 °C from ethyl acetate.

IR (Nujol): 3296, 1610, 1573, 1377, 1298, 1164, 820 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ= 2.50 (s, 3H), 7.92 (d, J= 2.2 Hz, 1H), 8.19 (d, J= 2.2 Hz, 1H) 10.97 (s, broad, 1H).

^{13}C NMR (400 MHz, DMSO): δ= 23.8, 111.8, 123.2, 123.7, 130.6, 133.0, 136.8, 159.7.

GC-MS (70eV): *m/z* 356 (90)[M+], 315 (97), 251 (100), 124 (40).

HRMS-ESI: calculated for $C_8H_6ClIN_2O_2S$ $[M+H]^+$ 355.8877; found 355.8879.

Step B

The compound was obtained from 3-furanylboronic acid and 7-chloro-5-iodo-3-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide by the general procedure A.

Yield: 92%.

m.p.: 134-136 °C from diethyl ether.

IR (Nujol) 3036, 1601, 1321, 1286, 1181, 1171, 1016, 866 cm^{-1}.

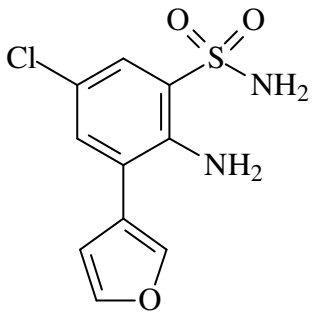
^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.60 (s, 3H), 6.87 (s, 1H) 7.53 (s, 1H) 7.74-7.76 (m, 2H) 8.45 (s, 1H), 10.99 (s, broad, 1H).

^{13}C NMR (400 MHz,$CDCl_3$): δ= 23.4, 109.8, 118.7, 120.9, 127.9, 131.6, 131.7, 132.1, 137.6, 142.7, 144.1, 153.6

GC-MS (70eV): *m/z* 296 (65)[M+], 255 (50), 191 (45), 163 (73), 128 (100).

HRMS-ESI: calculated for $C_{12}H_9ClN_2O_3S$ $[M+H]^+$ 296.0017; found 296.0019

Metabolites of compound 9



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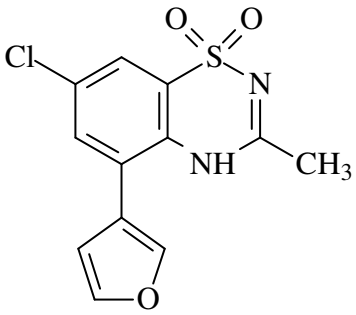

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Computational methods

Preliminary docking studies

The crystal structure of cyclothiazide in complex with S1S2 GluA2 subunits (PDB code 1LBC) and the crystal structure of IDRA21 in complex with S1S2 GluA2 subunits (PDB code 3IL1) were imported in YASARA and aligned using the option implemented in the software. The results were analyzed manually and the distance from selected residues was calculated in order to identify possible substituents on the 5-position of IDRA21.

Minimization of selected ligands

All the ligand structures were constructed using the software Spartan'08 (Wavefunction Inc., 18401 Von Karman Avenue, Suite 370 Irvine, CA 92612) installed on an Intel Pentium 4 computer. The structures were then minimized using Hartree-Fock *ab initio* method at the SCF level with 6-31G* basis set.

Docking procedures

The docking was performed with a maximum of 5 cavity detected using a sphere with a 15 Å of radius centered in the dimer interface (X=-5,78, Y= -52.78, Z= 26.08). All docking calculations were carried out using the grid-based MolDock score (GRID) function with a grid resolution of 0.30 Å. The MolDock optimization search algorithm with a maximum of 100 runs was used through the calculations, with all other parameters kept as defaults and with a maximum of 10 poses returned for each run. The results were analyzed manually and the best poses were retained.

The software MVD was evaluated on cyclothiazide, triflumethiazide, diazoxide, althiazide, hydroclorothiazide, clorothiazide, triclormethiazide and IDRA21. The average root mean square distance (RMSD) of the best ranking pose of tested compounds compared to their binding pose in the respective crystal structures was found to be 0,81Å proving that MVD is able to accurately dock this type of compounds.

Compound	RMSD MOLGrid
Cyclothiazide	0.41Å
IDRA21	0.50 Å
Hydrochlorothiazide	0.97 Å
Trichlomethiazide	0.77 Å
Althiazide	1.62 Å
Hydroflumethiazide	0.66 Å
Average RMSD	0.81 Å

The same docking procedure was then employed to evaluate the binding mode of compounds **5**, **9** and **10**. The results obtain for each ligand are reported in the table below.

Compound	MolDock Score	Rerank Score	HBond
IDRA21	-74.74	-66.12	-0.25
5	-120.38	-97.62	-1.75
9	-117.38	-97.26	-1.18
10	-120.056	-101.35	-1.03

Pharmacology

Primary Cultures of Cerebellar Granule Cells. Primary cultures of cerebellar granule neurons were prepared from 7-8 days old Sprague-Dawley rats as previously described [13]. Briefly, cells from cerebella were dispersed with trypsin (0.24 mg/ml) (SIGMA, St. Louis, MO) and plated at a density of 10^6 cells/ml on 35 mm Falcon dishes coated with poly-Lysine (10 μg/ml) (SIGMA). Cells were grown in basal Eagle's Medium (Irvine Scientific, Santa Ana, CA), supplemented with 10% fetal bovine serum (Hyclone Lab, Utah), 2mM glutamine (SIGMA), and 100 μg/ml gentamycin (SIGMA) and maintained at 37° C in 5% CO2. Cytosine arabinofuranoside (10 μg/ml) (SIGMA) was added to the cultures 24 hours after plating to prevent astroglial proliferation.
Electrophysiological Recordings. Recordings were performed on single cerebellar granule neurons after 7 days in culture using the voltage-clamp technique in the whole-cell configuration.
Electrodes were pulled from borosilicate glass on a vertical puller (PB-7, Narishige, Japan) and had a resistence of 5-7 MΩ when filled with KCl internal solution.
Currents were amplified with an Axopatch 1D amplifier (Axon Instruments, Foster City, CA), filtered at 5 kHz, and digitized at 10 kHz by using pClamp software (Axon Instruments, Foster City, CA).
Solutions. Intracellular solution containined (mM): KCl 140, MgCl2 3, EGTA 5, HEPES 5, ATP-Na 2, pH 7.3 with KOH. Cells were continuously perfused with the external solution (mM): NaCl 145, KCl 5, CaCl2 1, HEPES 5, glucose 5, sucrose 20, pH 7.4 with NaOH. The synthesized compounds were dissolved in DMSO and diluted at the final concentration in extracellular solution (DMSO at the final concentration less than 1%). All drugs were applied directly by gravity through a Y-tube perfusion system.
Data Analysis. Electrophysiological data were analyzed using the software PClamp 6.3 (Axon Instrument). Results are expressed as mean ± SE. Origin (Microcal Software, Northampton, MA) was used for figure preparation and statistical analysis.