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

Karen L. Lobb,*[,†] Philip A. Hipskind,[†] James A. Aikins,[†] Enrique Alvarez,[†,‡] Yiu-Yin Cheung,[§] Eileen L. Considine,[†] Alfonso De Dios,[∥] Gregory L. Durst,[†] Rafael Ferritto,[∥] Cora Sue Grossman,[†] Deborah D. Giera,[†] Beth A. Hollister,[⊥] Zhongping Huang,[§] Philip W. Iversen,[†] Kevin L. Law,[†] Tiechao Li,[†] Ho-Shen Lin,[†] Beatriz Lopez,[∥] Jose E. Lopez,[†] Luisa M. Martin Cabrejas,[∥] Denis J. McCann,[†] Victoriano Molero,[∥] John E. Reilly,[§] Michael E. Richett,[†] Chuan Shih,[†] Beverly Teicher,[†,#] James H. Wikel,[†] Wesley T. White,[†] and Mary M. Mader*[,†]

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, Albany Molecular Research Inc., Albany, New York 12212, Centro de Investigación Lilly, S. A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain, and Piedmont Research Center, 3300 Gateway Centre, Morrisville, North Carolina 27560

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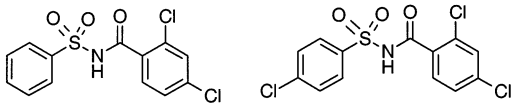
Two closely related diaryl acylsulfonamides were recently reported as potent antitumor agents against a broad spectrum of human tumor xenografts (colon, lung, breast, ovary, and prostate) in nude mice. Especially intriguing was their activity against colorectal cancer xenografts. In this paper, rapid parallel synthesis along with traditional medicinal chemistry techniques were used to quickly delineate the structure−activity relationships of the substitution patterns in both phenyl rings of the acylsufonamide anti-proliferative scaffold. Although the molecular target of the compounds remains unclear, we determined that the vascular endothelial growth factor-dependent human umbilical vein endothelial cells assay in combination with a soft agar disk diffusion assay allowed for optimization of potency in the series. The pharmacokinetic properties and in vivo activity in an HCT116 xenograft model are reported for representative compounds.

Introduction

Every year, colorectal cancer (CRC) leads to the deaths of approximately 400,000 people worldwide. In 2004, the American Cancer Society predicts that in the United States alone approximately 57,000 people will die from CRC and over 106,000 new cases of CRC will be diagnosed.[1] Thirty percent of CRC patients will have regional or distal metastases at the time of diagnosis. Distal metastasis of CRC almost uniformly predicts eventual death, and well over half of the patients diagnosed with regional metastases will die from the disease. Before the 1980s, 5-fluorouracil (5-FU) was the only treatment option for advanced CRC. At present, several new chemotherapeutic agents (irinotecan, capecitabine, and oxaliplatin) have been developed that offer an improved outcome for metastatic CRC patients. Nevertheless, even with the best combination chemotherapy regimens available, median survival for advanced CRC patients is still only about 16 months.[2]

Recently, we reported the discovery of two closely related diaryl acylsulfonamides (**1** and **2**, Scheme 1) that have the potential to produce a new treatment for CRC.[3,4] Historically, sulfonamides have been associated with antibacterial chemotherapy; however, these acylsulfonamides demonstrated no activity when tested against a variety of bacterial strains.[4] Compounds **1** and **2** were discovered in a collaborative drug discovery effort between Wayne State University (WSU) and Lilly Research Laboratories. In this collaboration, a diverse set of over 14,000 compounds computationally selected[5] from Lilly's chemical archives was screened using an in vitro soft agar disk diffusion (SADD) assay developed by Dr. Thomas Corbett of WSU.[6−9] The SADD assay was designed to identify small molecules with selective antiproliferative activity against solid tumor cell lines (such as the CRC cell lines HCT116, HCT15, and C38) vs leukemia cells (L1210) and normal human fibroblast cells.

Scheme 1



1 **2**

In vivo evaluation of **1** and **2** revealed remarkable antitumor effects against a broad range of human tumor xenografts in SCID mice.[4] Especially intriguing was their activity against human colon cancer xenografts (colon H116, colon 15, and colon CX1 H29), which are known to exhibit resistance to 5-FU and other marketed oncolytics. At this time, a molecular target for these compounds remains undetermined. Fortunately, early in our assessment of **1** and **2**, it was discovered that both compounds potently inhibit vascular endothelial growth factor (VEGF)-stimulated proliferation of human umbilical vein endothelial cells (HUVEC)[10] while producing no cell cycle specific effects at 2-fold IC_{50} in the HCT116

* To whom correspondence should be addressed. (K.L.L.) Tel: 317-276-6894. Fax: 317-433-1685. E-mail: Lobb_Karen@Lilly.com. (M.M.M.) Tel: 317-277-3400. Fax: 317-277-2035. E-mail: Mader_Mary@Lilly.com.
† Lilly Research Laboratories.
‡ Current address: CuraGen Corporation, 322 East Main Street, Branford, CT 06405.
§ Albany Molecular Research Inc.
∥ Centro de Investigación Lilly.
⊥ Piedmont Research Center.
Current address: Genzyme Corporation, One Kendall Square, Cambridge, MA 02139.

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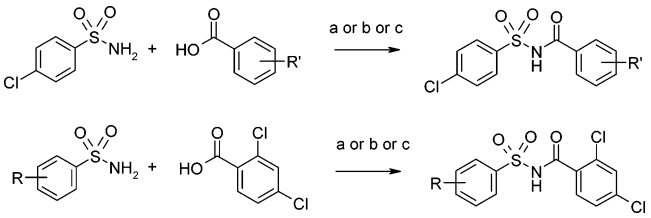
Scheme 2. Synthesis of Substituted Acylsulfonamides[a]



[a] Conditions: (a) Two equiv of PS-carbodiimide, 1.5 equiv of DMAP, in CH_2Cl_2, 72 h at room temperature followed by 3.0 equiv of MP-TsOH, 12 h at room temperature. (b) EDC, DMAP, CH_2Cl_2. (c) CDI, EtOAc, 60 °C.

cell assay.[11] With this information in hand, we sought to explore the structure−activity relationships (SAR) of these leads with the aim of optimizing potency and antitumor activity, especially activity against colorectal xenografts in vivo.

This article describes the trends for substituent effects on each of the two phenyl rings in our initial leads, named the acyl sulfonamide anti-proliferative (ASAP) compounds. The VEGF-HUVEC assay was used to evaluate the anti-proliferative potencies of the compounds and drive the SAR. In addition, the compounds were screened in the SADD assay to ensure that the series continued to exhibit selective activity toward CRC cell lines vs leukemia and normal fibroblast cell lines. The results of the National Cancer Institute's (NCI) 60 cell line COMPARE analysis are reported for compounds **1** and **2**. Both compounds demonstrated a negative correlation toward all other known oncolytics, indicating a unique mechanism of action.

Chemistry

The initial exploration of the SAR of compounds **1** and **2** was performed via rapid parallel synthesis (RPS) using commercially available starting materials (Scheme 2). We used a modification of a published coupling procedure for sulfonamides and carboxylic acids.[12−14] A resin-bound carbodiimide was employed as the coupling reagent,[15] along with 4-(dimethylamino)pyridine (DMAP) as the catalyst and methylene chloride as the solvent. A tosic acid resin was added to scavenge the DMAP and protonate the acidic[16] acylsulfonamide final products after a 72 h reaction time.[17−20] To isolate the final products, the two resins were simply filtered off, and the solvent was removed. Crude reaction mixtures were purified via ultraviolet (UV)-guided high-performance liquid chromatography (HPLC).

Derivatives requiring starting materials that were not commercially available were synthesized using traditional medicinal chemistry techniques. The required benzenesulfonamides were generally synthesized from benzenenesulfonyl chlorides, and the benzoic acids were prepared using standard literature procedures. Condensation of a sulfonamide with a benzoic acid remained the preferred mode of synthesis, using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as the coupling agent. This method was found to be cleaner and higher yielding than the reaction of sulfonic acids with benzamides or sulfonyl chlorides with benzamides. Alternatively, on a larger scale, the use of carbonyldiimidazole (CDI) as the coupling agent provided a product that could be purified by recrystallization rather than column chromatography.

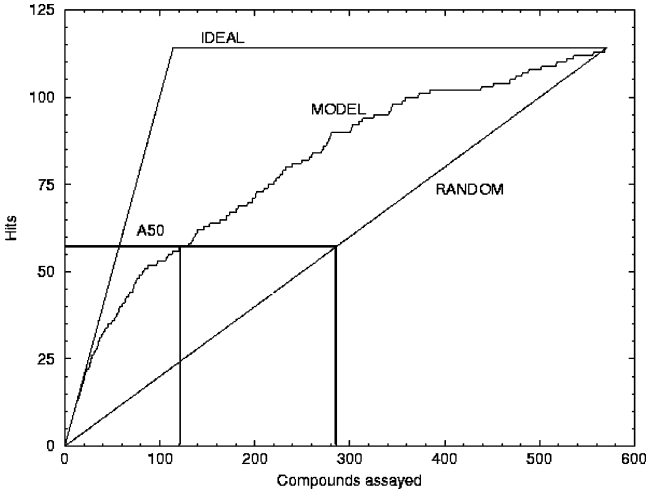


Figure 1. Accumulation of actives vs the rank order of the compounds assayed for a set of compounds never seen by the model. The first line is the upper bound (i.e., ideal or perfect ranking), the last line is the random rate, and the middle line is the model accumulation rate.

Use of an in Silico Quantitative Structure−Activity Relationship (QSAR) Model to Prioritize Targets

After the SAR effort began, a QSAR model was built to analyze the VEGF-HUVEC activity data and to aid in the prioritization of target molecules. The preliminary model was built from 135 HUVEC IC_{50} values, and as the effort progressed, the model was refined by the inclusion of new SAR data. A final set of 710 compounds was used in the last iteration of the model. In all iterations, the IC_{50} values ranged in activity from 0.02 to 20 μM.

As an example of the model's predictivity, Figure 1 shows the accumulation of actives vs rank order for a set of 570 molecules not used to build the model. This example is from the model built with 710 IC_{50} values (five way cross-validated spearman $\rho = 0.57$). The plot shows that the model predicts the top 114 compounds (<1 μM) out of 570 at a better rate than random. A measure of this predictivity can be described by a metric called an A50, where the A50 is the number of compounds that must be tested to find 50% of the designated actives. The A50 for this model is 120 vs 283 for randomly assigning activity, an enrichment greater than 2. In the absence of information regarding the identity or structure of our biological target, this model provided initial direction to the SAR effort. With a large number of possible combinations of sulfonamides and benzoic acids available to us, the model indicated that the best compounds should be found in the top 20% of a ranked list. We were, therefore, able to focus our efforts on a more specific set of substituents and substitution patterns; although to test the model's validity, we also made selected examples that were predicted to be less active.

Biological Assays

VEGF-HUVEC Assay. The final compounds were assayed in the VEGF-HUVEC assay to assess their anti-

proliferative potencies.[10] This assay measures the inhibition of the VEGF-stimulated proliferation of HUVEC. The minimum significant ratio (MSR) for comparing average VEGF-HUVEC IC_{50} values with $n \geq 3$ was calculated to be 2.6.[21] That is, the average IC_{50} values of two compounds can be considered statistically significantly different if the ratio of the two averages is greater than 2.6.

SADD Assay. Compounds were also evaluated in the SADD assay. The SADD assay was designed to identify small molecules with selective anti-proliferative activity toward solid tumor cell lines (such as the CRC cell lines HCT116, HCT15, and C38) vs leukemia cells (L1210) and normal human fibroblast cells. The SADD assay was run as described by Corbett et al.[6−9] Tumor cells, leukemia cells, and normal cells were seeded in soft agar in separate Petri dishes. A round filter paper, on which the compound had been applied, was placed on top of the agar. The activity was determined by measuring the magnitude of the zone of inhibition for cell colony formation created by the filter paper disk in the various Petri dishes. A zone of inhibition measuring 6.5 mm was equal to 200 units. A zero zone meant no inhibition. The limit of the dish (total inhibition) was 950 zone units. Ideally, an active compound would show little or no inhibition of the normal cells, would minimally inhibit the colony formation of the leukemia cells, and would maximally inhibit the colony formation of the various solid tumor cells.

