$$\%\,\mathrm{ILS} = \frac{\mathrm{MDD\ (treated\ animals)} - \mathrm{MDD\ (control\ animals)}}{\mathrm{MDD\ (control\ animals)}} \times 100\%$$

The results indicated in Table I are optimal values for at least two separate experiments. Animal deaths occuring before the median day of death of the control group animals were considered to be due to drug toxicity.

Registry No. **6**, 3029-19-4; **8**, 127856-48-8; **8** (free base), 127856-49-9; **9**, 127856-50-2; **9** (free base), 127856-51-3; **10**, 127856-53-5; **10** (free base), 127856-52-4; **11**, 127856-54-6; **11** (free base), 127856-55-7; **12**, 127856-56-8; **12** (free base), 127856-57-9; **13**, 127856-58-0; **13** (free base), 127856-59-1; **14**, 96403-75-7; **14** (free base), 96403-76-8; **15**, 96403-17-7; **15** (free base), 127856-60-4; **16**, 96403-71-3; **16** (free base), 96403-72-4; **17**, 127856-62-6; **17** (free base), 127856-61-5; **18**, 24463-15-8; **19**, 1086-00-6; **20**, 95948-96-2; **20** (free base), 3712-78-5; **21**, 96403-91-7; **21** (free base), 96403-92-8; **22**, 96403-99-5; **22** (free base), 96404-00-1; **23**, 96404-10-3; **23** (free base), 96404-11-4; **24**, 96422-29-6; **25**, 96404-38-5; **26**, 96404-37-4; **27**, 3786-56-9; **28**, 93324-65-3; **28** (free base), 3786-54-7; **29**, 100572-41-6; **30**, 127856-63-7; **31**, 127856-64-8; **31** (free base), 127856-65-9; **32**, 127856-66-0; **32** (free base), 127856-67-1; **33**, 127856-68-2; **34**, 127856-69-3; **35**, 4643-67-8; **36**, 61098-93-9; **37**, 61098-94-0; **38**, 127880-45-9; **39**, 127856-70-6; **39** (free base), 127856-71-7; **40**, 127856-72-8; **40** (free base), 127856-73-9; **41**, 127856-74-0; **41** (free base), 127856-75-1; **42**, 127856-76-2; **42** (free base), 3712-79-6; **43**, 127856-77-3; **43** (free base), 127856-78-4; **44**, 127856-79-5; **44** (free base), 127856-80-8; **45**, 127856-81-9; **45** (free base), 127856-82-0; **46**, 127856-83-1; **46** (free base), 127856-84-2; **47**, 127856-85-3; **47** (free base), 127856-86-4; **48**, 127856-87-5; **48** (free base), 127856-88-6; **49**, 127856-89-7; **49** (free base), 127856-90-0; **50**, 127856-91-1; **50** (free base), 127856-92-2; **51**, 127856-93-3; **51** (free base), 127856-94-4; **52**, 127856-95-5; **52** (free base), 127856-96-6; **53**, 127856-97-7; **53** (free base), 127856-98-8; **54**, 127856-99-9; **54** (free base), 127857-00-5; **55**, 127857-01-6; **55** (free base), 127857-02-7; **56**, 127857-03-8; 56 (free base), 127857-04-9; **57**, 127857-05-0; **57** (free base), 127857-06-1; **58**, 127857-07-2; **58** (free base), 127857-08-3; **59**, 127857-09-4; **59** (free base), 127857-10-7; **60**, 96404-16-9; **60** (free base), 96404-17-0; **61**, 96403-97-3; **61** (free base), 96403-98-4; **62**, 127857-11-8; **62** (free base), 127857-12-9; **63**, 127857-13-0; **63** (free base), 127857-14-1; **64**, 127857-15-2; **64** (free base), 127857-16-3; **65**, 96404-05-6; **65** (free base), 96404-06-7; **66**, 96404-08-9; **66** (free base), 96404-09-0; **67**, 96422-34-3; **67** (free base), 96403-96-2; **68**, 96404-14-7; **68** (free base), 96404-15-8; **69**, 127857-17-4; **69** (free base), 127857-18-5; **70**, 127857-19-6; **70** (free base), 127857-20-9; **71**, 127857-21-0; **71** (free base), 127857-22-1; **72**, 127857-23-2; **72** (free base), 127857-24-3; **73**, 127857-25-4; **73** (free base), 127857-26-5; **74**, 127857-27-6; **74** (free base), 127857-28-7; **75**, 127857-29-8; **75** (free base), 127857-30-1; **76**, 127857-31-2; **76** (free base), 127857-32-3; **77**, 127857-33-4; **77** (free base), 127857-34-5; **78**, 127857-35-6; **78** (free base), 127857-36-7; **79**, 127857-37-8; **79** (free base), 127857-38-9; **80**, 96404-12-5; **80** (free base), 96404-13-6; **81**, 127857-39-0; **81** (free base), 127857-40-3; **82**, 127857-41-4; $CH_2(COOEt)_2$, 105-53-3; $H_2NC(CH_3)(CH_2OH)_2$, 115-69-5; $H_2N(CH_2)_2CN$, 151-18-8; $H_2N(CH_2)_2OMe$, 109-85-3; $HN(CH_2CH_2OH)_2$, 111-42-2; H_2NCH_2Ph, 100-46-9; $H_2N(CH_2)_2Ph$, 64-04-0; $H_2N(CH_2)_3Ph$, 2038-57-5; $H_2N(CH_2)_4Ph$, 13214-66-9; 3,4-$ClC_6H_4CH_2NH_2$, 102-49-8; $H_2N(CH_2)_3OPr$-*i*, 2906-12-9; $H_2NCH_2CH{=}CH_2$, 107-11-9; $H_2N(CH_2)_4NH_2$, 110-60-1; $H_2N(CH_2)_5NH_2$, 462-94-2; $H_2N(CH_2)_6NH_2$, 124-09-4; $H_2N(CH_2)_2NHPh$, 1664-40-0; $H_2N(CH_2)_3N(CH_3)_2$, 109-55-7; $H_2N(CH_2)_3N(CH_2CH_2)_2O$, 123-00-2; $H_2NCH(CH_3)(CH_2)_3N(CH_2CH_3)_2$, 67459-49-8; $H_2N(CH_2)_2N(CH_2CH_3)_2$, 100-36-7; $H_2N(CH_2)_3NHCH(CH_2CH_2)_2CH_2$, 3312-60-5; $H_2NCH_2CH_2NHCH_2CH_2OH$, 111-41-1; $H_2NCH_2CH_2NHCH_2CH(CH_3)OH$, 121565-46-6; $H_2N(CH_2)_3N(CH_2CH_2OH)_2$, 4985-85-7; $H_2N(CH_2)_3N(CH_3)(CH_2)_3NH_2$, 105-83-9; $H_2N(CH_2)_3N(CH_2CH_2)_2N(CH_2)_3NH_2$, 7209-38-3; $H_2NCH_2CH_2OH$, 141-43-5; $H_2N(CH_2)_3OH$, 156-87-6; $H_2N(CH_2)_4OH$, 13325-10-5; $H_2N(CH_2)_5OH$, 2508-29-4; $H_2NCH(CH_3)CH_2OH$, 6168-72-5; $H_2NCH_2CH(CH_3)OH$, 1674-56-2; $MeNHCH_2CH_2OH$, 109-83-1; $H_2NC(CH_3)_2CH_2OH$, 124-68-5; $H_2NCH_2C(CH_3)_2OH$, 2854-16-2; $H_2NCH(i\text{-}Pr)CH_2OH$, 2026-48-4; $H_2NCH(CH_2\text{-}i\text{-}Pr)CH_2OH$, 16369-17-8; $H_2NCH(CH(CH_3)CH_2CH_3)CH_2OH$, 24629-25-2; $H_2NCH_2CH_2CH(CH_3)OH$, 127912-49-6; $H_2N(CH_2)_3C(CH_3)_2CH_2OH$, 13532-77-9; $H_2NCH_2CH(CH_2CH_3)OH$, 13552-32-4; $H_2NCH(CH_2CH_3)CH_2OH$, 5856-63-3; $H_2NCH(Ph)CH_2OH$, 71006-16-1; $H_2NCH_2CH(Ph)OH$, 1936-63-6; $H_2NCH(CH_3)(CH(Ph)OH)$, 48115-38-4; $H_2NCH_2CH(OH)CH_2OH$, 13552-31-3; $H_2NCH(CH_2OH)_2$, 534-03-2; $H_2NC(CH_2CH_3)(CH_2OH)_2$, 115-70-8; $H_2NC(CH_2OH)_3$, 77-86-1; $H_2NC(n\text{-pentyl})(CH_2OH)_2$, 95051-23-3; $H_2NC(CH_2OCH_2CH_3)(CH_2OH)_2$, 96422-30-9; $H_2NC(i\text{-}Pr)(CH_2OH)_2$, 60204-51-5; $H_2NCH(CH_2OH)(CH(Ph)OH)$, 28143-91-1; $H_2NC(CH_3)(CH(CH_3)OH)(CH_2OH)$, 96403-70-2; $H_2NC(CH_3)(CH_2OCH_3)(CH_2OH)$, 127857-42-5; glucosamine, 3416-24-8.

