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Carbonic anhydrase inhibitors: Synthesis and inhibition of cytosolic/membrane-associated carbonic anhydrase isozymes I, II and IX with sulfonamides incorporating hydrazino moieties[#]

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The detailed spectroscopic description of the compounds reported in the paper is contained in this file.

4-Sulfamoylbenzoic acid hydrazide 2 : mp 236-238 °C (litt. 238°C)[16]; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10 (s, 1H), 8 (d, 2H, *J*=7.1Hz), 7.9 (d, 2H, *J*=7.1Hz), 7.3 (s, 2H), 7.2, (s, 2H); MS ESI$^+$ *m/z* 216 (M+H)$^+$, 238 (M+Na)$^+$, 431 (2M+H)$^+$, 453 (2M+Na)$^+$. ESI$^-$ *m/z* 214 (M-H)$^-$, 429 (2M-H)$^-$.

2-Sulfamoylbenzoic acid hydrazide 6: mp 179-181 °C (litt. 180°C)[17]; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.8 (s, 1H), 7.9 (m, 2H), 7.6 (m, 3H), 7.1 (s, 2H), 7, (s, 2H); MS ESI$^+$ *m/z* 216 (M+H)$^+$, 238 (M+Na)$^+$, 431 (2M+H)$^+$, 453 (2M+Na)$^+$. ESI$^-$ *m/z* 214 (M-H)$^-$.

4-(N-(3,4-dichlorophenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3a: mp 178-179°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.5 (s, 1H), 8.1 (d, 2H, *J*=8.3Hz), 7.95 (d, 2H, *J*=8.3Hz), 7.9 (d, 1H, *J*=1.8Hz), 7.5 (m, 4H); MS. ESI$^-$ *m/z* 401 (M-H)$^-$, 804 (2M-H)$^-$.

4-(N-(4-acetylphenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3b: mp 212-213°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.6 (s, 1H), 9.4 (s, 1H), 8.5 (s, 1H), 8.1 (d, 2H, *J*=8Hz), 7.95 (d, 2H, *J*=8.6Hz), 7.9 (d, 2H, *J*=8.6Hz), 7.65 (d, 2H, J=8Hz), 7.55 (s, 2H), 2.5 (s, 3H); MS ESI$^+$ *m/z* 377 (M+H)$^+$, 399 (M+Na)$^+$. ESI$^-$ *m/z* 375 (M-H)$^-$.

4-(N-(4-ethyloxycarbonylphenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfona mide 3c: mp 215-217°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.6 s, 1H), 9.3 (s, 1H), 8.5 (s, 1H), 8.1 (d, 2H, *J*=5.9Hz), 7.95 (d, 2H, *J*=6.2Hz), 7.85 (d, 2H, *J*=6.2Hz), 7.6 (d, 2H, *J*=5.9Hz), 7.55 (s, 2H), 4.3 (q, 2H, *J*=4.4Hz), 1.3 (t, 3H, *J*=4.2Hz); MS ESI$^+$ *m/z* 429 (M+Na)$^+$. ESI$^-$ *m/z* 405 (M-H)$^-$, 811 (2M-H)$^-$.

4-(N-(4-nitrophenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3d: mp 226-228°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.6 (s, 1H), 9.7 (s, 1H), 8.7 (s, 1H), 8.2 (d, 2H, *J*=8.8Hz), 8.1 (d, 2H, *J*=8.4Hz), 7.9 (d, 2H, *J*=8.4Hz), 7.7 (d, 2H, *J*=8.8Hz), 7.55 (s, 2H); MS ESI$^+$ *m/z* 380 (M+H)$^+$, 402 (M+Na)$^+$. ESI$^-$ *m/z* 378 (M-H)$^-$.

4-(N-(4-bromophenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3e: mp 224-225°C ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.5 (s, 1H), 9.1 (s, 1H), 8.4 (s, 1H), 8.1 (d, 2H, *J*=8.2Hz), 8 (d, 2H, *J*=8.2Hz), 7.6 (d, 2H), 7.5 (m, 4H); MS ESI$^+$ *m/z* 435 (M+Na)$^+$, 849 (2M+Na)$^+$. ESI$^-$ *m/z* 412 (M-H)$^-$.

4-(N-(4-biphenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3f: mp 226-228°C, ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.6 (s, 1H), 9.1 (s, 1H), 8.4 (s, 1H), 8 (m, 4H), 7.5 (m, 11H); MS ESI$^+$ *m/z* 433 (M+Na)$^+$. ESI$^-$ *m/z* 409 (M-H)$^-$, 819 (2M-H)$^-$.