Results and Discussion

Compound **2** was chosen as the benchmark compound for our SAR because it was slightly more potent in the VEGF-HUVEC assay (IC_{50} = 0.17 μM). First, we investigated the substitutent patterns on the benzoyl side of the molecule by coupling a variety of carboxylic acids to 4-chlorobenzenesulfonamide (Scheme 2). Second, the substituents on the benzenesulfonamide ring were examined by coupling an assortment of benzenesulfonamides to 2,4-dichlorobenzoic acid. To ensure that a wide variety of lipophilic, electronic, and steric parameters were explored, many of the benzoic substitutions found in the Topliss Decision Tree were included in the SAR.[22,23]

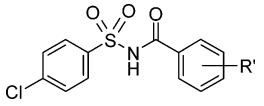
Benzoyl SAR. As we investigated the substituent requirements of the benzoyl ring (Table 1), we found that the unsubstituted derivative (**3**) and various monosubstituted analogues [**4**, 2-Cl; **5**, 3-Cl; **6**, 4-Cl; **7**, 2-CH_3; **8**, 3-Br; **9**, 4-NO_2; and **10**, 4-$N(CH_3)_2$], all exhibited substantially reduced potencies compared to the benchmark compound (**2**), which was 2,4-disubstituted. Indeed, the 2,4-disubstitution pattern found on the benzoyl ring of the lead compounds, **1** and **2**, generally achieved the highest potencies (compounds **14**−**21**). Other disubstitution patterns, such as in **11** (3,4-diCl), **12** (2,5-diCl), and **13** (3,5-diCl), produced compounds that were significantly less active than those with the 2,4-disubstitution pattern.

Halogen groups were among the favored substituents at both the 2- and the 4-positions of the disubstituted pattern. The most potent compounds of the series were the variously substituted dihalides (**2**, 2,4-diCl; **14**, 2-Cl, 4-Br; **15**, 2-Br, 4-Cl; and **16**, 2,4-diBr). In addition, the halogens fared well when in combination with other allowed substituents. For example, compounds **18** (2-CH_3, 4-Cl), **19** (2-CH_3, 4-Br), **20** (2-Cl, 4-NO_2), and **21** (2-CH_2CH_3, 4-Cl) were nearly as active as the dihalide series. The 2-fluoro-4-bromo analogue (**17**, IC_{50} = 4.6 μM) proved to be an exception to the general success of halogens, but this may be due to the fluorine atom's small size and the decreased polarizability of the fluoride relative to chloride and bromide.

Small alkyl groups were well-tolerated if placed at the 2-position of the 2,4-disubstituted pattern. The 2-methyl-4-chloro derivative (**18**) and the 2-methyl-4-bromo derivative (**19**) demonstrated anti-proliferative IC_{50} values of less than 0.65 μM. The influence of steric interactions was apparent within a series of 2-alkyl-substituted analogues where the activity declined as the total number of carbons increased (cf. **18**, 2-CH_3, 4-Cl; **21**, 2-CH_2CH_3, 4-Cl; and **22**, 2-$CH_2CH_2CH_3$, 4-Cl). Derivatives with alkyl groups at the 2- and 4-positions, such as compound **23** (IC_{50} = 2.7 μM), were not quite as potent as the 2-alkyl derivatives with a halogen group at the 4-position (**18**, **19**, and **21**).

Strongly electron-donating groups were generally detrimental at the 2-position. Compound **24** (2-OCH_3, 4-Cl) demonstrated an IC_{50} of 2.0 μM while its corresponding alkyl analogue, **21** (2-CH_2CH_3, 4-Cl), had an IC_{50} of 0.63 μM, and compound **25** (2-NH_2, 4-Cl) was over 10-fold less active than either **18** (2-CH_3, 4-Cl) or

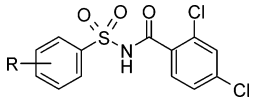
Table 1. SAR of Various Substituents on Benzoyl Ring



compd no.	R′	average VEGF-HUVEC IC_{50} (μM)[a]
2	2,4-diCl	0.17 ± 0.03
3	H	22 ± 0.9
4	2-Cl	14 ± 3
5	3-Cl	14 ± 2
6	4-Cl	6.3 ± 0.8
7	2-CH_3	15 ± 3
8	3-Br	15[b] ± 3
9	4-NO_2	11 ± 3
10	4-$N(CH_3)_2$	16 ± 5
11	3,4-diCl	5.9 ± 0.8
12	2,5-diCl	13[b] ± 7
13	3,5-diCl	18[b] ± 4
14	2-Cl, 4-Br	0.20 ± 0.06
15	2-Br, 4-Cl	0.24 ± 0.04
16	2,4-diBr	0.25 ± 0.03
17	2-F, 4-Br	4.6 ± 1.8
18	2-CH_3, 4-Cl	0.30 ± 0.04
19	2-CH_3, 4-Br	0.61 ± 0.09
20	2-Cl, 4-NO_2	0.62 ± 0.18
21	2-Et, 4-Cl	0.63 ± 0.17
22	2-Pr, 4-Cl	1.3 ± 0.5
23	2,4-diCH_3	2.7 ± 0.3
24	2-OCH_3, 4-Cl	2.0 ± 0.1
25	2-NH_2, 4-Cl	3.2 ± 0.8
26	2,4-bis(CF_3)	1.4 ± 0.4
27	2-NO_2, 4-Cl	5.9[b] ± 3
28	2-NO_2, 4-CF_3	11 ± 3
29	2-NO_2, 4-NO_2	13 ± 2
30	2-Cl, 4-CN	10 ± 4
31	2-Cl, 4-SO_2CH_3	>20
32	2-Cl, 4-OCH_3	9.9 ± 2.1
33	2-Cl, 4-OH	>15
34[c]	2-Cl, 4-NH_2	>15
35	2,4-diOCH_3	>20

[a] Shown with standard error. $n \geq 3$ unless indicated. [b] n = 2. [c] Trifluoroacetic salt.

Table 2. SAR of Various Substituents on Benzenesulfonamide Ring



compd no.	R	average VEGF-HUVEC IC_{50} (μM)[a]
1	H	0.53 ± 0.02
2	4-Cl	0.17 ± 0.03
36	4-CH_3	0.21 ± 0.04
37	4-Br	0.24 ± 0.07
38	3-Br	0.25 ± 0.08
39	4-OCH_3	0.35 ± 0.07
40	4-*tert*-butyl	0.35 ± 0.12
41	3-Cl, 4-CH_3	0.36 ± 0.19
42	3-Cl, 4-Fl	0.41 ± 0.12
43	4-F	0.41 ± 0.08
44	3-Cl	0.44 ± 0.14
45	3,4-diCl	0.46 ± 0.07
46	4-SCH_3	0.53 ± 0.23
47	4-acetyl	0.56 ± 0.12
48	3-CH_3	0.75 ± 0.03
49	3,4-diBr	0.91 ± 0.22
50	3-NO_2	0.91 ± 0.16
51	3-OCH_3	0.91 ± 0.29
52	4-$N(CH_3)_2$	0.93 ± 0.38
53	3-Ph	0.97 ± 0.18
54	4-CO_2CH_3	1.2 ± 0.1
55	4-NO_2	1.3 ± 0.4
56	4-Ph	1.4[b] ± 0.6
57	3,4-diOCH_3	3.9[b] ± 0.3
58	2-Cl	14[b] ± 2
59	2-Cl, 5-NO_2	>20
60	2-CH_3, 5-NO_2	16[b] ± 0.04
61	2-Br, 4-CH_3	>20
62	3,5-diCl	1.4 ± 0.4

[a] Shown with standard error. $n \geq 3$ unless indicated. [b] $n = 2$.

2 (2, 4-diCl). The strongly electron-withdrawing nitro group also decreased potency when placed at the 2-position. Compounds **27** (2-NO_2, 4-Cl), **28** (2-NO_2, 4-CF_3), and **29** (2-NO_2, 4-NO_2) were all less active than the corresponding analogues, **2** (2,4-diCl), **26** [2,4-bis(CF_3)], and **20** (2-Cl, 4-NO_2). The bis(trifluoromethyl) derivative (**26**) exhibited an IC_{50} of 1.4 μM. Although trifluoromethyl groups are electron-withdrawing ($\sigma_p = 0.54$, $\pi = 0.88$), they are similar in lipophilicity to the favored halogens (Cl, $\pi = 0.71$; Br, $\pi = 0.86$), which might explain this compound's relative potency.[24]

At the 4-position, the nitro group was better tolerated than other strongly electron-withdrawing groups. For example, compounds **30** (2-Cl, 4-CN) and **31** (2-Cl, SO_2CH_3) exhibited potencies 15-fold less than compound **20** (2-Cl, 4-NO_2, $IC_{50} = 0.62$ μM). Electron-donating groups, however, were universally unfavorable at the 4-position as can be seen by comparing compounds **32** (2-Cl, 4-OCH_3), **33** (2-Cl, 4-OH), and **34** (2-Cl, 4-NH_2) with compound **2** (2,4-diCl) and by comparing compound **35** (2,4-diOCH_3) with compound **24** (2-OCH_3, 4-Cl).

Benzenesulfonamide SAR. The benzenesulfonamide side of the molecule was less stringent in the substituent requirements needed to produce active compounds (Table 2). Compound **1**, one of our initial leads, bears no substituents and was quite potent with an IC_{50} of 0.53 μM. Our SAR demonstrates that monosubstitution at the 3- or 4-position along with the 3,4-disubstitution pattern usually produced the most potent analogues (**36**−**57**). A variety of substituents at these positions worked well.

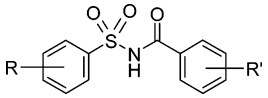
Halogens at the 3- and/or 4-positions (**2**, **37**, **38**, **42**−**45**, and **49**) led to numerous examples of potent compounds. Alkyl groups, as in the 4-methyl derivative (**36**), the 3-methyl derivative (**48**), and the 4-*tert*-butyl derivative (**40**), were also acceptable. A library of 3- and 4-substituted biaryl analogues was prepared, with **53** and **56** shown as representative examples. These compounds were active, consistent with the sulfonamide half of the molecule apparently having less demanding steric requirements. Electron-donating groups at the 3- or 4-position produced excellent to good anti-proliferative potencies. For instance, compounds **39** (4-OCH_3), **46** (4-SCH_3), **51** (3-OCH_3), and **52** [4-$N(CH_3)_2$] exhibited IC_{50} values between 0.35 and 0.93 μM. Analogues with electron-withdrawing groups at these positions (**47**, 4-acetyl; **50**, 3-NO_2; **54**, 4-CO_2CH_3; and **55**, 4-NO_2) were slightly less potent and demonstrated IC_{50} values between 0.56 and 1.3 μM.

Generally, the 4-substituted benzenesulfonamide derivatives were 2−3-fold more potent than those substituted at the 3-position with the same atom or functional group. For example, the IC_{50} of the 4-chloro analogue (**2**) was 0.17 μM, whereas that for the 3-chloro compound (**44**) was 0.44 μM. This phenomenon was observed for the 4- vs 3-methyl analogues (**36**, 4-CH_3, $IC_{50} = 0.21$ μM vs **48**, 3-CH_3, $IC_{50} = 0.75$ μM) as well as the methoxy pair (**39**, 4-OCH_3, $IC_{50} = 0.35$ μM vs **51**, 3-OCH_3, $IC_{50} = 0.91$ μM). However, the bromide pair, **37** and **38**, did not follow this trend, having essentially identical IC_{50} values of 0.24 and 0.25 μM, respectively.

Synergistic increases in activity were not found for 3,4-disubstitution of the benzenesulfonamide. The disubstituted analogues were either comparable in activity to the 3-substituted analogues (cf. **44**, 3-Cl, $IC_{50} = 0.44$ μM vs **45**, 3,4-diCl, $IC_{50} = 0.46$ μM and **42**, 3-Cl, 4-F, $IC_{50} = 0.41$ μM) or less active (cf. **38**, 3-Br, $IC_{50} = 0.25$ μM vs **49**, 3,4-diBr, $IC_{50} = 0.91$ μM and **51**, 3-OCH_3, $IC_{50} = 0.91$ μM vs **57**, 3,4-diOCH_3, $IC_{50} = 3.9$ μM). The reasons for this phenomenon are not obvious. The decreased activity of the disubstituted analogues could possibly be attributed to the greater hydrophobicity of these compounds relative to the monosubstituted analogues and a subsequent decrease in the ability to penetrate the HUVEC cell membrane. Examination of clogP[25,26] for representative compounds (Table 3) indicates that this parameter also plays a role in the activity of the compounds. Hydrophilic compounds with a clogP less than 2.5 tended to be less potent (cf. **9** and **10**), and a clogP ranging from 3.0 to 4.0 is observed for the more potent compounds (cf. **2**, **14**, **36**, **37**, and **39**). However, a clogP between 3.0 and 4.0 does not ensure activity in the HUVEC assay (cf. **58**, **8**, **59**, and **13**).

