

Supporting Information

Acyl Sulfonamide Anti-Proliferatives: Benzene Substituent Structure-Activity Relationships for a Novel Class of Anti-Tumor Agents

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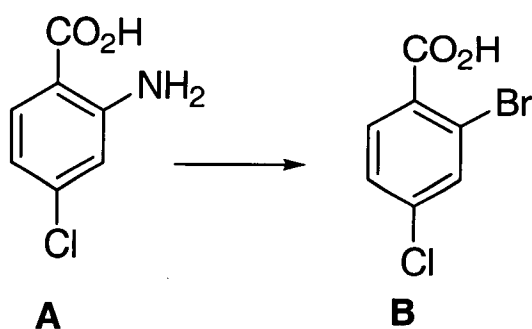
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General Methods. All solvents and reagents were used as obtained from commercial sources unless otherwise indicated. The abbreviations ACN, CDI, DMSO, DMAP, EDC, and THF refer to acetonitrile, carbonyldiimidazole, dimethylsulfoxide, 4-(dimethylamino)pyridine, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and tetrahydrofuran respectively.

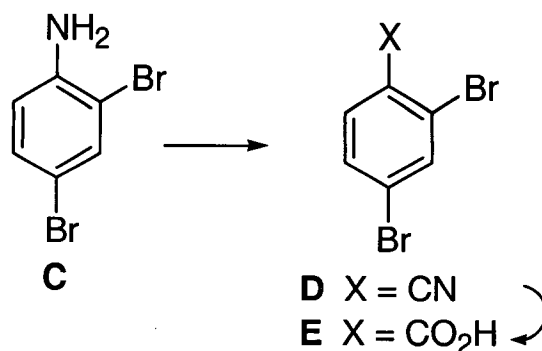
The ^1H -NMR's were taken on a Bruker 250 MHz nmr or a Bruker 300MHz nmr or a Mercury 400MHz nmr. Chemical shifts were reported in ppm relative to TMS or solvent. Midwest Microlab performed the elemental analyses after the samples had been blocked at 120°C unless otherwise noted. Melting points were determined on a Buchi apparatus and are not corrected. Analytical thin-layer chromatography (TLC) was performed on Merck TLC glass plates precoated with F254 silica gel 60 (UV, 254 nm, and iodine).

Noncommercially available building blocks that were prepared according to literature methods include 4-chloro-2-ethylbenzoic acid,¹ 4-chloro-2-propylbenzoic acid¹ and *N*-(4-(*t*-butoxycarbonyl)amino-2-chloro-benzoic acid².

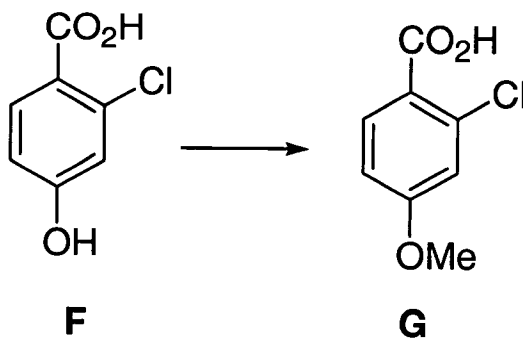
Synthesis of Benzoic Acid Starting Materials



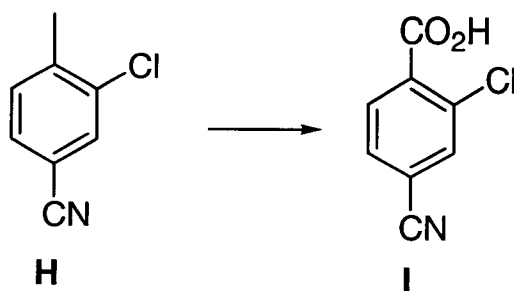
2-Bromo-4-chlorobenzoic acid (B). A solution of sodium nitrite (2.2 g) in H_2O (15 mL) was added dropwise to a stirred ice-cooled mixture of 2-amino-4-chlorobenzoic acid **A** (5.0 g, 29 mmol) and 48% HBr (150 mL) in H_2O (150 mL). The reaction mixture was stirred for 2 h at 0 °C and was then treated dropwise with a solution of copper (II) bromide (7.8 g) in H_2O (20 mL). Upon completion of addition, the reaction mixture was allowed to warm to ambient temp and was stirred overnight. The reaction mixture was then extracted with 3:1 EtOAc:hexane (400 mL x 2). The combined organic layers were washed with brine (200 mL), dried, concentrated *in vacuo*, and the residue subjected to silica gel chromatography, eluting with CHCl_3 containing 1% MeOH and 0.5% AcOH. Fractions containing product were combined and concentrated *in vacuo* to provide the title compound (4.0 g, 59% yield); mp = 154-155 °C; lit mp 155 °C.³