4-(N-(4-phenoxyphenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3g: mp 206-207°C, ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.5 (s, 1H), 9 (s, 1H), 8.3 (s, 1H), 8.1 (d, 2H, *J*=8Hz), 7.9 (d, 2H, *J*=8Hz), 7.5 (m, 4H), 7.35 (t, 2H, *J*=7.7Hz), 7.1 (t, 2H, *J*=6.7Hz), 7 (m, 3H); MS ESI$^+$ *m/z* 449 (M+Na)$^+$. ESI$^-$ *m/z* 425 (M-H)$^-$, 851 (2M-H)$^-$

4-(N-(4-benzyloxyphenyl)aminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3h: mp 202-204°C, ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.5 (s, 1H), 8.8 (s, 1H), 8.2 (s, 1H), 8.1 (d, 2H, *J*=8.4Hz), 7.95 (d, 2H, *J*=8.4Hz), 7.55 (s, 2H), 7.5 (m, 7H), 7 (d, 2H, *J*=8.8Hz), 5.1 (s, 2H); MS ESI$^+$ *m/z* 441 (M+H)$^+$, 463 (M+Na)$^+$. ESI$^-$ *m/z* 439 (M-H)$^-$, 879 (2M-H)$^-$.

4-(N-fluorenylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 3j: mp >240°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.6 (s, 1H), 8 (m, 8H), 7.6 (m, 1H), 7.5 (m, 4H), 7.4 (m, 3H), 2 (d, 1H, *J*=15Hz); MS ESI$^+$ *m/z* 445 (M+Na)$^+$. ESI$^-$ *m/z* 421 (M-H)$^-$, 843 (2M-H)$^-$.

4-(N-phenylsulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 4a: mp 202-204°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.5 (s, 1H), 8.8 (s, 1H), 7.9 (m, 6H), 7.7 (m, 4H), 7.5 (s, 2H); MS ESI$^+$ *m/z* 421 (M+Na)$^+$, 819 (2M+Na)$^+$. ESI$^-$ *m/z* 397 (M-H)$^-$, 795 (2M-H)$^-$.

4-(N-(2-methylphenyl)sulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 4b: mp 187-189°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.5 (s, 1H), 8.6 (s, 1H), 7.9 (m, 7H), 7.5 (s, 2H), 7.4 (d, 2H, *J*=6.8Hz), 2.6 (s, 3H); MS ESI$^+$ *m/z* 413 (M+H)$^+$, 435 (M+Na)$^+$. ESI$^-$ *m/z* 411 (M-H)$^-$, 823 (2M-H)$^-$.

4-(N-(4-methylphenyl)sulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 4c: mp 225-227°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.5 (s, 1H), 8.7 (s, 1H), 8 (m, 5H), 7.85 (d, 2H, *J*=7.2Hz), 7.5 (s, 2H), 7.4 (d, 2H, *J*=7.7Hz), 2.4 (s, 3H); MS ESI$^+$ *m/z* 413 (M+H)$^+$, 435 (M+Na)$^+$. ESI$^-$ *m/z* 411 (M-H)$^-$, 823 (2M-H)$^-$.

4-(N-(4-chlorophenyl)sulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 4d: mp 198-200°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.4 (s, 1H), 8.9 (s, 1H), 7.9 (m, 7H), 7.7 (d, 2H, *J*=8.3Hz), 7.5 (s, 2H); MS ESI$^+$ *m/z* 455 (M+Na)$^+$, 887 (2M+Na)$^+$. ESI$^-$ *m/z* 431 (M-H)$^-$, 863 (2M-H)$^-$.

2-(N-(2-methylphenyl)sulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 7b: mp 97-99°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.45 (s, 1H), 8.7 (s, 1H), 7.9 (m, 5H), 7.6 (m, 4H), 7.4 (s, 2H), 2.65 (s, 3H); MS ESI$^+$ *m/z* 413 (M+H)$^+$, 435 (M+Na)$^+$. ESI$^-$ *m/z* 411 (M-H)$^-$, 823 (2M-H)$^-$.

2-(N-(4-methylphenyl)sulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 7c: mp 90-92°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.4 (s, 1H), 8.85 (s, 1H), 7.8 (m, 5H), 7.4 (m, 4H), 7.3 (s, 2H), 2.4 (s, 3H); MS ESI$^+$ *m/z* 413 (M+H)$^+$, 435 (M+Na)$^+$. ESI$^-$ *m/z* 411 (M-H)$^-$, 823 (2M-H)$^-$.

2-(N-(4-fluorophenyl)sulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 7d: mp 88-90°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.45 (s, 1H), 9 (s, 1H), 8 (m, 4H), 7.6 (m, 5), 7.2 (s, 2H); MS ESI$^+$ *m/z* 439 (M+Na)$^+$, 855 (2M+Na)$^+$. ESI$^-$ *m/z* 415 (M-H)$^-$, 831 (2M-H)$^-$.