Novel Agents Effective against Solid Tumors: The Diarylsulfonylureas. Synthesis, Activities, and Analysis of Quantitative Structure–Activity Relationships

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A series of diarylsulfonylureas with exceptionally broad-spectrum activity against syngeneic rodent solid tumors in vivo is described. Their discovery resulted from a program dedicated to in vivo screening for novel oncolytics in solid tumor models, rather than traditional ascites leukemia models. The structures, oral efficacy, side-effect profile, and mechanism of action of these sulfonylureas appear to be distinct from previously known classes of oncolytics. An extensive series of analogues was prepared to probe structure–activity relationships (SAR), with particular focus on the substituent patterns of each aryl domain. Quantitative analysis of these substituent SARs, using the method of cluster significance analysis, showed the lipophilicity of the substituents to be the dominant determinant of activity. One compound from the series, LY186641 (**104**, sulofenur), has progressed to Phase I clinical trials as an antitumor drug.

Introduction

The chemotherapy of neoplastic disease has made impressive advances since the first clinically active regimens were introduced in the 1940s,[1] so that today chemotherapy constitutes front-line therapy for approximately 25% of all cancer patients. The advent of truly curative chemotherapy in the mid-1960s[2] generated continuing hope that most, if not all, of the diverse spectrum of clinical tumors would eventually be curable. Unfortunately, in terms of

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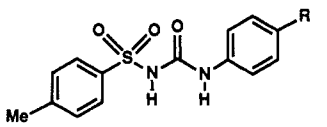
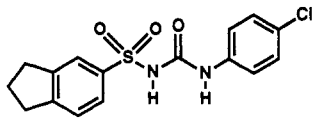
significant rates of long-term cure, progress has been largely confined to tumors of hematopoietic origin (i.e. leukemias and lymphomas). For the carcinomas and other nonhematogenous solid tumors, improvements in five-year survival rates have been at best modest, or occurred in relatively rare types of disease such as testicular cancer, and have come largely through refinement of combination protocols or hormonal manipulation. In conjunction with this has been a dramatic decline in the past 15 years of the number of new agents that have represented sufficient clinical advance to merit approval and widespread acceptance. Since nonhematogenous tumors represent more than 90% of the one million new cases of cancer diagnosed in the U.S. each year,[3] this seeming stagnation of both drug discovery and clinical progress has grim connotations for the average cancer patient.

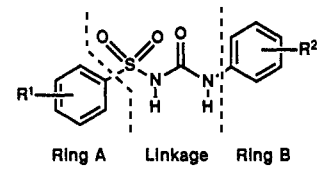
One notable consistency in the drug discovery programs in place at government, industrial, and academic labs for the past several decades has been a reliance on murine ascites leukemia models for initial screening and identification of lead structures, especially the P388 and L1210 lymphocytic leukemias. Such models played key roles in the discovery and characterization of numerous existing clinical agents. In turn, these agents have often shown their best clinical activity in a similar range of neoplasms, i.e. in leukemias and lymphomas, and been relatively inactive in most human solid tumors. It thus seems conceivable that the clinical profile for these agents is a direct consequence of the choice of experimental systems used in their original development. In response to this observation, our laboratories embarked on a program where all primary screening, as well as subsequent development work, was conducted with in vivo murine solid tumors, implanted subcutaneously.[4a] Besides providing access to nonhematogenous neoplasms, these models employ a site of tumor inoculation which provides a more realistic simulation of clinical pharmacokinetic phenomena. Since screening of new compounds on a large scale is most conveniently carried out with intraperitoneal dosing, and this same site is used for inoculation of the ascites tumors, such models present a continual risk of co-compartmentation of drug with tumor burden and resultant artifactual activity. In contrast, subcutaneously implanted tumors must vascularize to grow, and access by drugs from virtually any route of administration requires systemic absorption and delivery. Both these features adhere more closely to the realities of clinical disease and chemotherapy.

This paper describes a novel series identified in the course of screening synthetic organic compounds with our system of solid tumor models.[4,5] In addition to broad-spectrum activity in murine solid tumors and relatively low toxicity, they have structures and a mechanism of action which appear to be unrelated to known classes of oncolytics. Some of the preclinical pharmacology for two members of the series, LY186641[4] and LY181984[5] (Chart I), has been communicated previously. LY186641 has progressed to clinical development, and preliminary clinical pharmacology for it described.[6]

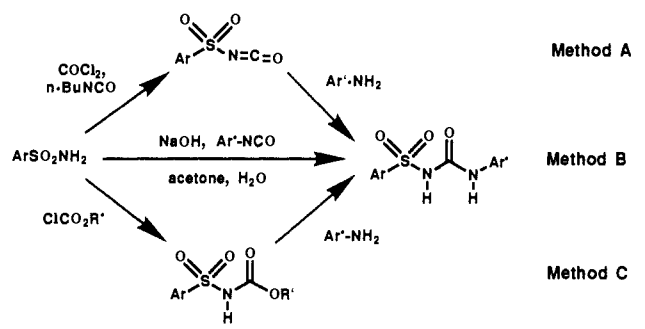
Chart I







Scheme I



Synthesis

Compounds synthesized and tested in the course of this study are listed in Table III. Nearly all of the compounds were sulfonylureas and were constructed from appropriate sulfonamide and amine (usually aniline) fragments. The fragments were first synthesized, when necessary, with the desired array of functional groups, then joined together through formation of the sulfonylurea linkage. All sulfonamides were prepared by standard literature procedures, except those required for compounds **109–111**, for which a new chlorosulfonylation process was developed.[7] Numerous reliable methods for forming sulfonylureas have been established over the years;[8–10] three methods were