Substitution at the 2-position of the benzenesulfonamide ring was not tolerated and substantially diminished the anti-proliferative activity. For example, the 2-chloro derivative (**58**, Table 2) was over 25-fold less potent than compound **1**, which has no substituents. In addition, the 2-chloro-5-nitro derivative (**59**) and the 2-methyl-5-nitro derivative (**60**) were over 10-fold less active than the 3-nitro derivative (**50**), and the 2-bromo-4-methyl derivative (**61**) was almost 100-fold less active than the 4-methyl derivative (**36**). Last, the activity of the 3,5-dichloro derivative (**62**, $IC_{50} = 1.4$ μM) was unremarkable as compared to the 3-chloro derivative

Table 3. Correlation of VEGF-HUVEC and SADD Data



					SADD assay			
					zone of inhibitions in various cell lines			
compd no.	R	R′	clogP	VEGF-HUVEC average IC_{50} (μM)	solid tumor HCT116[a]	leukemia L1210[a]	normal fibroblast[a,b]	dose (μg/disk)
2	4-Cl	2,4-diCl	3.8	0.17	660	200	0−350	200
14	4-Cl	2-Cl, 4-Br	3.9	0.20	460[c,d]	200	0−350	210
36	4-CH_3	2,4-diCl	3.4	0.21	840	0−320	0−510	190
37	4-Br	2,4-diCl	3.9	0.24	620	100−170	0−430	210
39	4-OCH_3	2,4-diCl	3.1	0.35	650	0−170	0−420	190
41	3-Cl, 4-CH_3	2,4-diCl	4.1	0.36	570	200−350	0−380	190
43	4-F	2,4-diCl	3.3	0.41	880	0−280	0−520	200
44	3-Cl	2,4-diCl	3.8	0.44	515	100−150	0−200	190
45	3,4-diCl	2,4-diCl	4.4	0.46	560	40−180	0−360	200
19	4-Cl	2-CH_3, 4-Br	3.5	0.61	700−750[c]	0[c]	0−300[c]	190
48	3-CH_3	2,4-diCl	3.4	0.75	220−250	100	0−200	210
49	3,4-diBr	2,4-diCl	4.6	0.91	425	0−210	0−270	190
52	4-$N(CH_3)_2$	2,4-diCl	3.2	0.93	900[c]	0−350[c]	0−400[c]	210
53	3-Ph	2,4-diCl	4.8	0.97	600	0	0−370	190
54	4-CO_2CH_3	2,4-diCl	3.0	1.2	650[c]	0−200	0−280	200
55	4-NO_2	2,4-diCl	3.0	1.3	540	0−110	0−310	190
26	4-Cl	2,4-bis(CF_3)	4.3	1.4	520[c]	0[c]	0−360[c]	200
62	3,5-diCl	2,4-diCl	4.4	1.4	380[c]	0−170[c]	0−200[c]	210
56	4-Ph	2,4-diCl	4.8	1.4	500	220−250	0−290	210
25	4-Cl	2-NH_2, 4-Cl	2.7	3.2	610	0−250	270	210
57	3,4-diOCH_3	2,4-diCl	3.1	3.9	500[c]	0	0−200	210
11	4-Cl	3,4-diCl	3.8	5.9	400[c]	200[c]	0−150[c]	200
6	4-Cl	4-Cl	3.1	6.3	330[c]	180[c]	0−70[c]	190
9	4-Cl	4-NO_2	2.3	11	270[c]	200[c]	0[c]	190
58	2-Cl	2,4-diCl	3.8	14	0[c]	0[c]	0[c]	210
8	4-Cl	3-Br	3.2	15	320[c]	210[c]	0−30[c]	190
10	4-Cl	4-$N(CH_3)_2$	2.5	16	360[c]	180[c]	0[c]	190
59	2-Cl, 5-NO_2	2,4-diCl	3.6	>20	0	0	0	200
13	4-Cl	3,5-diCl	3.8	18	330[c]	150[c]	0−80[c]	210

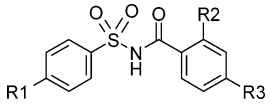
[a] Zone of inhibition units (200 units = 6.5 mm). A zero zone means no inhibition. The limit of the dish (total inhibition) was 950 zone units. In cases where a zone range was recorded, the colonies were reduced in size at the beginning of the zone, increasing in size to the top of the zone range, and from there to the edge of the plate, the colonies were uniformly large. $n > 2$ unless otherwise indicated. See refs 4, 7, and 8 for examples of other agents tested in the SADD assay. [b] The fibroblast cells were viable, but the replication of colonies was inhibited as indicated by their zone ranges. Many in vivo active agents display microcolony zones of this type. [c] $n = 1$. [d] Human tumor H15 (colon).

(**44**, $IC_{50} = 0.44$ μM) indicating that the 3,5-disubstitution pattern does not offer any improvements in potency for the benzenesulfonamide ring.

SADD and VEGF-HUVEC Data. The results from the semiquantitative SADD assay demonstrated that, in general, the ASAP derivatives continued to exhibit selective inhibition toward CRC cell lines, such as HCT116, vs leukemia (L1210) and normal fibroblast cells just as the lead compounds, **1** and **2**, had shown (Table 3). In addition, upon analysis of the VEGF-HUVEC data and the SADD data, the minimum VEGF-HUVEC potency necessary for significant activity in the SADD assay was delineated. Derivatives with a VEGF-HUVEC IC_{50} value of less than 1.0 μM were considerably more likely to exhibit substantial inhibitions of the HCT116 cell line's colony formation in the SADD assay. For example, out of 187 compounds tested at 200 ± 10 μg/disk, 79% of the compounds with a VEGF-HUVEC IC_{50} of less than 1 μM produced a zone of inhibition of 500 zone units (16.2 mm) or better in the HCT116 cell line. Of those compounds with a VEGF-HUVEC IC_{50} of greater than 1 μM, only 12% generated a zone of inhibition of greater than 500 zone units in the HCT116 cell line. This agreement between the SADD data and the VEGF-HUVEC data indicates that the VEGF-HUVEC assay is an appropriate predictor of the ASAP compounds' oncolytic activity in vivo.

Pharmacokinetic (PK) Properties. Compounds **1** and **14** were pursued in further in vivo studies based on their potency in the HUVEC and SADD assays. Because of the acidity of the acylsulfonamide moiety (**1**, $pK_a = 2.8$; **14**, $pK_a = 2.7$), the compounds were formulated in 1−1.5% sodium bicarbonate in phosphate-buffered saline solution, and exposure was observed by both oral and iv administration (Table 4). Exposure by oral administration was observed in rats for both **1** and **14**, and no significant accumulation of **1** was observed after 7 days of dosing relative to a single dose. The doses for the two compounds were those determined to be optimal with a minimal toxicity for each. Analysis of rat plasma showed no metabolites after 7 days of dosing compound **1**, indicating **1** to be metabolically stable. Compound **1** was excreted unchanged in rat urine and feces, with a total 29.1% of a single 100 mg/kg dose recovered in urine after 48 h and a total of 8.4% found in feces. Oral dosing in mice over 10 days resulted in a 2−4-fold higher exposure and a longer half-life for both compounds. The administration of **1** and **14** to mice by iv resulted in shorter half-lives and lower exposures relative to oral dosing.

Table 4. PK Properties of ASAP Compounds in Rodents



compd no.	R1	R2	R3	dose (mg/kg)	days of dosing	species (route)	AUC (0−24 h) (μg h/mL)	$T_{1/2}$ (h)	C_{max} (μg/mL)
1	H	Cl	Cl	100	1	rat[a] (po)	2023[c]	3	239
				100	7	rat[a] (po)	2917	4	221
				80	10	mouse[b] (po)	11300	27	568
				80	10	mouse[b] (iv)	10100	13	628
14	Cl	Cl	Br	10	7	rat[a] (po)	4200	59	200
				80	10	mouse[b] (po)	10700	132	547
				20	10	mouse[b] (iv)	4670	28	262

[a] For female F344 rats; the compounds were formulated in 1−1.5% sodium bicarbonate in phosphate-buffered saline; $n = 3$; once daily dosing as indicated; blood drawn at $t = 0.5$, 1, 2, 4, 6, 8, and 24 h after the final dose. [b] For BALBc mice; the compounds were formulated in 1−1.5% sodium bicarbonate in phosphate-buffered saline; $n = 3$ BALBc mice/time point; blood was drawn at $t = 0.5$, 1, 2, 4, 6, 8, and 24 h after the final dose. [c] AUC (0−infinity).

Table 5. TGD of Selected Compounds in HCT116 Xenograft Model in Nude Mice

compd	dose (iv) (mg/kg)	TGD (days ± SE)
CPT11	100	15 ± 8
1	64	14 ± 7
	85	15 ± 7
	128	22 ± 6
14	32	12 ± 6
	63	23 ± 6

HCT116 Tumor Xenograft Model. Compounds **1** and **14** were evaluated in a nude mouse xenograft model bearing human HCT116 colorectal carcinoma (Table 5 and Figure 2). After tumors had reached an average volume of 100 mm^3, the compound was administered intravenously as its sodium salt in a saline solution (pH 7.4) from days 1−5 and days 8−12. A marketed oncolytic approved for the treatment of CRC, CPT 11 (irinotecan), was employed as a positive control, at 100 mg/kg, and was dosed according to its reported optimal route and schedule (ip, days 1, 8, and 15).[27] Compound **1** was observed to show activity at three doses (64, 85, and 128 mg/kg), and the plot of the data appears to show a dose response (Figure 2), which is not reflected in Table 5 data due to the interanimal variability. Compound **14** showed a significantly different tumor growth delay (TGD) at two doses (32 and 63 mg/kg). In addition, **14** exhibited TGD at the 63 mg/kg dose, which was greater than what CPT-11 produced when dosed at its MTD of 100 mg/kg. Both **1** and **14** demonstrated tumor regression in the early phase postdosing at all doses. No body weight loss was observed in any of the treatment groups.

NCI COMPARE Analysis. A COMPARE analysis[28,29] at the NCI of compound **1** showed that no compound in the database had a Pearson correlation coefficient (PCC) of >0.7 relative to **1** at a high concentration of 100 μM against a panel of 60 cell lines in vitro (Table 6). The analysis compares a complete set of cell sensitivities to those of standard agents or other agents present in the NCI database. A correlation of >0.7 is considered significant for this type of analysis. With one exception, chloroquinoxaline sulfonamide (PCC = 0.589), no compound in the database was found to have a PCC > 0.4. These weakly correlated compounds are cytotoxic through diverse mechanisms of action, including inhibition of thymidylate synthase (5-FU), DNA synthase (tetraplatin), topoisomerase (pyrazoloacridine, chloroquinoxaline sulfonamide), and pyrimidine synthetase (PALA). However, in this analysis, the ASAP series tended to show their greatest activity in solid tumors rather than leukemia cell lines (Table 7), consistent with Corbett's early observations in the SADD assay with **1** and **2**. Additionally, as a group, colorectal cell lines were most sensitive to the ASAPs. On the basis of these data, it is difficult to speculate on the molecular target for the ASAP compounds. Investigations are currently underway to identify a molecular target, and these studies will be reported in due course.

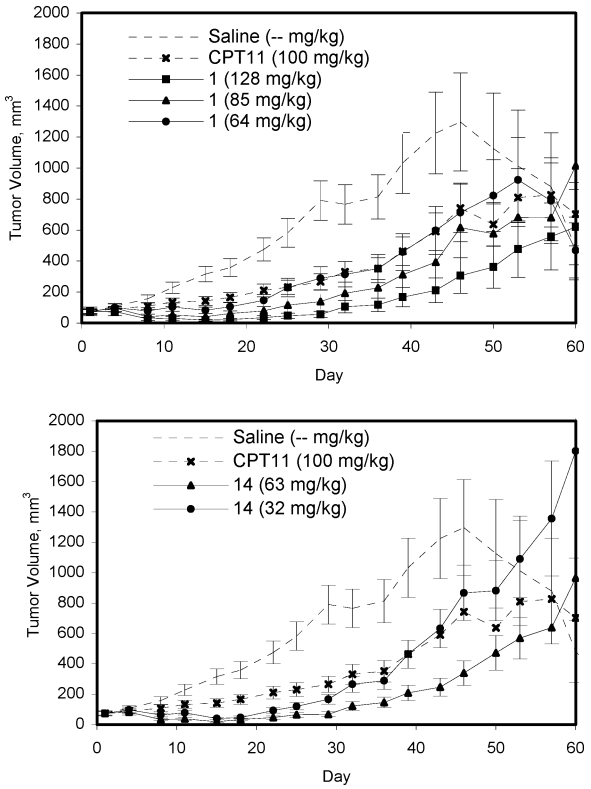


Figure 2. Effect of **1** and **14** on the growth of human colorectal cell line HCT116 in nude mice. Groups of five female mice were injected with HCT116 cells. Animals bearing tumors (100 mm^3) were treated iv on days 1−5 and 8−12 at the doses indicated. The relative tumor growth was determined every 4 days for a period of 63 days. Data are means and standard errors determined from repeated measures of the analysis of variance model that accounted for within animal correlation and removal from the study of animals with large tumors.

