

Supporting Information

Identification and Preliminary Structure-Activity Relationship Studies of Novel Pyridyl Sulfonamides as Potential Chagas Disease Therapeutic Agents

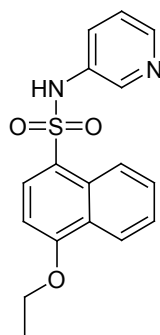
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¹H NMR and HRMS data of Sulfonamide derivatives

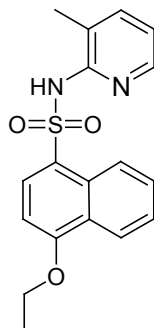
4-Ethoxy-naphthalene-1-sulfonic acid pyridin-3-ylamide (**1**).



¹H NMR (400MHz, d⁶-DMSO): δ /ppm = 10.82 (1H, s, NH), 8.63 (1H, d, J=8.5 Hz, Ar-H), 8.27 (1H, dd, J = 8.4 Hz + 0.74 Hz, Ar-H), 8.22-8.16 (2H, m, Ar-H), 8.11 (1H, dd, J = 4.7 Hz + 1.4 Hz, Ar-H), 7.79-7.72 (1H, m, Ar-H), 7.67-7.60 (1H, m, Ar-H) 7.38 (1H, ddd, J = 8.3 Hz + 2.7 Hz + 1.5 Hz, Ar-H), 7.18 (1H, ddd, J = 8.3 Hz + 4.7 Hz + 0.7 Hz, Ar-H), 7.04 (1H, d, J = 8.4Hz, Ar-H), 4.27 (2H,

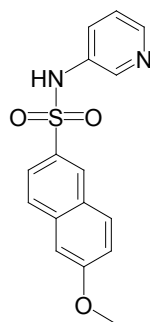
q, J = 7.0 Hz, CH₂) 1.46 (3H, t, J = 7.0 Hz, CH₃); HRMS; m/z (ES): found 329.0970 (C₁₇H₁₇N₂O₃S [M + H]⁺) requires 329.0882.

4-Ethoxy-naphthalene-1-sulfonic acid (3-methyl-pyridin-2-yl)-amide (**3**).



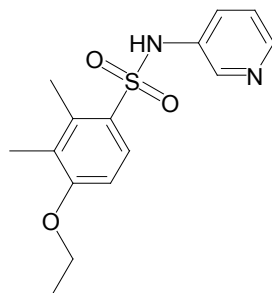
¹H NMR (400MHz,d⁶-DMSO): δ/ppm = 12.28 (1H, s, NH), 8.79 (1H, d, J = 8.5 Hz, Ar-H), 8.23 (2H, d, J = 8.2 Hz, Ar-H), 7.73-7.63 (2H, m, Ar-H), 7.62-7.53 (2H, m, Ar-H), 6.99 (1H, d, J = 8.3, Ar-H), 6.62 (1H, t, J = 6.7 Hz, Ar-H) 4.29 (2H, q, J = 7.0 Hz, OCH₂) 2.00 (3H, s, CH₃) 1.46 (3H, t, J = 6.9 Hz, CH₃); HRMS; m/z (ES): found 343.1123 (C₁₈H₁₉N₂O₃S [M + H]⁺) requires 343.1038.

6-Methoxy-naphthalene-2-sulfonic acid pyridin-3-ylamide (**4**)



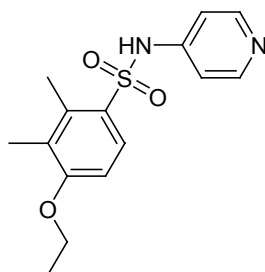
¹H NMR (400MHz,d⁶-DMSO): δ/pp = 10.58 (1H, s, NH), 8.36 (1H,d, J = 1.8 Hz, Ar-H), 8.29 (1H, d, J = 2.2 Hz Ar-H), 8.20 (1H, dd, J = 4.7 Hz + 1.4 Hz, Ar-H), 8.04 (1H, d, J = 9.1 Hz, Ar-H), 7.96 (1H, d, J = 8.8 Hz, Ar-H), 7.70 (1H, dd, J = 8.7 Hz + 1.9 Hz, Ar-H), 7.50 (1H, ddd, J = 8.3 Hz + 2.6 Hz + 1.5 Hz, Ar-H), 7.41 (1H, d, J = 2.5 Hz, Ar-H), 7.28 (1H, dd, J = 9.0 Hz + 2.5 Hz, Ar-H), 7.24 (1H, ddd, J = 8.3 Hz + 4.7 Hz + 0.6 Hz, Ar-H),, 3.89 (3H, s, CH₃). HRMS; m/z (ES): found 315.0805 (C₁₆H₁₅N₂O₃S [M + H]⁺) requires 315.0725.