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(6) Taylor, C. W.; Alberts, D. S.; Ketcham, M. A.; Satterlee, W. G.; Holdsworth, M. T.; Plezia, P. M.; Peng, Y.-M.; McCloskey, T. M.; Roe, D. J.; Hamilton, M.; Salmon, S. E. *J. Clin. Oncol.* 1989, *7*, 1733. Taylor, C. W.; Alberts, D. S.; Ketcham, M. A.; Peng, Y. M.; Satterlee, W. G. *Proc. Am. Soc. Clin. Oncol.* 1988, *7*, 60. Kuhn, J.; Craig, J.; Havlin, K.; Brown, T.; Beougher, K.; Von Hoff, D.; Satterlee, W.; Hamilton, M.; Grindey, G. *Proc. Am. Soc. Clin. Oncol.* 1988, *7*, 60. Kuttesch, J.; Hainsworth, J.; Satterlee, W.; Hamilton, M.; Grindey, G.; Hande, K. *Proc. Am. Soc. Clin. Oncol.* 1988, *7*, 63. Brown, T.; O'Rourke, T.; Craig, J.; Havlin, K.; Kuhn, J.; Cagnola, J.; Hamilton, M.; Grindey, G.; Satterlee, W.; Von Hoff, D. *Proc. Am. Soc. Clin. Oncol.* 1989, *8*, 70.

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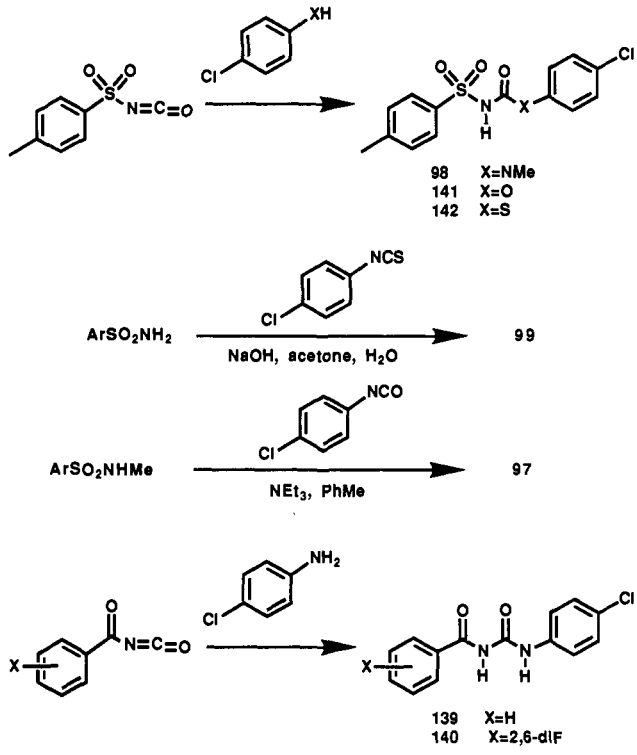
(8) Kurzer, F. *Chem. Rev.* 1952, *50*, 1.

(9) Ulrich, H. *Chem. Rev.* 1965, *65*, 369.

(10) Petersen, S. *Chem. Ber.* 1950, *83*, 551.

Scheme II



used for all compounds in this study (Scheme I). In method A, the sulfonylurea was generated by direct reaction of a substituted amine with a sulfonyl isocyanate in an inert, aprotic solvent.[8,9] This method was preferred when the sulfonyl isocyanate was available because the product generally precipitated from the reaction mixture and could be isolated in high yield and purity by simple filtration. Sulfonyl isocyanates were prepared from the corresponding sulfonamides by reaction with phosgene and a catalytic quantity of *n*-butyl isocyanate in chloro- or dichlorobenzene at high temperature.[11] The disadvantages of method A were the danger and inconvenience of working with phosgene at elevated temperature, along with the extreme moisture sensitivity of sulfonyl isocyanates. In method B, the preformed sodium salt of a sulfonamide was reacted with an isocyanate in aqueous acetone; the intermediate soluble sodium salt of the sulfonylurea was precipitated with acid and collected.[10] Method C was in essence a variation of method A, wherein a sulfonylcarbamate served as a masked, less reactive form of the sulfonyl isocyanate.[8] The coupling was performed under similar conditions, except that higher temperatures were required to induce reaction of the amine component with the carbamate. Sulfonamides were converted to the requisite sulfonylcarbamates by reaction with ethyl chloroformate in the presence of potassium carbonate (see Experimental Section).

Compounds **97–99** and **139–142**, which contain modifications of the sulfonylurea linkage, were constructed by using closely analogous procedures (Scheme II and Experimental Section).

Discovery and Antitumor Activity

Tumor models used in the discovery and development of this series were all syngeneic murine solid tumors, previously described in the literature (see Experimental Section). Tumors were grown subcutaneously in an axillary site from a trochar-implanted tumor fragment.

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Table I. Initial in Vivo Antitumor Activity of Compound 1

model	dose, mg/kg	route/schedule	toxic/ total[a]	percent inhibition
CA-755 mammary	100	ip/daily × 10	1/7	13
adenocarcinoma	50	ip/2 × daily × 10	2/10	87
	150	po/daily × 10	3/10	94
X-5563 multiple	100	ip/daily × 10	1/7	64
myeloma	150	po/daily × 10	3/10	77
6C3HED	100	ip/daily × 8	0/10	81
lymphosarcoma	200	ip/days 1-5-9	1/10	49
	50	po/2 × daily × 8	3/10	84
	200	po/daily × 8	1/10	100

[a] Number of drug-related deaths/total animals in treatment group.

Treatment of tumor-bearing animals with test compounds was generally initiated the day following implantation and continued for a period of 8–10 days. During this time large, well-defined tumors grew in untreated control groups. A positive response, i.e. reduction of tumor volume in a treated group relative to untreated controls, was expressed as percent inhibition of tumor growth. At higher doses, a number of analogues produced drug-related toxic deaths; all antitumor effects reported, however (Tables I–III), were at doses for which <30% (generally <20%) drug-related toxicity occurred. For the model used in structure–activity work, the 6C3HED lymphosarcoma, the standard protocol allowed 8 days of growth following implantation, with daily dosing by the oral route (see below).