Table 6. Mean Panel GI_{50} Values and COMPARE Correlation Coefficients (PCC) Using Compound **1** (NCS 716877) as Seed, Tested in the U.S. NCI 60 Cell Lines in Vitro Screen[a]

rank	NSC	high concn (M)	PCC	compd
1	339004	0.0001	0.589	chloroquinoxaline sulfonamide
2	19893	0.0001	0.397	5-FU
3	363812	0.0001	0.393	tetraplatin
4	366140	0.0001	0.392	pyrazoloacridine
5	740	0.0001	0.378	methotrexate
6	141537	0.0001	0.378	anguidine
7	755	0.0001	0.363	6-mercaptopurine
8	375575	0.0001	0.359	cyclopentyl cytosine
9	224131	0.0001	0.358	PALA
10	339638	0.0001	0.350	phosphotrienin
11	368390	0.0001	0.350	DUP785 (brequinar)

[a] For definitions and methods of calculation of the correlation coefficient from the COMPARE analysis, see ref 29.

Conclusions

ASAPs, such as compounds **1** and **2**, represent a novel series of antitumor agents. RPS along with traditional medicinal chemistry techniques were used to quickly delineate the benzene substituent SAR trends of the two phenyl rings in the ASAP scaffold. We employed the VEGF-HUVEC assay and the SADD assay to evaluate the anti-proliferative potencies of the compounds and to drive the SAR. The benzoyl side of the ASAP molecules required 2,4-disubstitution for optimal potency. Only limited variations to the benzoyl substituents were allowed with halides and small alkyl groups being preferred. On the benzenesulfonamide ring, a variety of substitutions at the 3- and/or 4-positions were well-tolerated, but substitution at the 2-position diminished activity. Data from the SADD assay showed that the ASAP analogues exhibited selective activity toward CRC cell lines vs leukemia and normal fibroblast cell lines. Furthermore, the SADD data agreed well with the VEGF-HUVEC data indicating that the HUVEC assay was an appropriate predictor of the ASAP compounds' oncolytic activity. Key compounds from the series demonstrated exposure in PK studies performed in rats and mice. In a nude mouse HCT116 xenograft model using iv adminstration, compounds **1** and **14** exhibited tumor growth inhibition and TGD. The molecular target of the ASAP compounds remains to be elucidated, as an NCI COMPARE analysis showed no matches. Efforts to determine the mechanism of action are ongoing. Additional details regarding the SAR of these compounds will be reported in the future.

Experimental Section

General Methods. All solvents and reagents were used as obtained from commercial sources unless otherwise indicated. The starting materials were obtained from commercial sources or synthesized using standard literature procedures. Experimental details for those starting materials that required synthesis are described in the Supporting Information. The abbreviations ACN, DMSO, and THF refer to acetonitrile, dimethyl sulfoxide, and tetrahydrofuran, respectively.

The ^{1}H NMRs were taken on a Bruker 250 MHz NMR or a Bruker 300 MHz NMR or a Mercury 400 MHz NMR. Chemical shifts were reported in ppm relative to tetramethylsilane or solvent. The exact masses were determined on a Micromass Q-TOF II time-of-flight mass spectrometer using negative mode electrospray ionization unless otherwise indicated. Midwest Microlab performed the elemental analyses after the samples had been blocked at 120 °C unless otherwise noted. The 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).

Except when noted otherwise, LC/MS analytical spectra were performed on a Waters Alliance 2690 HPLC system (auto sampler, quaternary pump, DAD-UV, heated column compartment) with a Micromass ZMD single quadrupole mass spectrometer. The column was an Xterra MS, C_{18}, 2.1 mm × 30 mm, 3.5 μM column. The solvent conditions were 5−100% ACN with 0.2% ammonium hydroxide in 3 min and held at 100% ACN with 0.2% NH_4OH for 0.5 min. The flow rate was 1 mL/min. Approximately 5 μL of a ∼0.5 mg/mL sample was injected. Negative mode electrospray ionization was used. The reported retention times were based on a UV chromatogram at 214 nM.

The pK_a values were determined using the following procedure. Three pK/UV titrations were performed in the same vial using the Sirius GLpK_a/DPAS instrument. The first titration was done by weighing ∼1 mg of material and adding 10 mL of 60% dioxane/40% ionic strength adjusted (ISA) water (0.15 M KCl) and 3 mL of ISA water. The second titration was done by adding 2 mL of ISA water to the first titration upon its completion. Similarly, the third titration added 3 mL of ISA water to the previous two titrations upon completion. For each titration, the initial pH was taken and then the solution was adjusted to pH 12 using 0.5 M KOH. The titrations were run from pH 12 to pH 1.8, titrating with 0.5 M HCl. The results were then interpreted via pK_a/UV Version 1.001 software (Sirius Analytical Instruments Ltd., East Sussex, RH18 5DW, England) and extrapolation to pure water using the Yasuda−Shedlovsky plot.[30,31]

RPS Coupling Procedure A. The reactions were performed in 8 mL glass vials fitted with caps lined with poly(tetrafluoroethylene). Each reaction vial was charged with the appropriate carboxylic acid (0.39 mmol, 1.5 equiv) and CH_2Cl_2 (2.0 mL). DMAP (48 mg, 0.39 mmol, 1.5 equiv) and 4-chlorobenzenesulfonamide (50 mg, 0.26 mmol, 1 equiv) were delivered to each reaction vial in 4.0 mL of a CH_2Cl_2 stock solution. *N*-Cyclohexylcarbodiimide, *N*′-methyl polystyrene HL (0.261 g, 0.52 mmol, 2.0 equiv, loading = 2.0 mmol/g) was added to each vial. The vials were rotated for 72 h. A sulfonated polystyrene resin, the resin-bound equivalent of *p*-toluenesulfonic acid, was then added to scavenge the DMAP. After the reaction vials were rotated for another 12 h, both resins were filtered off using a 0.8 cm × 4.0 cm polypropylene fritted funnel. A stream of nitrogen evaporated the solvent from each reaction vial. Crude reaction mixtures were purified using UV-guided HPLC purification.

Table 7. Cytotoxicity[a] of ASAP Analogues toward Human Cancer Cells

		colon			lung	breast	renal	leukemia	
compd no.	NSC	HCT116	HT29	SW620	NCI-H522	MCF7	RXF 393	HL-60 (TB)	MGM[b]
1	716877	5.4	52.0	8.6	18.7	18.9	4.3	32.9	33.1
2	716876	5.3	54.8	39.6	8.6	1.5	11.0	34.7	26.3
39	724610	3.5	41.5	9.5	39.6	23.9	6.4	38.9	28.8
18	724611	9.7	100.0	37.9	100.0	17.7	8.6	49.5	41.7

[a] Cytotoxicity: GI_{50} values are the concentrations corresponding to 50% growth inhibition. [b] MGM is the mean graph midpoint for growth inhibition of all human cancer cell lines successfully tested.

Preparative UV-guided HPLC purifications were performed on a Gilson HPLC system. The reaction mixtures were dissolved in DMSO to a concentration of ~0.25 g/mL. Two injections were made for each sample. The column was a YMC-ODSA, C_{18}, 5 μM, 120 Å pore size. The solvent conditions were a gradient over 12 min starting at 5% ACN/H_2O, 0.1% HCl going to 95% ACN/H_2O, 0.1% HCl. The flow rate was 20 mL/min. Fractionation was achieved based on UV absorbance at 214 nM.

RPS Coupling Procedure B. Coupling procedure B was performed in a manner similar to procedure A except the order of the starting material addition was reversed. The reaction vials were first charged with the appropriate sulfonamide (0.26 mmol, 1.0 equiv) and CH_2Cl_2 (2.0 mL). Then, 2,4-dichlorobenzoic acid (75 mg, 0.39 mmol, 1.5 equiv) and DMAP (48 mg, 0.39 mmol, 1.5 equiv) were delivered in 4.0 mL of a stock solution made in CH_2Cl_2.

General Solution Coupling Procedure C. To a stirring solution of the benzoic acid (1.2 equiv) in dry CH_2Cl_2 (10 mL/mmol), the phenylsulfonamide (1.0 equiv) was added in one portion followed by EDC (1.2−1.5 equiv) and then DMAP (1.2 equiv). The mixture was vigorously stirred under nitrogen for 16 h and concentrated under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with 1 N HCl (four times, 20 mL/mmol), and then, the combined aqueous phases were extracted with EtOAc (2 × 20 mL/mmol). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to silica gel chromatography or crystallization if necessary.

Large Scale Coupling Procedure D. To a reaction mixture of arylsulfonamide (81.4 mmol), CDI (15.8 g, 97.7 mmol), and EtOAc (300 mL) at room temperature was added a slurry of substituted benzoic acid (97.7 mmol) in EtOAc (100 mL) over a period of 15 min. Gas evolution was observed but could be controlled by the rate of slurry addition. The reaction mixture went into solution by the end of the slurry addition. Progress of the reaction was monitored by TLC with 1:1 EtOAc/heptane eluent or by HPLC. The reaction was stirred at room temperature for 30 min and then heated at 60 °C for 90 min or until no gas evolution was observed. It was cooled to 40 °C, and 1,8-diazabicyclo[5.4.0]undec-7-ene (14.6 mL) was added all at once. The mixture was stirred until it reached room temperature and then was quenched with deionized water (400 mL). The top organic layer was separated, washed with 1 N HCl (300 mL), dried with anhydrous $MgSO_4$, and filtered. The cake was washed with EtOAc (20 mL). The filtrate was concentrated to ca. 50 g of a syrupy solution, and then, heptane (250 mL) was added with vigorous stirring. The mixture was heated, a white slurry was formed, refluxed, and then allowed to equilibrate to room temperature. The white precipitate was filtered, and the cake was washed with heptane (20 mL). To recrystallize the crude, a mixture of ca. 20 g of the product and 1:2 EtOAc/heptane (150 mL) was heated at reflux for 30 min and then cooled to room temperature. The off-white precipitate was filtered, and the cake was washed with heptane (50 mL). The precipitate was dried under vacuum at 50 °C for 18 h.

***N*-(2,4-Dichlorobenzoyl)benzenesulfonamide (1).** Compound **1** was synthesized by refluxing 2,4-dichlorobenzoyl chloride (0.01 mol, 1.0 equiv), benzenesulfonamide (0.012 mol, 1.2 equiv), and K_2CO_3 (0.015 mol, 1.5 equiv) in dioxane for 4 h. The reaction mixture was diluted with H_2O, acidified with aqueous HCl solution, and extracted with EtOAc. The EtOAc extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude material was recrystallized in toluene and then chromatographed using a silica gel column and CH_2Cl_2 as solvent. Yield = 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.88 (br s, 1H), 7.99 (d, J = 8 Hz, 2H), 7.78−7.63 (m, 4H), 7.50 (m, 2H). The LC/MS was performed on a Waters Micromass ZQ with a Leap Technologies HTS PAL autosampler and an Agilent 1100 Series Diode Array Detector with the same column and method as described in the General Methods section. LC/MS t_r = 1.38, m/z 328, 330, 332. HRMS obsd mass $(M - H)^-$, 327.9614; calcd mass ($C_{13}H_9Cl_2NO_3S$-1H)$^-$, 327.9602. Anal. ($C_{13}H_9Cl_2NO_3S$) C, H, N.

4-Chloro-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (2). Compound **2** was synthesized from 2,4-dichlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 30%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.97 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H), 7.71 (m, 1H), 7.50 (m, 2H). LC/MS studies were performed as described for **1**. LC/MS t_r = 1.76 min, m/z 364, 362, 366 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 361.9212; calcd mass ($C_{13}H_8Cl_3NO_3S$-1H)$^-$, 361.9212. Anal. ($C_{13}H_8Cl_3NO_3S$) C, H, N (blocked 60 °C).

***N*-Benzoyl-4-chlorobenzenesulfonamide (3).** Compound **3** was synthesized from benzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 33%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.99 (d, J = 8 Hz, 2H), 7.86 (d, J = 7 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.62 (t, J = 7 Hz, 1H), 7.46 (t, J = 7 Hz, 2H). LC/MS t_r = 1.78 min (>99%), m/z 294, 296 $(M-H)^-$. HRMS obsd mass $(M-H)^-$, 294.0009; calcd mass ($C_{13}H_{10}ClNO_3S$-1H)$^-$, 293.9992. Anal. ($C_{13}H_{10}ClNO_3S$) C, H, N.