4-Ethoxy-2,3-dimethyl-N-pyridin-3-yl-benzenesulfonamide (**5**)



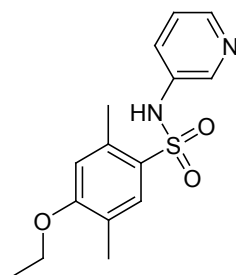
^1H NMR (400MHz, $\text{d}^6\text{-DMSO}$): δ/ppm = 10.57 (1H, s, NH), 8.27 (1H, d, J = 2.3 Hz, Ar-H), 8.17 (1H, dd, J = 4.7 Hz + 1.4 Hz, Ar-H), 7.78 (1H, d, J = 8.9 Hz, Ar-H), 7.41 (1H, ddd, J = 8.3 Hz + 2.7 Hz + 1.4/1.5 Hz, Ar-H), Ar-H), 7.23 (1H, ddd, J = 8.3 Hz + 4.7 Hz + 0.6 Hz, Ar-H), 6.93 (1H, d, J = 9.0 Hz, Ar-H), 4.05 (2H, q, J = 7.0 Hz, Ar-H), 2.49 (3H, s, CH_3), 2.1 (3H, s, CH_3), 1.33 (3H, t, J = 6.9 Hz, CH_3); HRMS; m/z (ES): found 307.1126 ($\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$) requires 307.1038.

4-Ethoxy-2,3-dimethyl-N-pyridin-4-yl-benzenesulfonamide (**6**)



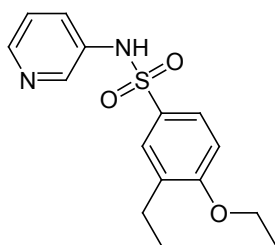
^1H NMR (400MHz, $\text{d}^6\text{-DMSO}$): δ/ppm = 12.51 (1H, s, NH), 7.98 (2H, bs, Ar-H), 7.81 (1H, d, J = 8.8 Hz, Ar-H), 6.89 (1H, d, J = 8.8 Hz, Ar-H), 6.84 (2H, d, J = 5.9 Hz, Ar-H), 4.05 (2H, q, J = 6.9 Hz, $-\text{OCH}_2\text{-CH}_3$), 2.46 (3H, s, CH_3), 2.07 (3H, s, CH_3), 1.34 (3H, t, J = 6.9 Hz, $-\text{OCH}_2\text{CH}_3$); HRMS; m/z (ES): found 307.1122 ($\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$) requires 307.1038.

2,5-Dimethyl-4-propoxy-N-pyridin-3-yl-benzenesulfonamide (**7**)



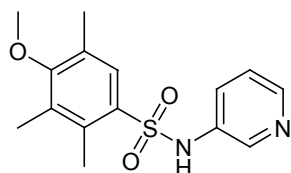
^1H NMR (400MHz, d^6 -DMSO): δ /ppm = 10.50 (1H, s, NH), 8.26 (1H, dd, J = 2.6 Hz + 0.5 Hz, Ar-H), 8.18 (1H, dd, J = 4.7 Hz + 1.4 Hz, Ar-H), 7.67 (1H, d, J = 0.5 Hz, Ar-H), 7.42 (1H, ddd, J = 8.3 Hz + 2.7 Hz + 1.5 Hz, Ar-H), 7.25 (1H, ddd, J = 8.3 Hz + 4.7 Hz + 0.7 Hz, Ar-H), 6.90 (1H, s, Ar-H), 4.0 (2H, t, J = 6.4 Hz, O-CH₂-CH₂-CH₃), 2.51 (3H, s, CH₃), 2.11 (3H, s, CH₃), 1.72 (2H, sextet, J = 7.4 Hz, O-CH₂-CH₂-CH₃), 0.97 (3H, t, J = 7.4 Hz, O-CH₂-CH₂-CH₃); HRMS; m/z (ES): found 321.1276 ($\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ [$\text{M} + \text{H}$]⁺) requires 321.1195.