Initial screening was carried out in the X5563 myeloma and CA-755 mammary adenocarcinoma models,[4a] using broadly based sources of candidate structures. From this the lead compound in the series, **1**, was identified as having potentially interesting antitumor activity (Table I). The activity of **1** seen with the initial ip dosing was only modest in the X5563 model (64%), and nonexistent in the CA-755 model (13%). Activity improved dramatically, however, when daily dosing was combined with oral administration. The superiority of this combination of route and schedule was evident in other models as well, e.g. the 6C3HED (Garner) lymphosarcoma (Table I). Evaluation of **1** was then extended into a large panel of syngeneic rodent solid tumors (Table II). Good to excellent activity was found across an impressive spectrum of histologic types. Structural modification of **1** led to several compounds with significantly enhanced activity (see next section), which was expressed throughout the spectrum panel, as seen for analogues **17** and **104** (Table II). In general, the models in this panel were relatively resistant to existing clinical agents. Even at optimum schedules, agents such as vincristine, cisplatin, methotrexate, and 5-FU showed a spectrum of activity clearly inferior to that of **1** and later sulfonylurea analogues.[12] Curiously, compounds of this series seemed to be essentially devoid of activity in the traditional murine ascites leukemia models, e.g. P388 and L1210 (Table II). This raises the possibility that compounds related to **1**, in either structure or mechanism of action, have been missed in previous screening operations that utilized such models. Additional testing of **104** was carried out against a variety of human tumors carried as xenografts in nude mice. Good to excellent activity was found against the National Cancer Institute panel of xenografts (MX-1, CX-1, LX-1)[4a,12] and against panels of human colon carcinomas[4a,12,13] and pediatric rhabdomyosarcomas.[14] Taken together, the activity in rodent and

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(13) Houghton, P. J.; Houghton, J. A.; Grindey, G. B. *NCI/EORTC Symposium on New Drugs in Cancer Therapy* **1989**, *6*, Abstract No. 426.

Table II. In Vivo Spectrum of Antitumor Activity of Diarylsulfonylureas with Daily Oral Dosing for 10 Days

model	type	% inhibition[b,h] 1	17	104[a]
solid tumors				
6C3HED	lymphosarcoma[c]	+++	+++	+++
CA-755	mammary adenocarcinoma	++	+++	+++
C3H	mammary adenocarcinoma	++	++	+++
C-26	colon carcinoma	++	++[d]	+++
M-5	ovarian carcinoma	++[d]	+++[d]	+++
P1534J	lymphatic leukemia	+++[e]	+++	nt
X5563	plasma cell myeloma	+	++	+
B-16	melanoma (solid)	-	+	-
Lewis	lung carcinoma	+	-	-
Madison	lung carcinoma	nt[g]	nt	++
Yoshida	sarcoma (rat)	++	+	nt

model	type	% increase in life span[b,h] 1	17	104
ascites tumors				
P388	lymphocytic leukemia	-	-	+
L1210V	lymphocytic leukemia	-[f]	-	nt
B-16	melanoma (ascites)	-	nt	nt

[a] All models dosed twice daily for 10 days, except 6C3HED (twice daily for 8 days). [b] At highest nontoxic dose (<30% drug-related deaths). [c] Oral dosing for 8 days. [d] Dosing delayed 3 days following implantation, then dosed daily for 10 days. [e] Dosed twice daily for 10 days. [f] Dosed daily for 9 days. [g] nt = not tested. [h] Solid tumors (sc implant): +++, 95–100% inhibition; ++, 80–94%; +, 60–79%; -, <60%. Ascites tumors (ip implant): +++, 200+% ILS; ++, 100–199%; +, 50–99%; -, <50%.

human tumor models is so broad that the prospects for clinical activity must be viewed as quite promising.

For all analogues entered into spectrum testing, the highest degree of activity was consistently found with the 6C3HED lymphosarcoma, and it was accordingly chosen as the sensitive model for structure–activity investigations. Dose–response experiments were routinely performed in this model with all highly active compounds. Characteristic dose–response curves for the original lead (**1**), two of the best compounds (**17**, **104**), and a representative inactive analogue (**34**) are shown in Figure 1. Complete inhibition of tumor growth, with no drug-related toxicity, was achieved at several doses with the best compounds. While members of the series were not exceptionally potent, their low acute toxicity gives them a therapeutic index (ratio of LD_{50} to ED_{50}) superior to that of most known oncolytics, ranging as high as ten in sensitive models (e.g. as in Figure 1).

Antitumor Structure–Activity Relationships

The antitumor activity of this series is associated with the *N*-(phenylsulfonyl)-*N'*-phenylurea structure,[15] exemplified by the lead compound **1**. Effects of structural modification were explored within three domains of this structure (Chart I): ring A bonded to the sulfonyl group,

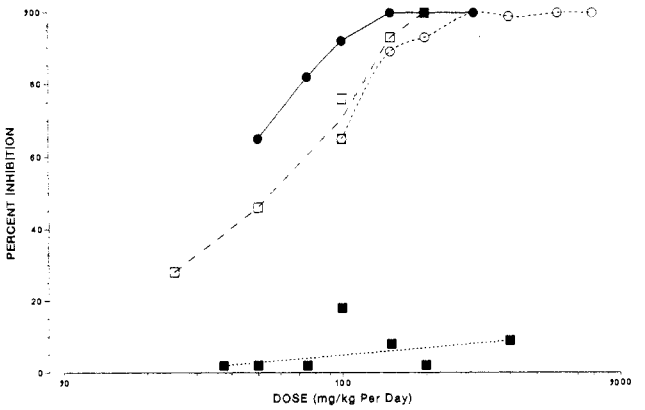

Figure 1. Antitumor activity of diarylsulfonylureas against 6C3HED lymphosarcoma (daily oral dosing for 8 days). Compounds are as follows: □, **1**; ●, **17** (LY181984); ■, **34**; ○, **104** (LY186641, dosed twice daily).

ring B bonded to the urea nitrogen, and the sulfonylurea linkage itself. New analogues were routinely tested in the 6C3HED model with daily oral administration for 8 days by using set screening doses of 300 and 150 mg/kg per day (Table III). With few exceptions, compounds were tolerated without undue toxicity at one or both of these dose levels. Activity reported in Table III is for the highest tolerated dose (fewer than 30% drug-related deaths in treated group). Compounds producing inhibitions less than ca. 60% were generally regarded as inactive, especially by comparison with the most highly active analogues.

Among the three domains, the least flexibility toward structural changes was found in the linkage, since every one thus far attempted resulted in complete abolition of activity (at least in the 6C3HED model with oral dosing). The linkage analogues synthesized were generally derivatives of the highly active **17**. Thus sulfonylthiourea **99**, sulfonylcarbamate **141**, and sulfonylthiocarbamate **142**, although identical with **17** in both aryl regions, were lacking in any significant activity. Likewise, substitution of either nitrogen of **17** with even a methyl group (**97** and **98**) produced inactive analogues. The closely homologous benzoylurea **139** was also devoid of activity, as was the related difluorobenzoylurea **140**, for which modest antitumor activity has been claimed[16] in other systems. The inactivity of **99**, **139**, and **140** did not simply reflect lack of oral absorption, since changing the route of administration to ip did not improve activity. While not an exhaustive survey of sulfonylurea replacements, it is evident that trivial substitutions are not productive.