4-Chloro-*N*-(2-chlorobenzoyl)benzenesulfonamide (4). Compound **4** was synthesized from 2-chlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 37%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.97 (d, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.52−7.43 (m, 3H), 7.42−7.34 (m, 1H). LC/MS t_r = 1.85 min, m/z 328, 330 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 327.9623; calcd mass ($C_{13}H_9Cl_2NO_3S$-1H)$^-$, 327.9602. Anal. ($C_{13}H_9Cl_2NO_3S$) C, H, N.

4-Chloro-*N*-(3-chlorobenzoyl)benzenesulfonamide (5). Compound **5** was synthesized from 3-chlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 51%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.97 (d, J = 8 Hz, 2H), 7.92 (s, 1H), 7.80 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 2H), 7.66 (s, 1H), 7.50 (t, J = 7 Hz, 1H). LC/MS t_r = 2.02 min, m/z 328, 330 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 327.9613; calcd ($C_{13}H_9Cl_2NO_3S$-1H)$^-$, 327.9602. Anal. ($C_{13}H_9Cl_2NO_3S$) C, H, N.

4-Chloro-*N*-(4-chlorobenzoyl)benzenesulfonamide (6). Compound **6** was synthesized from 4-chlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 49%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.99 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.56 (d, J = 8, 2H). LC/MS t_r = 2.03 min, m/z 328, 330 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 327.9629; calcd mass ($C_{13}H_9Cl_2NO_3S$-1H)$^-$, 327.9602. Anal. ($C_{13}H_9Cl_2NO_3S$) C, H, N.

4-Chloro-*N*-(2-methylbenzoyl)benzenesulfonamide (7). Compound **7** was synthesized from 2-methylbenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 47%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.0 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H), 7.36−7.46 (m, 2H), 7.26 (t, J = 6 Hz, 2H), 2.19 (s, 3H). LC/MS t_r = 1.87min (99%), m/z 308, 310 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 308.0159; calcd mass ($C_{14}H_{12}ClNO_3S$-1H)$^-$, 308.0148. Anal. ($C_{14}H_{12}ClNO_3S$) C, H, N.

***N*-(3-Bromobenzoyl)-4-chlorobenzenesulfonamide (8).** Compound **8** was synthesized from 3-bromobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 46%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.05 (m, 1H), 7.97 (d, J = 8 Hz, 2H), 7.82 (t, J = 9 Hz, 2H), 7.69 (d, J = 8 Hz, 2H), 7.44 (t, J = 8 Hz, 1H). The second HPLC was run on a Shimadzu 10ADvc HPLC system (autosampler, heated column compartment). The column was a Symmetry C_{18}, 4.6 mm × 50 mm, 5 μM column heated at 50 °C. The solvent conditions were 5−90% ACN with 0.05% TFA in 4 min and held at 90% ACN with 0.05% TFA for 1.0 min. The flow rate was 2 mL/min. Approximately 10 μL of a ~0.5 mg/mL sample was injected. The reported retention times and purities were based on a Polymer Lab PL-ELS1000 light scattering detector. LC/MS t_r = 2.09 min (>99%), m/z 374, 372, 376 $(M - H)^-$. Second HPLC t_r = 3.08 min (98%). HRMS obsd mass $(M - H)^-$, 371.9090; calcd mass ($C_{13}H_9BrClNO_3S$-1H)$^-$, 371.9097.

4-Chloro-*N*-(4-nitrobenzoyl)benzenesulfonamide (9). Compound **9** was synthesized from 4-nitrobenzoic acid and

4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 33%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.28 (d, J = 8 Hz, 2H), 8.08 (d, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 2H), 7.69 (d, J = 8 Hz, 2H). Second HPLC performed as described for **8**. LC/MS t_r = 1.86 min (>99%), m/z 339, 341, 340 (M − H)$^-$. Second HPLC t_r = 2.78 min (97%). HRMS obsd mass (M − H)$^-$, 338.9853; calcd mass ($C_{13}H_9ClN_2O_5S$-1H)$^-$, 338.9843.

4-Chloro-*N*-(4-(dimethylamino)benzoyl)benzenesulfonamide (10). Compound **10** was synthesized from 4-(dimethylamino)benzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 22%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.10 (br s, 1H), 7.97 (d, J = 8 Hz, 2H), 7.77 (d, J = 5 Hz, 2H), 7.71 (d, J = 5 Hz, 2H), 6.67 (d, J = 8 Hz, 2H), 3.34 (s, 6H). LC/MS t_r = 1.76 min (>99%) m/z 337, 339, 340 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 337.0419; calcd mass ($C_{15}H_{15}ClN_2O_3S$-1H)$^-$, 337.0414. Anal. ($C_{15}H_{15}ClN_2O_3S$) C, H, N.

4-Chloro-*N*-(3,4-dichlorobenzoyl)benzenesulfonamide (11). Compound **11** was synthesized from 3,4-dichlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 28%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.97 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 2H). Second HPLC performed as described for **8**. LC/MS t_r = 2.19 min (99%), m/z 364, 362, 366 (M − H)$^-$. Second HPLC t_r = 3.24 min (95%). HRMS obsd mass (M − H)$^-$, 361.9218; calcd mass ($C_{13}H_8Cl_3NO_3S$-1H)$^-$, 361.9212.

4-Chloro-*N*-(2,5-dichlorobenzoyl)benzenesulfonamide (12). Compound **12** was synthesized from 2,5-dichlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 28%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.99 (d, J = 9 Hz, 2H), 7.74 (d, J = 9, 2H), 7.65 (d, J = 2, 1H), 7.51 (m, 2H). LC/MS t_r = 2.18 min, m/z 362, 364, 366 (M − H)$^-$. HRMS (M − H)$^-$ obsd mass, 361.9217; calcd mass ($C_{13}H_8Cl_3NO_3S$-1H)$^-$, 361.9212. Anal. ($C_{13}H_8Cl_3NO_3S$) C, H, N.

4-Chloro-*N*-(3,5-dichlorobenzoyl)benzenesulfonamide (13). Compound **13** was synthesized from 3,5-dichlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 40%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.99 (d, J = 8 Hz, 2H), 7.89 (s, 3H), 7.70 (d, J = 8, 2H). LC/MS t_r = 2.22 min, m/z 364, 362, 366 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 361.9208; calcd mass ($C_{13}H_8Cl_3NO_3S$-1H)$^-$, 361.9212. Anal. ($C_{13}H_8Cl_3NO_3S$) C, H, N.

***N*-(4-Bromo-2-chlorobenzoyl)-4-chlorobenzenesulfonamide (14).** Compound **14** was synthesized from 4-bromo-2-chlorobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 33%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.98 (d, J = 8 Hz, 2H), 7.84 (s, 1H), 7.76 (d, J = 8 Hz, 2H), 7.63 (d, J = 7 Hz, 1H), 7.45 (d, J = 7 Hz, 1H). LC/MS t_r = 2.24 min, m/z 406, 407, 410 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 405.8708; calcd mass ($C_{13}H_8BrCl_2NO_3S$-1H)$^-$, 405.8707. Anal. ($C_{13}H_8BrCl_2NO_3S$) C, H, N.

4-Chloro-*N*-(2-bromo-4-chlorobenzoyl)benzenesulfonamide (15). Compound **15** was synthesized from 2-bromo-4-chlorobenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 55%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 (dd, J = 8.4 Hz, J = 2.0, 1H), 7.56 (m, 3H), 7.61 (s, 1H), 8.09 (d, J = 8.8 Hz, 2H), 8.67 (s, 1H). Anal. ($C_{13}H_8BrCl_2NO_3S$) C, H, N (vacuum-dried).

4-Chloro-*N*-(2,4-dibromobenzoyl)benzenesulfonamide (16). Compound **16** was synthesized from 2,4-dibromobenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 76%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 10.0 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.94−7.99 (m, 3H). Anal. ($C_{13}H_8Br_2ClNO_3S$) C, H, N.

4-Chloro-*N*-(4-bromo-2-fluorobenzoyl)benzenesulfonamide (17). Compound **17** was synthesized from 4-bromo-2-fluorobenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 64%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47−7.54 (m, 2H), 7.69−7.75 (m, 3H), 7.96 (d, J = 8.8 Hz, 2H). Anal. ($C_{13}H_8BrClFNO_3S$) C, H, N.

4-Chloro-*N*-(4-chloro-2-methylbenzoyl)benzenesulfonamide (18). Compound **18** was synthesized from 4-chloro-2-methylbenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 57%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.99 (d, J = 9 Hz, 2H), 7.74 (d, J = 9 Hz, 2H), 7.47 (d, J = 8 Hz, 1H), 7.39−7.30 (m, 2H), 2.19 (s, 3H). LC/MS t_r = 1.97 min, m/z 342, 344, 346 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 341.9776; calcd mass ($C_{14}H_{11}Cl_2NO_3S$-1H)$^-$, 341.9758. Anal. ($C_{14}H_{11}Cl_2NO_3S$) C, H, N.

***N*-(4-Bromo-2-methyl-benzoyl)-4-chlorobenzenesulfonamide (19).** Compound **19** was synthesized from 4-bromo-2-methylbenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 67%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (dd, J = 9 Hz, 2 Hz, 2H), 7.74 (dd, J = 9 Hz, 2 Hz, 2H), 7.51 (d, J = 1 Hz, 1H), 7.47 (dd, J = 8 Hz, 2 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 2.17 (s, 3H). LC/MS t_r = 2.01 min, m/z 386, 388, 390 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 385.9258; calcd mass ($C_{14}H_{11}BrClNO_3S$-1H)$^-$, 385.9253. Anal. ($C_{14}H_{11}BrClNO_3S$) C, H, N.

4-Chloro-*N*-(2-chloro-4-nitrobenzoyl)benzenesulfonamide (20). Compound **20** was synthesized from 2-chloro-4-nitrobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 8.18 (dd, J = 8 Hz, 2 Hz, 1H), 7.97 (d, J = 9 Hz, 2H), 7.75 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 1H). LC/MS t_r = 1.71 min, m/z 373, 375, 377 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 372.9448; calcd mass ($C_{13}H_8Cl_2N_2O_5S$-1H)$^-$, 372.9453. Anal. ($C_{13}H_8Cl_2N_2O_5S$) C, H, N.

4-Chloro-*N*-(4-chloro-2-ethylbenzoyl)benzenesulfonamide (21). Compound **21** was synthesized from 4-chloro-2-ethylbenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 61%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.32−7.45 (m, 3H), 2.47−2.54 (m, 2H), 0.91 (t, J = 7.7 Hz, 3H). HRMS obsd mass, 355.9944 (M − H)$^-$; calcd mass ($C_{15}H_{13}Cl_2NO_3S$-1H)$^-$, 355.9915. Anal. ($C_{15}H_{13}Cl_2NO_3S$) C, H, N.

4-Chloro-*N*-(4-chloro-2-propylbenzoyl)benzenesulfonamide (22). Compound **22** was synthesized from 4-chloro-2-propylbenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 39%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 9.1 Hz, 1H), 7.32−7.35 (m, 2H), 2.44 (t, J = 7.9 Hz, 2H), 1.12−1.24 (m, 2H), 0.61 (t, J = 7.3 Hz, 3H). LC/MS performed as described for **1**. Second HPLC performed as described for **8**. LC/MS t_r = 1.63 min (>99%), m/z 370, 372 (M − H)$^-$. Second HPLC t_r = 4.01 min (99%). HRMS obsd mass (M − H)$^-$, 370.0094; calcd mass ($C_{16}H_{15}Cl_2NO_3S$-1H)$^-$, 370.0072.

4-Chloro-*N*-(2,4-dimethylbenzoyl)benzenesulfonamide (23). Compound **23** was synthesized from 2,4-dimethylbenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 59%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (dd, J = 8, 2 Hz, 2H), 7.77 (dd, J = 9, 3 Hz, 2H), 7.38 (d, J = 8 Hz, 1H), 7.09−7.10 (m, 2H), 2.31 (s, 3H), 2.19 (s, 3H). LC/MS t_r = 1.90 min, m/z 322, 324 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 322.0299; calcd mass ($C_{15}H_{14}ClNO_3S$-1H)$^-$, 322.0305. Anal. ($C_{15}H_{14}ClNO_3S$) C, H, N.

4-Chloro-*N*-(4-chloro-2-methoxybenzoyl)benzenesulfonamide (24). Compound **24** was synthesized from 4-chloro-2-methoxybenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 34%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H), 7.41 (d, J = 8 Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 7.07 (dd, J = 8 Hz, 2 Hz, 1H), 3.87 (s, 3H). LC/MS t_r = 2.02 min, m/z 358, 360, 362 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 357.9725; calcd mass ($C_{14}H_{11}Cl_2NO_4S$-1H)$^-$, 357.9708. Anal. ($C_{14}H_{11}Cl_2NO_4S$) C, H, N.