4-Ethoxy-3-ethyl-N-pyridin-3-yl-benzenesulfonamide (**8**)



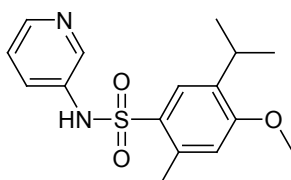
^1H NMR (400MHz, d^6 -DMSO): δ /ppm = 10.33 (1H, s, NH), 8.25 (1H, dd, J = 2.6 Hz + 0.6 Hz, Ar-H), 8.23 (1H, dd, J = 4.7 Hz + 1.4 Hz, Ar-H), 7.56 (1H, dd, J = 8.6 Hz + 2.5 Hz, Ar-H), 7.52-7.46 (2H, m, Ar-H), 7.27 (1H, ddd, J = 8.3 Hz + 4.7 Hz + 0.7 Hz, Ar-H), 7.04 (1H, d, J = 8.7 Hz, Ar-H), 4.07 (2H, q, J = 7.0 Hz, O-CH₂), 2.54 (2H, q, J = 7.5 Hz, CH₂), 1.32 (3H, t, J = 7.0 Hz, O-CH₂-CH₃), 1.07 (3H, t, J = 7.5 Hz, CH₃); HRMS; m/z (ES): found 307.1126 ($\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ [$\text{M} + \text{H}$]⁺) requires 307.1038.

4-Methoxy-2,3,5-trimethyl-N-pyridin-3-yl-benzenesulfonamide (**9**)



^1H NMR (400MHz, $\text{d}^6\text{-DMSO}$): δ/ppm = 10.65 (1H, s, NH), 8.30 (1H, dd, J = 2.6 Hz + 0.5 Hz, Ar-H), 8.18 (1H, dd, J = 4.7 Hz + 1.4 Hz, Ar-H), 7.68 (1H, s, Ar-H), 7.43 (1H, ddd, J = 8.3 Hz + 2.7 Hz + 1.5 Hz, Ar-H), 7.25 (1H, ddd, J = 8.3 Hz + 4.7 Hz + 0.7 Hz, Ar-H), 3.63 (3H, s, OCH_3), 2.46 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.15 (3H, s, CH_3). HRMS; m/z (ES): found 307.1125 ($\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$) requires 307.1038.

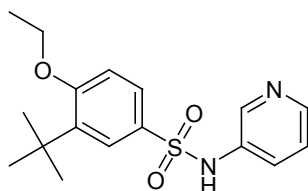
5-Isopropyl-4-methoxy-2-methyl-N-pyridin-3-yl-benzenesulfonamide (**10**)



^1H NMR (400MHz, $\text{d}^6\text{-DMSO}$): δ/ppm = 10.50 (1H, s, NH), 8.26 (1H, d, J = 2.5 Hz, Ar-H), 8.18 (1H, dd, J = 4.6 Hz + 1.3 Hz, Ar-H), 7.60 (1H, s, Ar-H), 7.43 (1H, ddd, J = 8.3 Hz + 2.6 Hz + 1.4 Hz, Ar-H), 7.24 (1H, dd, J = 8.3 Hz + 4.7 Hz, Ar-H), 6.93 (1H, s, Ar-H), 3.81 (3H, s, OCH_3), 3.14 (1H, Septet, J = 6.9 Hz, CH of isopropyl), 2.54 (3H, s, CH_3), 1.07 (6H, d, J = 6.9 Hz, $(\text{CH}_3)_2$ of isopropyl);

HRMS; m/z (ES): found 321.1279 ($\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$) requires 321.1195.

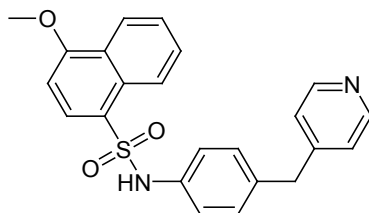
3-tert-Butyl-4-ethoxy-N-pyridin-3-yl-benzenesulfonamide (**11**)



^1H NMR (400MHz, $\text{d}^6\text{-DMSO}$): δ/ppm = 10.17 (1H, s, NH), 8.30 (1H, dd, J = 2.6 Hz + 0.4/0.5 Hz, Ar-H), 8.17 (1H, dd, J = 4.7 Hz + 1.4 Hz, Ar-H), 7.75 (1H, d, J = 2.5 Hz, Ar-H), 7.57 (1H, dd, J = 8.7/8.8 Hz + 2.6 Hz, Ar-H), 7.47 (1H, ddd, J = 8.3 Hz + 2.7 Hz + 1.4 Hz, Ar-H), 7.24 (1H, ddd, J =