2-(N-(4-chlorophenyl)sulfonylaminocarbonyl-hydrazinocarbonyl)-benzenesulfonamide 7e: mp 138-140°C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.45 (s, 1H), 9.05 (s, 1H), 7.95 (d, 2H, *J*=8.4Hz), 7.9 (m, 1H), 7.7 (m, 6H), 7.5 (s, 2H); MS ESI$^+$ *m/z* 455 (M+Na)$^+$, 887 (2M+Na)$^+$. ESI$^-$ *m/z* 431 (M-H)$^-$, 863 (2M-H)$^-$.

4-Hydrazino-3-fluorobenzenesulfonamide 15; m.p. 176 ^{o}C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 7.37 (ddd, 1H, *J* = 11.6, *J*= 2.1, *J*= 1.1 Hz), 7.33 (dd, 1H, *J* = 8.5, J=2.1 Hz), 7.07 (s, 2H), 6.80 (dt, 1H, *J* = 8.5, *J*=8.4, *J*=1.1 Hz), 5.69 (d, 2H, *J* = 4.0 Hz); ^{1}H NMR (DMSO-d_6, 250MHz) δ: 148.73, 140.13, 130.21, 123.05, 114.72, 112.93; Anal. $C_6H_8FN_3O_2S$ (C, H, N).

4-Hydrazino-3-chlorobenzenesulfonamide 16; m.p. 176-178 ^{o}C; ^{1}H NMR (DMSO-d_6, 250MHz) δ 7.60 (d, 1H, *J* = 2.1 Hz), 7.44 (dd, 1H, *J* = 8.5, *J*= 2.1 Hz), 7.08 (s, 2H), 6.83 (d, , 1H, *J* = 8.5 Hz), 6.10 (s, 2H); ^{13}C NMR (DMSO-d_6, 250MHz) δ: 147.8, 131.2, 127.1, 125.8, 115.7, 114.14; Anal. $C_6H_8ClN_3O_2S$ (C, H, N).

2-Hydrazinobenzenesulfonamide 18: An amount of 5 g (0.029 mole) of 2-aminobenzenesulfonamide were mixed with 15 ml of concentrated hydrochloride acid and 35 g of ice, then 2.5 g of $NaNO_2$ (0.0362 mole) dissolved in 5 ml water were added over 30 minutes maintaining the temperature between 5 - 10°C. The obtained solution was then added rapidly to a cold solution of 15g stannous chloride in 25mL concentrated (36 %) hydrochloride acid. The obtained suspension was stirred for 2 hours at a temperature of 5 - 10°C. The white precipitate obtained over night was filtered, dissolved in water and neutralized to pH 7 with a solution of NaOH (2.5 % w/v). The obtained suspension was crystallization from water. The obtained precipitate was washed and dried at 40°C to obtain 4.25g of pure product (TLC: $CHCl_3$-MetOH 9/1). Yield: 78%. Elemental analysis, calcd. (found): C, 38.49 (38.39); H, 4.85 (4.82); N, 22.44 (22.41); S, 17.13 (17.35). ^{1}H NMR (DMSO-d_6, 250MHz) δ 7.6 (d, 1H, *J*=7.7Hz), 7.3 (m, 4H), 6.9 (s, 1H), 6.7 (t, 1H, *J*=6.6Hz), 4.3 (s, 2H); MS ESI$^+$ *m/z* 210 (M+Na)$^+$. ESI$^-$ *m/z* 186 (M-H)$^-$.

N-Acetyl-2-hydrazinobenzenesulfonamide 19: An amount of 2 g (; 0,011 mole) of 2-hydrazinobenzenesulfonamide **18** was mixed with a solution of 20 mL of acetic acid and 3 g of sodium acetate. Then, 5 g (4,62 mL, 0,049 mole) of acetic anhydride were added over the next 10 minutes to the suspension at room temperature, and the mixture was stirred for 3 hours under reflux. The obtained solution was rapidly added to water and ice (30 mL). The white precipitate obtained was filtered, washed with water and dried at 40°C to obtain 1.2 g of pure product in TLC: $CHCl_3$-MetOH 9/1. Yield: 53%. Elemental analysis, calcd. (found): C, 41.91 (42.06); H, 4.84 (4.82); N, 18,33 (18.39); S, 13.99 (14.23); ^{1}H NMR (DMSO-d_6, 250MHz) δ 10.1 (s, 1H), 7.7 (m, 2H), 7.45

(m, 3H), 6.9 (m, 2H), 2 (s, 3H); MS ESI$^+$ *m/z* 252 $(M+Na)^+$, 481 $(2M+Na)^+$. ESI$^-$ *m/z* 228 $(M-H)^-$, 457 $(2M-H)^-$.