4-Chloro-*N*-(2-amino-4-chlorobenzoyl)benzenesulfonamide (25). Compound **25** was synthesized from 2-amino-4-chlorobenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 8%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.43 (d, J = 8.5 Hz, 1H), 6.77 (s, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.5 Hz, 2H), 8.00 (br s, 2H). LC/MS performed as described for **1**. A

second HPLC was performed on a YMC ODS-A, 2.0 mm × 50 mm, S3 μm column. The solvent conditions were 5−100% ACN with 0.2% formic acid in 3 min and held at 100% ACN with 0.2% formic acid for 0.5 min. The flow rate was 1.0 mL/min, and 5 μL was injected. Light scattering detection was used. LC/MS t_r = 1.68 min (>99%), *m/z* 343, 345 $(M - H)^-$. Second HPLC t_r = 2.40 min (>99%). HRMS (positive mode) obsd mass $(M + H)^+$, 344.9860; calcd mass $(C_{13}H_{10}Cl_2N_2O_3S+1H)^+$, 344.9867.

***N*-(2,4,-Bis-trifluoromethyl-benzoyl)-4-chlorobenzenesulfonamide (26).** Compound **26** was synthesized from 2,4-bis(trifluoromethyl)benzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 49%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10−8.13 (m, 2H), 7.95 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 2H). LC/MS t_r = 2.01 min, *m/z* 430, 432 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 429.9720; calcd mass $(C_{15}H_8ClF_6NO_3S\text{-}1H)^-$, 429.9739. Anal. ($C_{15}H_8ClF_6NO_3S$) C, H, N.

4-Chloro-*N*-(4-chloro-2-nitrobenzoyl)benzenesulfonamide (27). Compound **27** was synthesized from 4-chloro-2-nitrobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 76%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 2 Hz, 1H), 7.99 (d, J = 9 Hz, 2H), 7.94 (dd, J = 8, 2 Hz, 1H), 7.78 (d, J = 9 Hz, 2H), 7.75 (d, J = 8 Hz, 1H). LC/MS t_r = 1.78 min, *m/z* 373, 375, 377 $(M - H)^-$. HRMS obsd mass $(M-H)^-$, 372.9443; calcd mass $(C_{13}H_8C_{l2}N_2O_5S\text{-}1H)^-$, 372.9453. Anal. ($C_{13}H_8C_{l2}N_2O_5S$) C, H, N (vacuum-dried at 80 °C).

4-Chloro-*N*-(2-nitro-4-trifluoromethylbenzoyl)benzenesulfonamide (28). Compound **28** was synthesized from 2-nitro-4-trifluoromethylbenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 57%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 8.24 (d, J = 8 Hz, 1H), 8.00 (d, J = 9 Hz, 2H), 7.96 (d, J = 8 Hz, 1H), 7.78 (d, J = 9 Hz, 2H). LC/MS t_r = 1.85 min, *m/z* 407, 409 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 406.9734; calcd mass $(C_{14}H_8ClF_3N_2O_5S\text{-}1H)^-$, 406.9716. Anal. ($C_{14}H_8ClF_3N_2O_5S$) C, H, N.

4-Chloro-*N*-(2,4-dinitrobenzoyl)benzenesulfonamide (29). Compound **29** was synthesized from 2,4-dinitrobenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 47%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (d, J = 2 Hz, 1H), 8.60 (dd, J = 8, 2 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 7.98 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H). LC/MS t_r = 1.56 min, *m/z* 384, 386 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 383.9705; calcd mass $(C_{13}H_8ClN_3O_7S\text{-}1H)^-$, 383.9693. Anal. ($C_{13}H_8ClN_3O_7S$) C, H, N.

4-Chloro-*N*-(2-chloro-4-cyanobenzoyl)benzenesulfonamide (30). Compound **30** was synthesized from 2-chloro-4-cyanobenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 16%. TLC R_f = 0.20 (9:1 CH_2Cl_2/MeOH); mp 98−100 °C. ^{1}H NMR (300 MHz, methanol-d_4): δ 7.47−7.55 (m, 3H), 7.60 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.96 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 6.7 Hz, 1H). LC/MS was performed as described for **1**. The second HPLC was performed as described for **8**. LC/MS t_r = 1.31 min (94%), *m/z* 353, 355 $(M - H)^-$. Second HPLC t_r = 3.67 min (96%). HRMS obsd mass $(M - H)^-$, 352.9591; calcd mass $(C_{14}H_8Cl_2N_2O_3S\text{-}1H)^-$, 352.9554.

4-Chloro-*N*-(2-chloro-4-methanesulfonylbenzoyl)benzenesulfonamide (31). Compound **31** was synthesized from 2-chloro-4-methanesulfonylbenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 66%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 2 Hz, 1H), 8.03 (dd, J = 9, 2 Hz, 2H), 7.96 (dd, J = 8, 2 Hz, 1H), 7.79−7.81 (m, 3H), 3.35 (s, 3H). LC/MS t_r = 1.57 min, *m/z* 406, 408, 410 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 405.9381; calcd mass $(C_{14}H_{11}Cl_2NO_5S_2\text{-}1H)^-$, 405.9377. Anal. ($C_{14}H_{11}Cl_2NO_5S_2$) C, H, N.

4-Chloro-*N*-(2-chloro-4-methoxybenzoyl)benzenesulfonamide (32). Compound **32** was synthesized from 2-chloro-4-methoxybenzoic acid and 4-chlorobenzenesulfonamide using coupling procedure C. Yield = 98%. R_f = 0.51 (94:6 CH_2Cl_2/MeOH); mp 42−47 °C. ^{1}H NMR (300 MHz, methanol-d_4): δ 3.82 (s, 3H), 6.91 (dd, J = 2, 9 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 8.6 Hz, 2H). LC/MS was performed as described for **1**. The second HPLC was performed as described for **25**. LC/MS t_r = 1.53 min (>99%), *m/z* 358, 360 $(M - H)^-$. Second HPLC t_r = 2.42 min (99%). APCI-MS *m/z* 358 $[C_{14}H_{11}Cl_2NO_4S\text{-}1H]^-$.

4-Chloro-*N*-(2-chloro-4-hydroxybenzoyl)benzenesulfonamide (33). The methyl ether derivative, **32** (147 mg; 0.408 mmol), was dissolved in CH_2Cl_2 and chilled to −20 °C. An excess of BBr_3 (4 mL; 1 M in CH_2Cl_2) was added, and the reaction solution was stirred for 1 h at −20 °C, for 1 h at room temperature, and finally for 2 h at 40 °C. Slow addition of saturated aqueous $NaHCO_3$ quenched the reaction. The product was extracted into CH_2Cl_2. The organic layer was washed with 0.5 M HCl, dried with Na_2SO_4, filtered, and concentrated in vacuo. Silica chromatography with an isocratic mobile phase (MeOH/CH_2Cl_2; 5:95, v/v) purified the desired product (130 mg; 90% yield). ^{1}H NMR (400 MHz, methanol-d_4): δ 8.05 (d, 2H, J = 8.8 Hz), 7.62 (d, 2H, J = 8.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 6.82 (d, 1H, J = 2.2 Hz), 6.74 (dd, 1H, J = 8.4, 2.2 Hz). The first HPLC was performed on a YMC C_{18}, 2.1 mm × 150 mm, 3.5 μm column with gradient conditions that went from 5 to 100% ACN/MeOH (50/50) with 0.2% NH_4CO_2H in 7.0 min and then were held at 100% for 1.0 min. The flow rate was 0.7 mL/min. Approximately 5 μL was injected. The column temperature was 60 ± 10 °C. UV detection was used. The second HPLC was performed as described for **25**. First HPLC t_r = 5.36 min (>99%). Second HPLC t_r = 2.18 min (>99%). HRMS (positive mode) obsd mass $(M)^+$, 345.9724; calcd mass $(C_{13}H_9\text{-}Cl_2NO_4S)^+$, 345.9707.

4-Chloro-*N*-(4-amino-2-chlorobenzoyl)benzenesulfonamide (34). The starting material, 4-chloro-*N*-(4-(*t*-butoxycarbonyl)amino-2-chlorobenzoyl)benzenesulfonamide, was prepared by the reaction of *N*-(4-(*tert*-butoxycarbonyl)amino-2-chlorobenzoic acid and 4-chlorobenzenesulfonamide and was isolated in 81% yield following silica gel chromatography. ESI-MS *m/z* 443.0 $(C_{18}H_{18}Cl_2N_2O_5S - 1H)^-$. The Boc-protected material (130 mg, 0.3 mmol) was treated with 1:1 TFA:CH_2Cl_2 (2 mL) at room temperature for 40 min. The reaction mixture was concentrated in vacuo and then lyophilized from 1:1 MeOH:H_2O (5 mL) to provide the title compound (103 mg; 0.21 mmol, 70%) as its TFA salt. ^{1}H NMR (400 MHz, methanol-d_4): δ 8.03 (d, 2 H, J = 8.4 Hz), 7.61 (d, 2 H, J = 8.4 Hz), 7.26 (d, 1 H, J = 2.2 Hz), 6.60 (d, 1 H, J = 8.4 Hz), 6.59 (dd, 1 H, J = 8.4 Hz, 2.2 Hz), 4.92 (br s, 3 H). ^{13}C NMR (75 MHz, methanol-d_4): δ 165.9, 151.8, 139.9, 138.5, 133.5, 131.4, 129.9, 129.1, 120.3, 115.5, 112.5. LC/MS was performed as described for **1**. The second HPLC was performed as described for **25**. LC/MS t_r = 1.23 min (91%), *m/z* 343, 345 $(M - H)^-$. Second HPLC t_r = 2.14 min (93%). HRMS (positive mode) obsd mass $(M + H)^+$, 344.9873; calcd mass $(C_{13}H_{10}Cl_2N_2O_3S+1H)^+$, 344.9867.

4-Chloro-*N*-(2,4-dimethoxybenzoyl)benzenesulfonamide (35). Compound **35** was synthesized from 2,4-dimethoxybenzoic acid and 4-chlorobenzenesulfonamide using RPS coupling procedure A. Yield = 84%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 11.49 (br. s, 1H), 7.99 (d, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 1H), 6.64 (d, J = 2 Hz, 2H), 6.57 (dd, J = 8, 2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H). LC/MS t_r = 2.15 min, *m/z* 354, 356 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 354.0193; calcd mass $(C_{15}H_{14}ClNO_5S\text{-}1H)^-$, 354.0203. Anal. ($C_{15}H_{14}ClNO_5S$) C, H, N.

4-Methyl-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (36). Compound **36** was synthesized from 2,4-dichlorobenzoic acid and 4-methylbenzenesulfonamide using RPS coupling procedure B. Yield = 73%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.76 (br. s, 1H), 7.85 (2, J = 7 Hz, 2H), 7.68 (s, 1H), 7.47 (s, 2H), 7.43 (d, J = 7 Hz, 2H), 2.43 (s, 3H). LC/MS t_r = 1.87 min, *m/z* 342, 344, 346 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 341.9748; calcd mass $(C_{14}H_{11}Cl_2NO_3S\text{-}1H)^-$, 341.9758. Anal. ($C_{14}H_{11}Cl_2NO_3S$) C, H, N.

4-Bromo-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (37). Compound **37** was synthesized from 2,4-dichloro-

benzoic acid and 4-bromobenzenesulfonamide using RPS coupling procedure B. Yield = 66%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.90(s, 4H), 7.71 (d, J = 2 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.48 (dd, J = 8, 2 Hz, 1H) ppm. LC/MS t_r = 1.94 min, m/z 408, 406, 410 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 405.8693; calcd mass ($C_{13}H_8BrCl_2NO_3S$-1H)$^-$, 405.8707. Anal. ($C_{13}H_8BrCl_2NO_3S$) C, H, N.

3-Bromo-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (38). Compound **38** was synthesized from 2,4-dichlorobenzoic acid and 3-bromobenzenesulfonamide using RPS coupling procedure B. Yield = 22%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.06 (t, J = 2 Hz, 1H), 7.96 (dt, J = 8 Hz, 2H), 7.71 (d, J = 2 Hz, 1H), 7.67−7.45 (m, 4H). LC/MS t_r = 1.90 min (>99%), m/z 408, 406, 410 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 405.8695; calcd mass ($C_{13}H_8BrCl_2NO_3S$-1H)$^-$, 405.8707. Anal. ($C_{13}H_8BrCl_2NO_3S$) C, H, N (vacuum-dried at 80 °C).

***N*-(2,4-Dichloro-benzoyl)-4-methoxybenzenesulfonamide (39).** Compound **39** was synthesized from 2,4-dichlorobenzoic acid and 4-methoxybenzenesulfonamide using RPS coupling procedure B. Yield = 68%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.67 (br s, 1H), 7.91 (d, J = 9 Hz, 2H), 7.69 (s, 1H), 7.48 (s, 2H), 7.16 (d, J = 9 Hz, 2H), 3.86 (s, 3H). LC/MS t_r = 1.77 min, m/z 358, 360, 362 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 357.9695; calcd mass ($C_{14}H_{11}Cl_2NO_4S$-1H)$^-$, 357.9708. Anal. ($C_{14}H_{11}Cl_2NO_4S$) C, H, N.