The requirements for activity in each aryl region were also well-defined, although less restrictive than in the linkage. In both cases, the phenyl moiety found in the original lead, **1**, seemed to have optimal properties. For ring B, no other ring system tested (compounds **126–138**) gave any significant activity, even when substituted similarly to the most active phenyl analogues (cf. **131** and **17**). Somewhat more leeway was available with ring A. Although a 3-pyridyl replacement (**102**) was inactive, the annelated aromatic 2-naphthyl system proved to be exceptional; compound **101** was comparable to **17** in nearly every respect.

Because the diphenylsulfonylurea structure seemed central, if not essential, to the antitumor activity of the series, it was chosen as a platform for the exploration of substituent effects. The substituents on each ring were

(14) Houghton, P. J.; Myers, L.; Cheshire, P.; Grindey, G. B.; Houghton, J. A. *Proc. Am. Assoc. Cancer Res.* **1989**, *30*, 577. Houghton, P. J.; Houghton, J. A.; Myers, L.; Cheshire, P.; Howbert, J. J.; Grindey, G. B. *Cancer Chemother. Pharmacol.* **1989**, *26*, 84.

(15) The only activity consistently ascribed to such structures previously has been lowering of blood sugar: (a) Ruschig, H. v.; Korger, G.; Aumuller, W.; Wagner, H.; Weyer, R.; Bander, A.; Scholz, J. *Arzneim.-Forsch.* **1958**, *8*, 448. (b) Onisi, S. J. *Pharm. Soc. Jpn.* **1959**, *79*, 632. (c) Holland, G. F.; Jaeger, D. A.; Wagner, R. L.; Laubach, G. D.; McLamore, W. M.; P'an, S. Y. *J. Med. Pharm. Chem.* **1961**, *3*, 99. (d) Gandhi, T. P.; Jindal, M. N. *Arzneim.-Forsch.* **1971**, *21*, 968. (e) Soliman, R.; Mokhtar, H.; Mohamed, H. *J. Pharm. Sci.* **1983**, *72*, 1004. (f) Soliman, R.; Darwish, S. A. R. *J. Med. Chem.* **1983**, *26*, 1659.

(16) Jenkins, V. K.; Mayer, R. T.; Perry, R. R. *Invest. New Drugs* **1984**, *2*, 19.

systematically varied with respect to size, electronic character, and position; this was pursued for each ring more or less independently of the other. The highly active **17** again served as a point of departure. Thus a set of compounds varied on ring B was produced, in which the substituent on ring A was kept constant at 4-methyl (**1–54**, **112–114**, **116**). Similarly, a set of ring A analogues, in which the ring B substituent was constant (generally) at 4-chloro, was synthesized (e.g. **58**, **60**, **62**, **65**, etc.; see set 3 in Table IV for a complete listing). In these two sets, it was again evident that the active patterns on ring B were more limited than on ring A. In sum, ring B seemed to require a small, neutral, lipophilic group in the 4-position, lacking strong conjugative interaction, either donating or withdrawing, with the ring. The only 4-substituents which gave indisputable activity were methyl, CF_3, and halogen, with a rank order of activity of Cl ≈ Br > CF_3 > Me ≈ F > I.[17] Substitution of the 4-position of ring B with a wide range of electron-donating or conjugative-electron-withdrawing groups uniformly abolished activity. Limits on the size of the 4-substituent were also evident, as replacement of the methyl group of **2** with *n*-butyl produced the inactive **3**. The position of substitution proved equally crucial. Movement of a substituent that was highly active in the 4-position to the 3- or 2-position of ring B gave only inactive isomers (**26**, **31**, **33**). In combination with an active 4-substituent, groups such as halogen and methyl seemed to be tolerated at the 3-position; in fact, 3,4-dichloro compounds were generally as good as their 4-monochloro congeners (e.g. **39**). In contrast, substitution at the 2-position remained deleterious, even when coupled with an otherwise active 4-substituent (**36**).

On ring A, both electron-donating and neutral groups were compatible with good activity, although clear limitations on the size and positions of the groups were apparent. Any of the substituents H, Me, Et, OMe, OEt, or halo (F, Cl, or Br) gave good to excellent activity when placed in the 3- or 4-positions relative to the sulfonyl. As with ring B, however, electron-withdrawing groups were associated with poor activity (compounds **70–73**, **79–80**, **92**), regardless of position of substitution. In comparing pairs of positional isomers, the 3- and 4-isomers were generally equivalent (compounds **75–78** vs **62**, **17**, **87**, and **68**). Moving the substituent to the 2-position, however, led to a marked drop off in activity (cf. 4- vs 2-methyl in **1** and **74**). In the series of 4-alkyl-substituted homologues, **87–91**, activity underwent a fairly continuous decline as the total number of carbon atoms increased. When groups that were independently active in the 3- and/or 4-positions were used in combination, an interesting pattern emerged, wherein activity was retained until the combined size of the groups exceeded a certain limit. Thus, the high degree of activity seen with 3,4-dichloro or dimethyl substitution (**82**, **83**) disappeared with diethyl or dimethoxy (**84**, **85**). A similar trend was evident with the analogous 3,4-fused rings. The excellent activity associated with the indanyl and benzodioxolyl rings of **104** and **110** was markedly diminished in the next larger size systems (tetralyl, **108**; benzodioxanyl, **111**). This repeated dependence of activity on the size of the substituents at positions 3 and 4 of the ring A seemed to be a function of their lipophilicity rather than steric bulk (see below).

The trends in substituent structure–activity relationship (SAR) for the two phenyl rings appeared general for all diphenylsulfonylureas, implying a lack of interaction between them. A given pattern on either ring could be classed as consistently "active" or "inactive". Compounds having active patterns on both rings were always active, while the presence of an inactive pattern on either ring led to inactive compounds. Thus the active pattern 4-CF_3 on ring B was associated with good antitumor activity in compounds **1**, **56**, **61**, **66**, **81**, and **107**, where it was matched with active patterns on ring A. Each of these compounds was also somewhat less active than its 4-Cl congener, in keeping with the rank order for the most active ring B 4-monosubstituents discussed previously. The ring B 4-CF_3 group could also be found on compounds lacking antitumor activity if paired with an inactive ring A pattern (CO_2CH_3 on **72**). An example of an inherently inactive ring B pattern was 4-OMe (**10**, **69**).

Quantitative Analysis of Substituent Effects. Because antitumor activity clearly had strong dependences on the substituent patterns of both phenyl rings, a quantitative structure–activity analysis was undertaken to elucidate the physical properties responsible for these trends. Three sets of homologues were assembled, two which varied only in ring B, and one which varied only in ring A (Table IV). The compounds chosen had substitution restricted to the 3-, 4-, and/or 5-positions of each phenyl ring, so that Hammett-type aromatic substituent parameters could be appropriately used as quantitative descriptors of structure. Compounds in set 1 contained a single substituent at the 4-position of ring B. The other regions of the structure were invariant, and near the apparent optimum for activity in each region, i.e. 4-methyl substitution on ring A, and an unsubstituted sulfonylurea linkage. Set 2 was similar to set 1, but ring B was instead 3-monosubstituted, 3,4- or 3,5-disubstituted, or 3,4,5-trisubstituted. Set 3 was variable on ring A, and included compounds that were 3- or 4-monosubstituted, or 3,4-disubstituted on that phenyl ring. The fixed pattern on ring B in this set was the apparently optimal 4-chloro, except for three instances in which an analogue having 4-bromo or 4-trifluoromethyl was accepted (**65**, **80**, **94**).