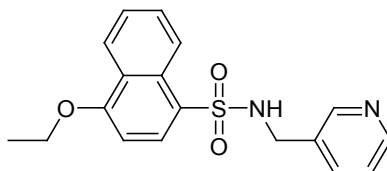
8.3 Hz + 4.7 Hz + 0.5 Hz, Ar-H), 7.09 (1H, d, J = 8.8 Hz, Ar-H), 4.11 (2H, q, J = 7.0 Hz, -OCH₂-CH₂), 1.23 (3H, t, J = 7.0 Hz, -OCH₂-CH₃), 1.23 (9H, s, (CH₃)₃ of t-Bu); HRMS; m/z (ES): found 335.1438 (C₁₇H₂₃N₂O₃S [M + H]⁺) requires 335.1351.

4-Methoxy-naphthalene-1-sulfonic acid (4-pyridin-4-ylmethyl-phenyl)-amide (**12**)



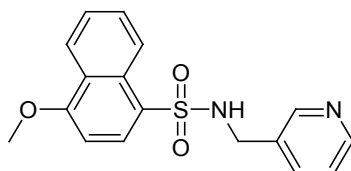
¹H NMR (400 MHz, d⁶-DMSO): δ/ppm = 10.48 (1H, s, NH), 8.63 (1H, d, J = 8.5 Hz, Ar-H), 8.38 (2H, d, J = 5.9 Hz, Ar-H), 8.24 (1H, d, J = 8.0 Hz, Ar-H), 8.16 (1H, d, J = 8.3 Hz, Ar-H), 7.71 (1H, dt, J = 7.0/8.4 Hz + 1.2 Hz, Ar-H), 7.61 (1H, t, J = 7.4 Hz, Ar-H), 7.09 (2H, d, J = 5.8 Hz, Ar-H), 7.05-6.90 (5H, m, Ar-H), 4.01 (3H, s, OCH₃), 3.76 (2H, s, CH₂); HRMS; m/z (ES): found 405.1278 (C₂₃H₂₁N₂O₃S [M + H]⁺) requires 405.1195.

4-Ethoxy-naphthalene-1-sulfonic acid (pyridin-3-ylmethyl)-amide (**13**)



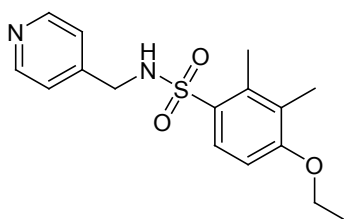
¹H NMR (400 MHz, d⁶-DMSO): δ/ppm = 8.56 (1H, d, J = 8.3 Hz, Ar-H), 8.41 (1H, t, J = 6.2 Hz, NH), 8.31 (1H, dd, J = 4.8 Hz + 1.6 Hz, Ar-H), 8.29-8.25 (2H, m, Ar-H), 8.06 (1H, d, J = 8.3 Hz, Ar-H), 7.74-7.68 (1H, m, Ar-H), 7.66-7.60 (1H, m, Ar-H), 7.48 (1H, dt, J = 8.2 Hz + 1.8/2.0 Hz, Ar-H), 7.13 (1H, ddd, J = 7.8 Hz + 4.8 Hz + 0.7 Hz, Ar-H), 7.02 (1H, d, J = 8.4 Hz, Ar-H), 4.30 (2H, q, J = 6.9 Hz, O-CH₂-CH₃), 3.99 (2H, d, J = 6.1 Hz, CH₂), 1.50 (3H, t, J = 6.9 Hz, O-CH₂-CH₃); HRMS; m/z (ES): found 343.1123 (C₁₈H₁₉N₂O₃S [M + H]⁺) requires 343.1038.