2,4-Dibromobenzoic Acid (E). A solution of copper (I) cyanide (2.3 g, 26 mmol) in anhydrous DMSO (50 mL) was stirred at 60 °C, and to this solution was added *t*-butylnitrite (7.1 mL, 60 mmol) all at once. A solution of 2,4-dibromoaniline **C** (5.0 g, 20 mmol) in anhydrous DMSO (30 mL) was added dropwise, via cannula, to the mixture. After the addition was complete the reaction mixture was stirred for 1 h, cooled to 45 °C, and then treated slowly with 5 N HCl (50 mL). Five minutes later, the reaction mixture was cooled to ambient temp and extracted with 1:1 EtOAc:hexane (300 x 2 mL). The combined organic layers were washed with H₂O (100 mL) and brine (100 mL), dried, concentrated *in vacuo* and the residue subjected to silica gel chromatography, eluting with an EtOAc:hexane gradient. Fractions containing product were combined and concentrated *in vacuo* to provide 2,4-dibromobenzonitrile **D**⁴ (1.6 g, 31% yield); mp 76-78 °C; lit mp 79-80 °C.⁵ A stirred suspension of **D** (1.6 g, 6.0 mmol) in H₂SO₄ (6 M, 150 mL) was heated at reflux for 3 days. The reaction mixture was cooled to ambient temp and then extracted with EtOAc (75 mL x 2). The combined organic layers was washed with H₂O (100 mL) and brine (50 mL), dried, concentrated, and subjected to silica gel chromatography, eluting with CHCl₃ containing 0.5% MeOH and 0.1% AcOH. Fractions containing product were combined and concentrated *in vacuo* to provide the title compound (0.81 g, 48% yield); mp 171-172 °C; lit mp 172-173 °C.⁶



2-Chloro-4-methoxy-benzoic acid (G). To a solution of 2-chloro-4-hydroxybenzoic acid **F** (3.0 g, 17 mmol) in acetone (150 mL) was added K_2CO_3 (14 g, 100 mmol) and dimethyl sulfate (13 g, 100 mmol). The heterogeneous reaction mixture was refluxed under a N_2 atmosphere for 6 h then cooled to room temp and stirred for 18 h. The solids were dissolved in a minimum amount of H_2O , and most of the acetone was removed under reduced pressure (the organics oiled out). The resulting mixture was diluted with MeOH until homogeneous and 2 M NaOH solution (90 mL) was added. The resulting solution was stirred for 7 h. Most of the MeOH was removed under reduced pressure and the basic solution was acidified with 2 M HCl and extracted with EtOAc (3 x). The combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **G** (2.5 g, 77%) as a white solid, mp 211-213 °C (lit mp 210-212 °C).⁷ ^1H NMR (300 MHz, methanol- d_4) δ 3.84 (s, 3H), 6.92 (dd, J = 1.4, 7.0 Hz, 1H), 7.01 (d, J = 1.4 Hz, 1H), 7.91 (d, J = 7.0 Hz, 1H); ESI MS m/z 185 [$\text{C}_8\text{H}_7\text{ClO}_3 - \text{H}$].