Among available Hammett-type aromatic substituent parameters, π was used as a hydrophobic parameter throughout; electronic contributions were gauged by using either σ, σ^+, σ^- or the field (F) or resonance (R) components.[18–20] Attempts to describe the steric bulk of substituents with unitary indices of volume such as molar refractivity (MR),[20] the Taft steric parameter (E_s),[20,21] or Charton's van der Waals radius (E_s-ν),[22] as well as the multidimensional parameters sets of Verloop,[23] were frustrated by insufficiently extensive parameter bases or difficulties in adapting the descriptor for use with poly-

(17) For substituents producing 100% inhibition of growth in the 6C3HED model at some nontoxic dose, i.e. Cl, Br, and CF_3, the relative order reflects differences in the therapeutic index, as determined in dose–response experiments.

(18) Values generally obtained from the online computer database version of the compilation of Hansch, C. et al., Pomona College, Claremont, CA. This was supplied in the form of a tape containing the contents of ref 19, which was processed at Lilly into a 1032 database by D. B. Boyd (unpublished work). His assistance in the use of this database is gratefully acknowledged.

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Table III. Preparation, in Vivo Activity against 6C3HED Lymphosarcoma, in Vitro Cytotoxicity, and Hypoglycemic Activity for Compounds 1–142

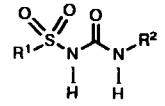
compd	R^1	R^2	method	solvent	yield, %	mp, °C	formula[a]	6C3HED lymphosarcoma[b] daily dose, mg/kg	6C3HED lymphosarcoma[b] percent inhibn	CCRF-CEM IC_{50}, μg/mL[c]	blood sugar drop/h[d]
					Diphenylsulfonylureas						
1	4-CH_3	4-CF_3	A	CH_2Cl_2	73	193–5	$C_{15}H_{13}F_3N_2O_3S$[e]	200	100	5.3[f]	36/5
2	4-CH_3	4-CH_3	A	PhMe	92	153–5	$C_{15}H_{16}N_2O_3S$	300	91	11.6[f]	39/1
3	4-CH_3	4-*n*-Bu	A	PhMe	93		$C_{18}H_{22}N_2O_3S$	300	8	19.7	40/5
4	4-CH_3	4-CH_2CN	A	PhMe	56[g]	193–4	$C_{16}H_{15}N_3O_3S$	300	10	>20	
5	4-CH_3	4-Ph	A	PhMe	100	218–20	$C_{20}H_{18}N_2O_3S$	300	0	>20	
6	4-CH_3	4-OH	*h*		88	179–80 dec	$C_{14}H_{14}N_2O_4S$	300	10	>20	
7	4-CH_3	4-OCF_3	A	CH_2Cl_2	95	185	$C_{15}H_{13}F_3N_2O_4S$[e]	300	17[f]	18.4	
8	4-CH_3	4-OCF_2H	A	CH_2Cl_2	82	160–4	$C_{15}H_{14}F_2N_2O_4S$[e]	300	15	nt[p]	
9	4-CH_3	4-OCH_2CF_3	A	Et_2O	35	178	$C_{16}H_{15}F_3N_2O_4S$[e]	300	30	>20	
10	4-CH_3	4-OCH_3	A	PhMe	60	108–10	$C_{15}H_{16}N_2O_4S$[e]	300	6	>20	55/2
11	4-CH_3	4-SCH_3	A	CH_2Cl_2	75		$C_{15}H_{16}N_2O_3S_2$	300	17	>20	
12	4-CH_3	4-OCH_2Ph	A	CH_2Cl_2	63		$C_{21}H_{20}N_2O_4S$	300	0	>20	
13	4-CH_3	4-OPh	A	PhMe	71	165–6	$C_{20}H_{18}N_2O_4S$	300	0	>20	
14	4-CH_3	4-$N(CH_3)_2$	A	PhMe/CH_2Cl_2	96		$C_{16}H_{19}N_3O_3S$	300	51	>20	
15	4-CH_3	4-I	A	CH_2Cl_2	87	197[i]	$C_{14}H_{13}IN_2O_3S$	150	76	19.6	
16	4-CH_3	4-Br	A	CH_2Cl_2	88	188–9	$C_{14}H_{13}BrN_2O_3S$	150	100	8.2	28/2
17	4-CH_3	4-Cl (LY181984)	A	PhMe	96		$C_{14}H_{13}ClN_2O_3S$	300	100	8.9	63/3
18	4-CH_3	4-F	A	CH_2Cl_2	84	172–3	$C_{14}H_{13}FN_2O_3S \cdot {}^1/_2CH_2Cl_2$	300	95	17.4	19/2
19	4-CH_3	H	A	CH_2Cl_2	72	170–2	$C_{14}H_{14}N_2O_3S$[e]	275	44	>20	
20	4-CH_3	4-CN	A	CH_2Cl_2	94		$C_{15}H_{13}N_3O_3S$	300	31	>20	
21	4-CH_3	4-CO_2Et	A	CH_2Cl_2	82		$C_{17}H_{18}N_2O_5S$	300	12	>20	
22	4-CH_3	4-CO_2-*n*-Bu	A	PhMe/CH_2Cl_2	92		$C_{19}H_{22}N_2O_5S$	300	0	>20	
23	4-CH_3	4-SO_2CH_3	A	CH_2Cl_2/MeCN	89		$C_{15}H_{16}N_2O_5S_2$	300	7	>20	
24	4-CH_3	4-SO_2NH_2	A	MeCN	93		$C_{14}H_{15}N_3O_5S_2$	300	27	>20	
25	4-CH_3	4-NO_2	A	CH_2Cl_2/MeCN	58		$C_{14}H_{13}N_3O_5S$	300	34	7.4	
26	4-CH_3	3-CH_3	A	CH_2Cl_2	90	183–5	$C_{15}H_{16}N_2O_3S$[a,e]	300	0	>20	
27	4-CH_3	3-Et	A	PhMe	92	162–3	$C_{16}H_{18}N_2O_3S$	300	0	>20	
28	4-CH_3	3-OEt	A	PhMe	91		$C_{16}H_{18}N_2O_4S$	300	6	>20	
29	4-CH_3	3-O-*n*-Pr	A	PhMe	93		$C_{17}H_{20}N_2O_4S$	300	0	>20	
30	4-CH_3	3-SCH_3	A	PhMe	98		$C_{15}H_{16}N_2O_3S_2$	300	20	>20	
31	4-CH_3	3-Cl	A	PhMe	98		$C_{14}H_{13}ClN_2O_3S$	300	13	>20	
32	4-CH_3	2-CH_3	A	PhMe	91	149–51	$C_{15}H_{16}N_2O_3S$[e]	300	32	>20	
33	4-CH_3	2-Cl	A	CH_2Cl_2	85	188–91	$C_{14}H_{13}ClN_2O_3S$	300	1	>20	
34	4-CH_3	2,3-$(CH_3)_2$	A	PhMe	79	141–2	$C_{16}H_{18}N_2O_3S$[e]	300	8	nt	
35	4-CH_3	2,3-Cl_2	A	CH_2Cl_2	84	177–9	$C_{14}H_{12}Cl_2N_2O_3S$[e]	300	37	>20	
36	4-CH_3	2,4-Cl_2	A	CH_2Cl_2	95		$C_{14}H_{12}Cl_2N_2O_3S$	300	39	>20	
37	4-CH_3	2-CF_3, 4-Cl	A	PhMe	90		$C_{15}H_{12}ClF_3N_2O_3S$	300	24	>20	
38	4-CH_3	3,4-F_2	A	PhMe	89	179–80	$C_{14}H_{12}F_2N_2O_3S$	300	60	12.8	
39	4-CH_3	3,4-Cl_2	A	CH_2Cl_2	88	199–200	$C_{14}H_{12}Cl_2N_2O_3S$	300	100	5.8	16/2
40	4-CH_3	3-CH_3, 4-Cl	A	PhMe	90	184–5	$C_{15}H_{15}ClN_2O_3S$	300	85	7.3	
41	4-CH_3	3-CH_3, 4-Br	A	PhMe	80		$C_{15}H_{15}BrN_2O_3S$	300	81	7.3	
42	4-CH_3	3-NO_2, 4-Cl	A	PhMe/CH_2Cl_2	84	199–200	$C_{14}H_{12}ClN_3O_5S$[e]	300	30	15.8	
43	4-CH_3	3-CF_3, 4-Cl	A	PhMe	81	144–5	$C_{15}H_{12}ClF_3N_2O_3S$	300	18	18.6	
44	4-CH_3	3-Cl, 4-OCH_3	A	PhMe/CH_2Cl_2	92	184–5	$C_{15}H_{15}ClN_2O_4S$	300	0	>20	
45	4-CH_3	3,4-$(OCH_3)_2$	A	PhMe	68		$C_{16}H_{18}N_2O_5S$	300	12	>20	
46	4-CH_3	2-F, 4,5-diCl	A	PhMe	87	188–9	$C_{14}H_{11}Cl_2FN_2O_3S$	300	45	13.4	