4-Methoxy-naphthalene-1-sulfonic acid (pyridin-3-ylmethyl)-amide (**14**)



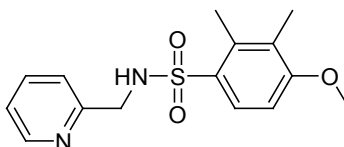
^1H NMR (400MHz, d^6 -DMSO): δ /ppm = 8.60 (1H, d, J = 8.4Hz, Ar-H), 8.42 (1H, t, J = 6.2 Hz, NH), 8.30 (1H, dd, J = 4.7/4.8 Hz + 1.6 Hz, Ar-H), 8.28-8.23 (2H, m, Ar-H), 8.09 (1H, d, J = 8.3Hz, Ar-H), 7.74-7.67 (1H, m, Ar-H), 7.66-7.59 (1H, m, Ar-H), 7.50 (1H, dt, J = 8.0 Hz + 1.8/2.1 Hz, Ar-H), 7.13 (1H, ddd, J = 7.8 Hz + 4.8 Hz + 0.7 Hz, Ar-H), 7.05 (1H, d, J = 8.4 Hz, Ar-H), 4.05 (3H, s, OCH₃), 3.99 (2H, d, J = 6.2 Hz, CH₂); HRMS; m/z (ES): found 329.0972 (C₁₇H₁₇N₂O₃S [M + H]⁺) requires 329.0882.

4-Ethoxy-2,3-dimethyl-N-pyridin-4-ylmethyl-benzenesulfonamide (**15**)



^1H NMR (400MHz, d^6 -DMSO): δ /ppm = 8.44-8.41 (2H, m, Ar-H), 8.19 (1H, t, J = 5.8 Hz, NH), 7.67 (1H, d, J = 8.8 Hz, Ar-H), 7.22-7.19 (2H, m, Ar-H), 6.89 (1H, d, J = 8.8 Hz, Ar-H) 4.07 (2H, q, J = 6.9 Hz, O-CH₂-CH₃), 3.98 (2H, d, J = 5.7 Hz, CH₂), 2.44 (3H, s, CH₃), 2.09 (3H, s, CH₃), 1.36 (3H, t, J = 6.9 Hz, -OCH₂-CH₃); HRMS; m/z (ES): found 321.1277 (C₁₆H₂₁N₂O₃S [M + H]⁺) requires 321.1195.

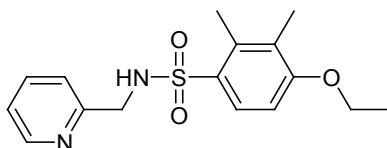
4-Methoxy-2,3-dimethyl-N-pyridin-2-ylmethyl-benzenesulfonamide (**16**)



^1H NMR (400MHz, d^6 -DMSO): δ /ppm = 8.40 (1H, ddd, J = 2.1Hz, J = 4.8 Hz + 1.8 Hz + 0.9 Hz, Ar-H), 8.14 (1H, t, J = 6.3 Hz, NH), 7.73-7.65 (2H, m, Ar-H), 7.29 (1H, d, J = 7.8 Hz, Ar-H), 7.20 (1H, ddd, J = 8.0 Hz + 4.8 Hz + 1.1 Hz, Ar-H), 6.90 (1H, d, J = 8.9 Hz, Ar-H), 3.98 (2H, d, J = 7.1

Hz, CH₂), 3.82 (3H, s, OCH₃), 2.45 (3H, s, CH₃), 2.08 (3H, s, CH₃); HRMS; m/z (ES): found 307.1127 (C₁₅H₁₉N₂O₃S [M + H]⁺) requires 307.1038.

4-Ethoxy-2,3-dimethyl-N-pyridin-2-ylmethyl-benzenesulfonamide (**17**)



¹H NMR (400MHz, d⁶-DMSO): δ/ppm = 8.40 (1H, ddd, J = 4.8 Hz + 1.8 Hz + 0.9 Hz, Ar-H), 8.13 (1H, t, J = 5.8 Hz, NH), 7.72-7.64 (2H, m, Ar-H), 7.29 (1H, d, J = 7.8 Hz, Ar-H), 7.20 (1H, ddd, J = 8.0 Hz + 4.8 Hz + 1.0 Hz, Ar-H), 6.88 (1H, d, J = 8.9 Hz, Ar-H), 4.06 (2H, q, J = 7.0 Hz, O-CH₂-CH₃), 4.03 (2H, d, J = 6.0 Hz, CH₂), 2.45 (3H, s, CH₃), 2.09 (3H, s, CH₃), 1.35 (3H, t, J = 6.9 Hz, O-CH₂-CH₃); HRMS; m/z (ES): found 321.1270 (C₁₆H₂₁N₂O₃S [M + H]⁺) requires 321.1195.