4-*tert*-Butyl-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (40). Compound **40** was synthesized from 2,4-dichlorobenzoic acid and 4-*tert*-butylbenzenesulfonamide using RPS coupling procedure B. Yield = 70%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.67 (br s, 1 H), 7.91 (d, J = 9 Hz, 2 H), 7.69 (s, 1H), 7.48 (s, 2H), 7.16 (d, J = 9 Hz, 2H), 3.86 (s, 3H). LC/MS t_r = 1.53 min, m/z 385, 387, 389 (M)$^-$. HRMS obsd mass (M − H)$^-$, 384.0247; calcd mass ($C_{17}H_{17}Cl_2NO_3S$-1H)$^-$, 384.0228. Anal. ($C_{17}H_{17}Cl_2NO_3S$) C, H, N.

3-Chloro-*N*-(2,4-dichloro-benzoyl)-4-methylbenzenesulfonamide (41). Compound **41** was synthesized from 2,4-dichlorobenzoic acid and 3-chloro-4-methylbenzenesulfonamide using RPS coupling procedure B. Yield = 56%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.82 (d, J = 7 Hz, 1H), 7.70 (s, 1H), 7.63 (d, J = 7 Hz, 1H), 7.53 (d, J = 6 Hz, 1H), 7.46 (d, J = 7 Hz, 1H), 2.44 (s, 3H). LC/MS t_r = 2.04 min, m/z 378, 376, 380 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 375.9382; calcd mass ($C_{14}H_{10}Cl_3NO_3S$-1H)$^-$, 375.9369. Anal. ($C_{14}H_{10}Cl_3NO_3S$) C, H, N.

3-Chloro-*N*-(2,4-dichloro-benzoyl)-4-fluorobenzenesulfonamide (42). Compound **42** was synthesized from 2,4-dichlorobenzoic acid and 3-chloro-4-fluorobenzenesulfonamide using RPS coupling procedure B. Yield = 84%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (dd, J = 7, 2 Hz, 1H), 7.98−8.02 (m, 1H), 7.70−7.74 (m, 2H), 7.55 (d, J = 8 Hz, 1H), 7.49 (dd, J = 8, 2 Hz, 1H). LC/MS t_r = 1.96 min, m/z 380, 382, 384 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 379.9128; calcd mass ($C_{13}H_7Cl_3FNO_3S$-1H)$^-$, 379.9118. Anal. ($C_{13}H_7Cl_3FNO_3S$) C, H, N.

***N*-(2,4-Dichloro-benzoyl)-4-fluorobenzenesulfonamide (43).** Compound **43** was synthesized from 2,4-dichlorobenzoic acid and 4-fluorobenzenesulfonamide using RPS coupling procedure B. Yield = 61%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.10−8.00 (m, 2H), 7.71 (d, J = 1.6 Hz, 1H), 7.56−7.44 (m, 4H). LC/MS t_r = 1.80 min, m/z 346, 348, 350 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 345.9497; calcd mass ($C_{13}H_8Cl_2FNO_3S$-1H)$^-$, 345.9508. Anal. ($C_{13}H_8Cl_2FNO_3S$) C, H, N.

3-Chloro-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (44). Compound **44** was synthesized from 2,4-dichlorobenzoic acid and 3-chlorobenzenesulfonamide using RPS coupling procedure B. Yield = 82%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.97−7.91 (m, 2H), 7.84 (d, J = 8 Hz, 1H), 7.74−7.66 (m, 2H), 7.56 (d, J = 9 Hz, 1H), 7.49 (dd, J = 8, 2 Hz, 1H). LC/MS t_r = 1.94 min, m/z 364, 362, 366 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 361.9197; calcd mass ($C_{13}H_8Cl_3NO_3S$-1H)$^-$, 361.9212. Anal. ($C_{13}H_8Cl_3NO_3S$) C, H, N.

3,4-Dichloro-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (45). Compound **45** was synthesized from 2,4-dichlorobenzoic acid and 3,4-dichlorobenzenesulfonamide using RPS coupling procedure B. Yield = 61%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.11 (d, J = 2 Hz, 1H), 7.98−7.89 (m, 2H), 7.71 (d, J = 2 Hz, 1 H), 7.58 (d, J = 8 Hz, 1H), 7.49 (dd, J = 8, 2 Hz, 1H). LC/MS t_r = 2.13 min, m/z 398, 396, 400 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 395.8827; calcd mass ($C_{13}H_7Cl_4NO_3S$-1H)$^-$, 395.8823. Anal. ($C_{13}H_7Cl_4NO_3S$) C, H, N.

***N*-(2,4-Dichlorobenzoyl)-4-methylsulfanylbenzenesulfonamide (46).** Compound **46** was synthesized from 2,4-dichlorobenzoic acid and 4-methylsulfanylbenzenesulfonamide using RPS coupling procedure B. Yield = 78%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.85 (d, J = 7 Hz, 2H), 7.68 (s, 1H), 7.50 (s, 2H), 7.47 (d, J = 7 Hz, 2H). LC/MS t_r = 1.91 min, m/z 374, 376, 378 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 373.9474; calcd mass ($C_{14}H_{11}Cl_2NO_3S_2$-1H)$^-$, 373.9479. Anal. ($C_{14}H_{11}Cl_2NO_3S_2$) C, H, N.

4-Acetyl-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (47). Compound **47** was synthesized from 2,4-dichlorobenzoic acid and 4-acetylbenzenesulfonamide using RPS coupling procedure B. Yield = 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, J = 8 Hz, 2H), 8.14 (d, J = 8 Hz, 2H), 7.76 (d, J = 2 Hz, 1H), 7.52−7.58 (m, 2H), 2.69 (s, 3H). LC/MS t_r = 1.65 min, m/z 370, 372, 374 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 369.9713; calcd mass ($C_{15}H_{11}Cl_2NO_4S$-1H)$^-$, 369.9708. Anal. ($C_{15}H_{11}Cl_2NO_4S$) C, H, N.

***N*-(2,4-Dichlorobenzoyl)-3-methylbenzenesulfonamide (48).** Compound **48** was synthesized from 2,4-dichlorobenzoic acid and 3-methylbenzenesulfonamide using coupling procedure C. Yield = 35%. ^{1}H NMR (400 MHz, methanol-d_4): δ 7.87 (m, 2H), 7.54 (m, 2H), 7.49 (m, J = 7.7 Hz, 1H), 7.40 (m, 2H), 2.46 (s, 3H). LC/MS was performed as described for **1**. The second HPLC was performed as described for **8**. LC/MS t_r = 1.37 min (>99%), m/z 342, 344 (M − H)$^-$. Second HPLC t_r = 3.71 min (98%). HRMS obsd mass (M − H)$^-$, 341.9756; calcd mass ($C_{14}H_{11}Cl_2NO_3S$-1H)$^-$, 341.9759.

3,4-Dibromo-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (49). Compound **49** was synthesized from 2,4-dichlorobenzoic acid and 3,4-dibromobenzenesulfonamide using coupling procedure C. Yield = 34%. ^{1}H NMR (400 MHz, methanol-d_4): δ 8.32 (d, J = 2.2 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 1.3 Hz, 1H). LC/MS was performed as described for **1**. The second HPLC was performed as described for **8**. LC/MS t_r = 1.63 min (>99%), m/z 486, 488, 484 (M − H)$^-$. Second HPLC t_r = 3.89 min (95%). HRMS obsd mass (M − H)$^-$, 483.7822; calcd mass ($C_{13}H_7Br_2Cl_2NO_3S$-1H)$^-$, 483.7812.

***N*-(2,4-Dichlorobenzoyl)-3-nitrobenzenesulfonamide (50).** Compound **50** was synthesized from 2,4-dichlorobenzoic acid and 3-nitrobenzenesulfonamide using RPS coupling procedure B. Yield = 78%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.66 (t, J = 2 Hz, 1H), 8.56 (dd, J = 8, 2 Hz, 1H), 8.39 (d, J = 8 Hz, 1H), 7.96 (t, J = 8 Hz, 1H), 7.70 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.49 (dd, J = 8, 2 Hz, 1H). LC/MS t_r = 1.75 min, m/z 373, 375, 377 (M − H)$^-$. HRMS obsd mass (M − H)$^-$, 372.9472; calcd mass ($C_{13}H_8Cl_2N_2O_5S$-1H)$^-$, 372.9453. Anal. ($C_{13}H_8Cl_2N_2O_5S$) C, H, N.

***N*-(2,4-Dichlorobenzoyl)-3-methoxybenzenesulfonamide (51).** Compound **51** was synthesized from 2,4-dichlorobenzoic acid and 3-methoxybenzenesulfonamide using coupling procedure C. Yield = 41%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.9 Hz, 1H), 7.60 (dt, J = 2.2 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.44 (dd, J = 7.9, 8.3 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 2.2, 8.3 Hz, 1H), 7.16 (dd, J = 2.6, 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 159.9, 139.3, 138.9, 132.3, 131.8, 130.6, 130.4, 130.3, 128.0, 121.2, 120.8, 113.2, 56.0. LC/MS was performed as described for **1**. The second HPLC was performed as described for **8**. LC/MS t_r = 1.56 min (>99%), m/z 358, 360 (M − 1)$^-$. Second HPLC t_r = 2.83 min (98%). ESI-MS m/z: 358.0 ($C_{14}H_{11}Cl_2NO_4S$ − 1H)$^-$. HRMS (positive mode) obsd mass (M + H)$^+$, 359.9886; calcd mass ($C_{14}H_{11}Cl_2NO_4S$+1H)$^+$, 359.9859.

***N*-(2,4-Dichlorobenzoyl)-4-(dimethylamino)benzenesulfonamide (52).** Compound **52** was synthesized from 2,4-

dichlorobenzoic acid and 4-(dimethylamino)benzenesulfonamide using RPS coupling procedure B. Yield = 16%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, J = 9 Hz, 2H), 7.69 (d, J = 2 Hz, 1H), 7.48 (dd, J = 8 Hz, 2 H), 7.43 (d, J = 8 Hz, 1H), 6.81 (d, J = 9 Hz, 2H), 3.03 (s, 6H). LC/MS studies were performed as described for **1** except that positive mode ES ionization was used. LC/MS t_r = 1.51 min, m/z 373 $(M + 1)^+$. HRMS (negative mode ES) obsd mass $(M - H)^-$, 371.0045; calcd mass $(C_{15}H_{14}Cl_2N_2O_3S\text{-}1H)^-$, 371.0024. Anal. ($C_{15}H_{14}Cl_2N_2O_3S$) C, H, N.

Biphenyl-3-sulfonic Acid 2,4-Dichlorobenzoylamide (53). To a solution of 3-bromo-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (**38**) (0.10 mmol) in toluene/ethanol 20/1 (3 mL) were added arylboronic acid (0.18 mmol, 0.18 mL, 1.0 M in DMF) and tetrakis(triphenylphosphine)palladium(0) (10 mol %). Then, 2 M aqueous Na_2CO_3 was added (0.3 mL) and the stirred mixture was heated to 100 °C overnight (17 h). The reaction mixture was concentrated. H_2O (2.5 mL) and EtOAc (5 mL) were added. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The solvents were evaporated, and the corresponding crude product was purified by HPLC to give the title compound. Yield = 14%. ^{1}H NMR (200 MHz, methanol-d_4): δ 7.40−7.55 (m, 5H), 7.62−7.77 (m, 4H), 7.90−8.04 (m, 2H), 8.17 (m, 1H). ^{13}C NMR (50 MHz, methanol-d_4): δ 125.8; 126.7; 127.2 (2C); 127.8; 128.7; 129.6 (2C); 129.8; 130.3; 130.8; 131.6; 132.2; 133.4; 136.2; 138.3; 138.8; 140.5 and 141.3. ESI-MS m/z 404.0 $(C_{19}H_{13}Cl_2NO_3S\text{-}1H)^-$.

4-(2,4-Dichlorobenzoylsulfamoyl)benzoic Acid Methyl Ester (54). Compound **54** was synthesized from 2,4-dichlorobenzoic acid and 4-sulfamoyl-benzoic acid methyl ester using coupling procedure C. Yield = 75%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.97 (s, 3 H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 8.23 (s, 4H). LC/MS was performed as described for **1**. The second HPLC was performed as described for **8**. LC/MS t_r = 1.65 min (>99%), m/z 386, 388 $(M - H)^-$. Second HPLC t_r = 2.85 min (99%). HRMS (positive mode) obsd mass $(M)^+$, 386.9735; calcd mass $(C_{15}H_{11}Cl_2NO_5S)^+$, 386.9735. Anal. ($C_{15}H_{11}Cl_2NO_5S \cdot 0.15\ CH_2Cl_2$) C, H, N.