2-Chloro-4-cyano-benzoic acid (I).⁸ To a suspension of 3-chloro-4-methylbenzonitrile **H** (1.0 g, 6.6 mmol) in 70% H_2SO_4 (18 mL) was added chromium (VI) oxide (0.9 g, 8.9 mmol). The reaction mixture was stirred at room temp for 3 h. The reaction mixture was extracted with EtOAc (300 mL). The organic layer was washed with brine then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was chromatographed on silica gel, eluting with CH_2Cl_2 :MeOH (50:1) to afford **I** (300 mg, yield = 25%). ^1H NMR (300 MHz, CDCl_3) δ 7.63 (d, J = 8.1 Hz, 1H), 7.79 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H).

Synthesis of Benzenesulfonamide Starting Materials

Benzenesulfonamide general procedure. To an ice cold stirred solution of the sulfonyl chloride in acetone (ca. 1.5 mL/mmol) was added a 30% aqueous solution of ammonia (4 mL/mmol). The resulting mixture was stirred at room temp for 3 h and then evaporated *in vacuo* to reduce the total volume to one half so that the solid sulfonamide precipitated out of solution. The solid was filtered, thoroughly rinsed with H_2O , and dried under high vacuum for 16 h's. The sulfonamide was used without further purification.⁹

3-Methylbenzenesulfonamide. Prepared from 3-methylbenzenesulfonyl chloride using the sulfonamide general procedure. Yield = 80%; mp 109-110 °C; lit mp 108 °C.¹⁰ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.29 (br s, 2H), 2.37 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 144.8, 139.2, 133.0, 129.5, 126.7, 123.4, 21.5; ESI MS *m/z* 170 (C₇H₉NO₂S-H)⁺.

3,4-Dibromobenzenesulfonamide. Prepared from 3,4-dibromobenzenesulfonyl chloride using the sulfonamide general procedure. Yield = 96%; mp 170-172 °C; lit mp 175-176 °C.¹¹ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (d, J = 1.8 Hz, 1H), 7.95 (d, J = 8.4, 1H), 7.70 (dd, J = 1.8, 8.4 Hz, 1H), 7.56 (brs, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 145.5, 135.2, 131.2, 128.6, 126.9, 125.1; ESI MS *m/z* 314 (C₆H₅Br₂NO₂S - H)⁺.

3-Methoxybenzenesulfonamide. Prepared from 3-methoxybenzenesulfonyl chloride using the sulfonamide general procedure. Yield = 72%; mp 130-132 °C; lit mp 130 °C.¹² ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.45 (t, J = 7.9 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.35 (t, J = 2.0, 1H), 7.34 (brs, 2H), 7.15 (dd, J = 2.0, 7.92 Hz, 1H), 3.80 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.9, 146.1, 130.8, 118.3, 118.2, 111.5, 56.2; ESI MS *m/z* 186 (C₇H₉NO₃S - H)⁺.

4-Sulfamoyl-benzoic acid methyl ester. 4-Carboxybenzenesulfonamide (2.0 g, 9.9 mmol) was added to a 1:3 MeOH:CHCl₃ (200 mL). This reaction mixture was a suspension. (Trimethylsilyl)diazomethane was added as a 2.0 M solution in hexanes (7.4 mL, 15 mmol) at ambient temperature and stirred for 5 min. The solution was concentrated *in vacuo*, and the crude was chromatographed in silica gel, 0.5% MeOH/0.1% AcOH in CH₂Cl₂. The product was a white solid (2.1 g, 98% yield), mp 180 °C, lit mp 181-183 °C.¹³

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Appendix

Elemental Analyses

Compound #	Theory	Found
1	C 47.29 H 2.75 N 4.24	C 47.12 H 2.67 N 4.18
2 (blocked 60 °C)	C 42.82 H 2.21 N 3.84	C 42.56 H 2.14 N 3.76
3	C 52.79 H 3.41 N 4.74	C 53.10 H 3.56 N 4.70
4	C 47.29 H 2.75 N 4.24	C 47.47 H 2.88 N 4.17
5	C 47.29 H 2.75 N 4.24	C 47.07 H 2.85 N 4.12
6	C 47.29 H 2.75 N 4.24	C 47.54 H 2.91 N 4.20
7	C 54.28 H 3.90 N 4.52	C 54.27 H 3.97 N 4.41
10	C 53.18 N 4.46 N 8.27	C 53.11 H 4.61 N 8.22
12	C 42.82 H 2.21 N 3.84	C 42.88 H 2.36 N 3.75
13	C 42.82 H 2.21 N 3.84	C 42.88 H 2.36 N 3.75
14	C 38.17 H 1.97 N 3.42	C 38.27 H 2.06 N 3.34
15	C 38.17	C 37.82