47	4-CH_3	2-CH_3, 4,5-Cl_2	A	PhMe	48[g]	185–7	$C_{15}H_{14}Cl_2N_2O_3S$[a]	300	15	16.0		
48	4-CH_3	2-OCH_3, 4,5-Cl_2	A	PhMe	30	190–1	$C_{15}H_{14}Cl_2N_2O_4S$	300	3	>20		
49	4-CH_3	3,5-$(CH_3)_2$	A	PhMe	71[g]	181–2	$C_{16}H_{18}N_2O_3S$	300	9	>20		
50	4-CH_3	3,5-F_2	A	PhMe	91	192–3	$C_{14}H_{12}F_2N_2O_3S$	300	52	>20		
51	4-CH_3	3,5-Cl_2	A	CH_2Cl_2	100		$C_{14}H_{12}Cl_2N_2O_3S$	300	21	>20		
52	4-CH_3	3,4,5-Cl_3	A	CH_2Cl_2	98		$C_{14}H_{11}Cl_3N_2O_3S$	300	44	>20	0	
53	4-CH_3	2,4,6-F_3	A	PhMe	61[g]	205–6	$C_{14}H_{11}F_3N_2O_3S$	300	27	>20		
54	4-CH_3	2,3,5,6-F_4	A	PhMe	84	196–8	$C_{14}H_{10}F_4N_2O_3S$	300	0	>20		
55	H	H	A	CH_2Cl_2	44	158–60	$C_{13}H_{12}N_2O_3S$[e]	225	35	>20		
56	H	4-CF_3	A	CH_2Cl_2	75		$C_{14}H_{11}F_3N_2O_3S$	150	81	6.0[f]	56/5	
57	H	4-Br	A	CH_2Cl_2	77	191–2	$C_{13}H_{11}BrN_2O_3S$	150	82	7.1	29/2	
58	H	4-Cl	A	CH_2Cl_2	76	180–1	$C_{13}H_{11}ClN_2O_3S$	150	100	3.8	62/5	
59	H	3,4-Cl_2	A	CH_2Cl_2	83	194–5	$C_{13}H_{10}Cl_2N_2O_3S$	150	100	1.5	41/3	
60	4-F	4-Cl	B		67		$C_{13}H_{10}ClFN_2O_3S$[e]	150	79	6.3		
61	4-Cl	4-CF_3	A	CH_2Cl_2	82	197–8.5	$C_{14}H_{10}ClF_3N_2O_3S$	150	94	5.8	0	
62	4-Cl	4-Cl	A	CH_2Cl_2	75		$C_{13}H_{10}Cl_2N_2O_3S$[e]	100	100	19.3	36/3	
63	4-Cl	4-F	A	CH_2Cl_2	98	201–2	$C_{13}H_{10}ClFN_2O_3S$[a]	300	74	14.5	55/3	
64	4-Cl	3,4-Cl_2	A	CH_2Cl_2	92	195–6	$C_{13}H_9Cl_3N_2O_3S$	150	85	9.9	17/3	
65	4-Br	4-Br	A	CH_2Cl_2	68	213–5	$C_{13}H_{10}Br_2N_2O_3S$[e]	150	100	14.1	56/5	
66	4-OCH_3	4-CF_3	A	CH_2Cl_2	71		$C_{15}H_{13}F_3N_2O_4S$	150	100	8.0	21/3	
67	4-OCH_3	4-Br	B		92		$C_{14}H_{13}BrN_2O_4S$	150	99	14.3	45/5	
68	4-OCH_3	4-Cl	A	CH_2Cl_2	72	163–5	$C_{14}H_{13}ClN_2O_4S$	150	100	12.6	51/3	
69	4-OCH_3	4-OCH_3	A	CH_2Cl_2	70	108–11	$C_{15}H_{16}N_2O_5S$[e]	300	16	15.3	21/2	
70	4-NO_2	4-Cl	A	CH_2Cl_2	80		$C_{13}H_{10}ClN_3O_5S$	300	70	12.1		
71	4-NO_2	3-CF_3	A	CH_2Cl_2	55	148–51	$C_{14}H_{10}F_3N_3O_5S$[e]	270	20	>20		
72	4-CO_2CH_3	4-CF_3	B		74		$C_{16}H_{13}F_3N_2O_5S$	150	0	2.6		
73	4-CO_2CH_3	4-Cl	B		76		$C_{15}H_{13}ClN_2O_5S$	300	49	17.4		
74	2-CH_3	4-CF_3	A	CH_2Cl_2	54	188–9	$C_{15}H_{13}F_3N_2O_3S$[e]	150	67	13.7		
75	3-Cl	4-Cl	B		79		$C_{13}H_{10}Cl_2N_2O_3S$	150	98	9.0		
76	3-CH_3	4-Cl	B		80[i]	171–3[i]	$C_{14}H_{13}ClN_2O_3S$[e]	150	100	4.3	10/2	
77	3-Et	4-Cl	B		93		$C_{15}H_{15}ClN_2O_3S$	300	95	10.4		
78	3-OCH_3	4-Cl	B		91		$C_{14}H_{13}ClN_2O_4S$	300	100	8.0		
79	3-CN	4-Cl	B		91		$C_{14}H_{10}ClN_3O_3S$	300	19	13.1		
80	3-CF_3	4-CF_3	B		89		$C_{15}H_{10}F_6N_2O_3S$	150	39	15.6		
81	3,4-Cl_2	4-CF_3	B		86		$C_{14}H_9Cl_2F_3N_2O_3S$	150	85	15.5		
82	3,4-Cl_2	4-Cl	B		82		$C_{13}H_9Cl_3N_2O_3S$	150	100	14.2		
83	3,4-$(CH_3)_2$	4-Cl	B		83		$C_{15}H_{15}ClN_2O_3S$	300	100	13.6		
84	3,4-Et_2	4-Cl	B		87		$C_{17}H_{19}ClN_2O_3S$	300	46	12.4		
85	3,4-diOCH_3	4-Cl	B		27		$C_{15}H_{15}ClN_2O_5S$	300	43	>20		
86	4-CH_2OH	4-Cl	B		42		$C_{14}H_{13}ClN_2O_4S$[e]	300	15	>20		
87	4-Et	4-Cl	B		92	176–7[i]	$C_{15}H_{15}ClN_2O_3S$[e]	150	100	7.5	33/2	
88	4-*n*-Pr	4-Cl	B		79		$C_{16}H_{17}ClN_2O_3S$	300	79	13.8		
89	4-*i*-Pr	4-Cl	B		89		$C_{16}H_{17}ClN_2O_3S$	300	65	8.7		
90	4-*t*-Bu	4-Cl	B		86		$C_{17}H_{19}ClN_2O_3S$	300	84	13.5		
91	4-*n*-octyl	4-Cl	B		92		$C_{21}H_{27}ClN_2O_3S$	300	9	9.0		
92	4-COMe	4-Cl	B		86		$C_{15}H_{13}ClN_2O_4S$	300	55	16.9		
93	4-NH_2	4-Cl	B		67		$C_{13}H_{12}ClN_3O_3S$	300	43	13.9		
94	4-NHAc	4-CF_3	B		90		$C_{16}H_{14}F_3N_3O_4S$	300	22	>20		
95	4-OEt	4-Cl	B		65		$C_{15}H_{15}ClN_2O_4S$	300	100	13.0		
96	4-OPh	4-Cl	B		69		$C_{19}H_{15}ClN_2O_4S$	300	32	19.7		
97	4-CH_3	4-Cl, N_1-CH_3	B[h]		95	123–4	$C_{15}H_{15}ClN_2O_3S$	300	17	>20		
98	4-CH_3	4-Cl, N_2-CH_3	A	CH_2Cl_2	98		$C_{15}H_{15}ClN_2O_3S$	300	30	>20		