***N*-(2,4-Dichlorobenzoyl)-4-nitrobenzenesulfonamide (55).** Compound **55** was synthesized from 2,4-dichlorobenzoic acid and 4-nitrobenzenesulfonamide using RPS coupling procedure B. Yield = 60%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.46 (d, J = 9 Hz, 2H), 8.22 (d, J = 9 Hz, 2H), 7.70 (d, J = 2 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.49 (dd, J = 8, 2 Hz, 1H). LC/MS t_r = 1.80 min, m/z 373, 375, 377 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 372.9468; calcd mass $(C_{13}H_8Cl_2N_2O_5S\text{-}1H)^-$, 372.9453. Anal. ($C_{13}H_8Cl_2N_2O_5S$) C, H, N.

Biphenyl-4-sulfonic Acid 2,4-Dichlorobenzoylamide (56). Compound **56** was synthesized from 4-bromo-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (**37**) using a procedure similar to that described for **53**. Yield = 32%. White solid. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.88 (d, J = 8.1 Hz, 2H), 7.69 (br d, J = 7.8 Hz. 4H), 7.51−7.29 (m, 6H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 169.6, 145.3, 141.9, 139.8, 132.8, 131.6, 131.3, 129.6, 129.3, 129.2, 128.1 (2C), 127.7, 127.2 (2C), 126.8 (2C), 126.3 (2C). LC/MS was performed as described in **1**. The second HPLC was performed as described in **25**. LC/MS t_r = 1.88 (>99%) m/z 404, 406 $(M - H)^-$. Second HPLC t_r = 2.70 min (>99%).

***N*-(2,4-Dichlorobenzoyl)-3,4-dimethoxybenzenesulfonamide (57).** Compound **57** was synthesized from 2,4-dichlorobenzoic acid and 3,4-dimethoxybenzenesulfonamide using RPS procedure B. Yield = 39%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (s, 1H), 7.62 (dd, J = 8, 2 Hz, 1H), 7.52 (d, J = 1 Hz, 2H), 7.45 (d, J = 2 Hz, 1H), 7.23 (d, J = 9 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H). LC/MS t_r = 1.63 min, m/z 388, 390, 392 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 387.9830; calcd mass $(C_{15}H_{12}Cl_2NO_5S)^-$, 387.9813. Anal. ($C_{15}H_{13}Cl_2NO_5S$) C, H, N.

2-Chloro-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (58). Compound **58** was synthesized from 2,4-dichlorobenzoic acid and 2-chlorobenzenesulfonamide using general RPS procedure B. Yield = 75%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.17 (d, J = 8 Hz, 1H), 7.72 (d, J = 2 Hz, 3H), 7.66−7.58 (m, 1H), 7.53 (s, 2H) ppm. LC/MS t_r = 1.81 min, m/z 364, 362, 366 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 361.9223; calcd mass $(C_{13}H_8Cl_3NO_3S\text{-}1H)^-$, 361.9212. Anal. ($C_{13}H_8Cl_3NO_3S$) C, H, N.

2-Chloro-*N*-(2,4-dichlorobenzoyl)-5-nitrobenzenesulfonamide (59). Compound **59** was synthesized from 2,4-dichlorobenzoic acid and 2-chloro-5-nitrobenzenesulfonamide using RPS coupling procedure B. Yield = 62%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.81 (d, J = 2 Hz, 1H), 8.49 (dd, J = 9 Hz, 1 H), 7.99 (d, J = 9 Hz, 1H), 7.70 (d, J = 2 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.51 (dd, J = 8, 2 Hz, 1H). LC/MS t_r = 1.77 min, m/z 409, 407, 411 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 406.9070; calcd mass $(C_{13}H_7Cl_3N_2O_5S\text{-}1H)^-$, 406.9063. Anal. ($C_{13}H_7Cl_3N_2O_5S$) C, H, N.

***N*-(2,4-Dichlorobenzoyl)-2-methyl-5-nitrobenzenesulfonamide (60).** Compound **60** was synthesized from 2,4-dichlorobenzoic acid and 2-methyl-5-nitrobenzenesulfonamide using RPS coupling procedure B. Yield = 84%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.72 (d, J = 3 Hz, 1H), 8.44 (dd, J = 8, 2 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.71 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1 H), 7.50 (dd, J = 8, 2 Hz, 1H), 2.73 (s, 3H). LC/MS t_r = 1.89 min (>99%), m/z 387, 389, 391 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 386.9627; calcd mass $(C_{14}H_{10}Cl_2N_2O_5S\text{-}1H)^-$, 386.9609. Anal. ($C_{14}H_{10}Cl_2N_2O_5S$) C, H, N.

2-Bromo-*N*-(2,4-dichlorobenzoyl)-4-methylbenzenesulfonamide (61). Compound **61** was synthesized from 2,4-dichlorobenzoic acid and 4-methylbenzenesulfonamide using RPS coupling procedure B. Yield = 79%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, J = 2 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.71 (d, J = 1 Hz, 1H), 7.49−7.54 (m, 2H), 7.43 (dd, J = 8, 1 Hz, 1H), 2.29 (s, 3H). LC/MS t_r = 1.91 min, m/z 420, 422, 424 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 419.8880; calcd mass $(C_{14}H_{10}BrCl_2NO_3S\text{-}1H)^-$, 419.8864. Anal. ($C_{14}H_{10}BrCl_2NO_3S$) C, H, N.

3,5-Dichloro-*N*-(2,4-dichlorobenzoyl)benzenesulfonamide (62). Compound **62** was synthesized from 2,4-dichlorobenzoic acid and 3,5-dichlorobenzenesulfonamide using RPS coupling procedure B. Yield = 73%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.02 (t, J = 2 Hz, 1H), 7.88 (d, J = 2 Hz, 2H), 7.68 (d, J = 2 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 7.48 (dd, J = 8, 2 Hz, 1H). LC/MS t_r = 2.13 min, m/z 398, 396, 400 $(M - H)^-$. HRMS obsd mass $(M - H)^-$, 395.8852; calcd mass $(C_{13}H_7Cl_4NO_3S\text{-}1H)^-$, 395.8823. Anal. ($C_{13}H_7Cl_4NO_3S$) C, H, N.

HUVEC Proliferation Assay.[10] HUVECs (Clonetics/Biowhittaker) were maintained in EGM media (endothelial cell growth medium, Clonetics/Biowhittaker). On the day of the assay, the cells were trypsinized and harvested using basal medium (EBM) with 0.5% FBS (Clonetic/Biowhittaker). The cells were seeded into 96 well plates at a concentration of 5000 cells/well at a volume of 160 μL. The plates were incubated in the low serum media overnight at 37 °C, 5% CO_2, to quiesce the cells. The next day, serial dilutions of the compounds were prepared for a final dosage range of 0.027−20 μM. Twenty microliters of compounds was added, followed by the addition of 20 μL of 100 μg/mL VEGF stock in phosphate-buffered saline/0.1% BSA (R&D Systems), for a final concentration of 20 ng/mL. The cells were placed back in the incubator. After 72 h, 20 μL of WST-1 proliferation reagent (Roche Diagnostics Corporation) was added to the medium. After 1 h of incubation at 37 °C, the absorbances were read at 440 nM with a Spectramax Spectrophotometer (Molecular Devices). The growth fraction was determined from the absorbance of treated wells with and without VEGF divided by the absorbance obtained from control wells set to zero and 1.0. The IC_{50} values were calculated using a two parameter logistic curve fit program, $Y = 1/[1 + (X/c)]^b$, to the dose−response data where Y = fraction activity, X = concentration, c = IC_{50}, and b = slope. The MSR for comparing average IC_{50} values with $n > 3$ was 2.6 for this assay.[21] That is, the average IC_{50} values of two compounds were considered statistically significantly different if the ratio was more than 2.6. For IC_{50} values with $n = 2$, the MSR was 3.3.

SADD Assay. The SADD assay to differentiate the antiproliferative activity of an agent against normal cells (fibroblasts cells, CFU-GM), leukemia cells (L1210), and solid tumor cells (including multidrug resistant solid tumors) was performed as described by Corbett et al.[8,9] The leukemia cells, solid tumor cells, and normal cells were seeded in soft agar in separate 60 mm Petri dishes. The drug was placed on a filter paper disk (standard hole punch of Whatman no. 1) that was then placed on top of the soft agar. The drug diffused off the disk as the cancerous cells and normal cells were replicating, creating a zone of inhibition of colony formation. The zones were recorded after 6−7 days of incubation at 37 °C. Cytotoxicity was measured by the zone of inhibition, with 200 zone units = 6.5 mm. In general, a 330 zone unit change was effected by a one log dilution in the concentration of a cytotoxic agent. A 950 zone was the limit of the dish (total inhibition). A zero zone meant no inhibition. In cases where a zone range was recorded, the colonies were reduced in size at the beginning of the zone, increasing in size to the top of the zone range, and from there to the edge of the plate, the colonies were uniformly large. Ideally, an active compound would have little or no activity against the normal cells, would inhibit to some extent the colony formation of the leukemia cells, and would inhibit greatly the colony formation of the various solid tumors.

PK Studies. For the study in female F344 rats ($n = 3$), compounds were formulated in 1−1.5% sodium bicarbonate in phosphate-buffered saline and dosed as indicated (oral gavage or iv bolus injection). For the seven day study, the animals were treated once daily. Blood was drawn at $t = 0.5$, 1, 2, 4, 6, 8, and 24 h after the final dose. For the study in BALBc mice ($n = 3$ mice/time point), compounds were formulated in 1−1.5% sodium bicarbonate in phosphate-buffered saline. The compounds were dosed as indicated (oral gavage or iv bolus injection) and administered once daily from days 1−5 and 8−12. Blood was drawn at $t = 0.5$, 1, 2, 4, 6, 8, and 24 h after the final dose.

HCT116 Tumor Xenograft Model. Female nude mice were housed in microisolator cages and received food and water ad libitum. In each experiment, test mice were implanted with HCT116 human colon tumor cells by transferring tissue from donor mice. When tumors reached an average volume of 100 mm^3, animals were randomized and separated into treatment groups of 10 animals per group and dosing initiated. The compound dissolved in saline was administered daily from days 1−5 and 8−12 by iv bolus injection. Body weights and tumor volumes were recorded two times weekly. Calculations of TGD were performed as below.

Quantified End Points for Assessing Antitumor Activity in Solid Tumors. The following quantified end points were used to assess antitumor activity. (i) Tumor volume (mm^3) = $(a \times b^2)/2$ where a = tumor length (mm) and b = tumor width (mm). (ii) TGD ($T - C$ value) = $T - C$ where T is the median time (days) required for the treatment group tumors to reach a predetermined size and C is the median time (in days) for the control group tumors to reach the same size.

TGD was determined by first fitting a cytotoxic mechanistic model of tumor growth to the data for each compound, including the control group. The time for each group to reach 500 mm^3 (and standard error) was determined from the fitted model. TGD was calculated by subtracting the time for the control group (C) from the time for each treated group (T).

NCI COMPARE Analysis. The COMPARE analysis and subsequent calculations were performed at the NCI according to published procedures.[28,29]

In Silico Model Building for QSAR Prediction. For model building, the IC_{50} data obtained by VEGF-HUVEC assay were transformed to their log values [log10 ($1/IC_{50}$)]. A set of molecular descriptors comprised of Daylight fingerprints,[32] MACCS,[33] keys, charged partial surface areas,[34] and proprietary in-house defined atom types were calculated and compiled for the entire data set. Columns of nonvarying descriptors were removed using a SAS script. The model was built using proprietary decision tree software. Decision trees (or recursive partitioning) have been shown to be useful in analyzing large QSAR data sets.[35] The data set was split into five random groups for cross-validation such that four groups were used as a training set and the fifth group was left out, to be predicted as a test set. This was done five times so that each compound was eventually left out of the training set and predicted once. Spearman's ρ statistic was used to evaluate the model ability to rank order the test sets. A final model with no cross-validation was then built and used in subsequent work to predict and prioritize new series and ideas for the project members. The five way cross-validated model gave a Spearman $\rho = 0.61$, and the final model with no cross-validation gave a Spearman $\rho = 0.95$.

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Supporting Information Available: Procedures and characterization data for benzoic acid starting materials (2-bromo-4-chlorobenzoic acid, 2,4-dibromobenzoic acid, 2-chloro-4-methoxybenzoic acid, and 2-chloro-4-cyanobenzoic acid) and for benzenesulfonamide starting materials (3-methylbenzenesulfonamide, 3,4-dibromobenzenesulfonamide, 3-methoxybenzenesulfonamide, and 4-sulfamoylbenzoic acid methyl ester) and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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