vacuum dried room temp.	H 1.97 N 3.42	H 1.69 N 3.40
16	C 34.43 H 1.78 N 3.09	C 34.67 H 1.83 N 2.95
17	C 39.77 H 2.05 N 3.57	C 39.38 H 2.08 N 3.49
18	C 48.85 H 3.22 N 4.07	C 48.76 H 3.20 N 3.99
19	C 43.26 H 2.85 N 3.60	C 43.34 H 2.82 N 3.52
20	C 41.62 H 2.15 N 7.47	C 41.65 H 2.20 N 7.36
21	C 50.29 H 3.66 N 3.91	C 50.50 H 3.66 N 3.84
23	C 55.64 H 4.36 N 4.33	C 55.74 H 4.43 N 4.18
24	C 46.68 H 3.08 N 3.89	C 46.41 H 3.22 N 3.76
26	C 41.73 H 1.87 N 3.24	C 41.90 H 1.90 N 3.14
27 (vacuum dried 80 °C)	C 41.62 H 2.15 N 7.47	C 41.69 H 2.33 N 7.30
28	C 41.14 H 1.97 N 6.85	C 41.37 H 1.97 N 6.73
29	C 40.48 H 2.09 N 10.89	C 40.71 H 2.21 N 10.75
31	C 41.19	C 41.41

	H 2.72 N 3.43	H 2.81 N 3.34
35	C 50.64 H 3.97 N 3.94	C 50.80 H 4.05 N 3.90
36	C 48.85 H 3.22 N 4.07	C 48.46 H 3.12 N 3.96
37	C 38.17 H 1.97 N 3.43	C 37.83 H 1.93 N 3.30
38 (vacuum dried 80 °C)	C 38.17 H 1.97 N 3.42	C 37.88 H 2.15 N 3.33
39	C 46.68 H 3.08 N 3.89	C 46.66 H 3.26 N 3.88
40	C 52.86 H 4.44 N 3.63	C 52.83 H 4.49 N 3.64
41	C 44.41 H 2.66 N 3.70	C 44.37 H 2.75 N 3.67
42	C 40.81 H 1.84 N 3.66	C 40.82 H 1.86 N 3.58
43	C 44.85 H 2.32 N 4.02	C 44.91 H 2.40 N 3.94
44	C 42.82 H 2.21 N 3.84	C 43.09 H 2.42 N 3.85
45	C 39.13 H 1.77 N 3.51	C 39.40 H 1.86 N 3.51
46	C 44.69 H 2.95 N 3.72	C 44.90 H 3.09 N 3.68
47	C 48.40	C 48.48

	H 2.98 N 3.76	H 2.97 N 3.75
50	C 41.62 H 2.15 N 7.47	C 41.86 H 2.16 N 7.39
52	C 48.27 H 3.78 N 7.51	C 48.65 H 3.82 N 7.45
54 (0.15CH ₂ Cl ₂)	C 45.38 H 2.84 N 3.49	C 45.39 H 2.68 N 3.41
55	C 41.62 H 2.15 N 7.47	C 41.40 H 2.17 N 7.22
57	C 46.17 H 3.36 N 3.59	C 46.12 H 3.29 N 3.58
58	C 42.82 H 2.21 N 3.84	C 42.87 H 2.19 N 3.77
59	C 38.12 H 1.72 N 6.84	C 38.34 H 1.74 N 6.75
60	C 43.20 H 2.59 N 7.20	C 43.25 H 2.53 N 7.06
61	C 39.74 H 2.38 N 3.31	C 39.72 H 2.37 N 3.29
62	C 39.13 H 1.77 N 3.51	C 39.30 H 1.82 N 3.47