Table III (Continued)

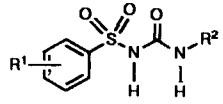
compd	R^1	R^2	method	solvent	yield, %	mp, °C	formula[a]	6C3HED lymphosarcoma[b] daily dose, mg/kg	6C3HED lymphosarcoma[b] percent inhibn	CCRF-CEM IC_{50}, μg/mL[c]	blood sugar drop/h[d]
					Diphenylsulfonylthioureas						
99	4-CH_3	4-Cl	B		25	184–5 dec	$C_{14}H_{13}ClN_2O_2S_2$	300 300[j]	35 45[j]	12.9	
					Arylsulfonylphenylureas						
100	1-naphthyl	4-Cl	B		91		$C_{17}H_{13}ClN_2O_3S$	300	29	15.2	
101	2-naphthyl	4-Cl	B		88	169–71[i]	$C_{17}H_{13}ClN_2O_3S$	300	100	11.2	0
102	3-pyridyl	4-Cl	B		82		$C_{12}H_{10}ClN_3O_3S$	300	3	7.1	
					Cyclo-fused Phenylsulfonylphenylureas						
103	5-indanyl	4-F	C	PhMe	77		$C_{16}H_{15}FN_2O_3S$	300	39	>20	
104	5-indanyl	4-Cl (LY186641)	B		77	169–72[i]	$C_{16}H_{15}ClN_2O_3S$	300	100	11.2[f]	0
			A	PhMe	88	172–3.5					
105	5-indanyl	4-Br	C	PhMe	83	168–71 dec	$C_{16}H_{15}BrN_2O_3S$	300	92	17.6	
106	5-indanyl	3,4-Cl_2	A	PhMe	85	155.5–8	$C_{16}H_{14}Cl_2N_2O_3S$	300	97	9.1	
107	5-indanyl	4-CF_3	C	PhMe	25		$C_{17}H_{15}F_3N_2O_3S$	300	71	12.0	
108	6-tetralyl	4-Cl	B		56	163–5	$C_{17}H_{17}ClN_2O_3S$	300	70	14.6	16/5
109	5-dihydrobenzofuryl	4-Cl	B		26[l]	190–4	$C_{15}H_{13}ClN_2O_4S$	300	94	16.1	
110	5-benzodioxolyl	4-Cl	B		75	189–90	$C_{14}H_{11}ClN_2O_5S$[e]	300	100	9.1	
111	6-benzodioxanyl	4-Cl	B		71[k]	191[k]	$C_{15}H_{13}ClN_2O_5S$[e]	300	49	13.5	
					Phenylsulfonyl(cyclo-fused phenyl)ureas						
112	4-CH_3	3,4-$(CH_2)_3$	A	PhMe	94		$C_{17}H_{18}N_2O_3S$	300	5	15.7	
113	4-CH_3	3,4-$(COCH_2CH_2)$	A	CH_2Cl_2/MeCN	77		$C_{17}H_{18}N_2O_4S$[e]	300	0	>20	
114	4-CH_3	3,4-(OCH_2O)	A	CH_2Cl_2	76	151–3	$C_{15}H_{14}N_2O_5S$	300	54[f]	>20	
115	4-Cl	3,4-(OCH_2O)	A	CH_2Cl_2	82	166–8	$C_{14}H_{11}ClN_2O_5S$[e]	300	28[f]	>20	
116	4-CH_3	3,4-(CH=N—NH)	A	THF	35[l]		$C_{15}H_{14}N_4O_3S$[e]	300	0	>20	
					Phenylsulfonylalkylureas						
117	4-CH_3	cyclohexyl	A	CH_2Cl_2	35		$C_{14}H_{20}N_2O_3S$	300	56	>20	
118	4-CH_3	4-CH_3-cyclohexyl (cis/trans)	A	PhMe	73[m]		$C_{15}H_{22}N_2O_3S$	300	2	>20	
119	4-CH_3	4-OH-cyclohexyl (trans)	A	MeCN	59		$C_{14}H_{20}N_2O_4S$	300	0	>20	
120	4-CH_3	*n*-Bu (tolbutamide)						600	45	nt	62/2
121	4-CH_3	CH_2Ph	A	PhMe	97		$C_{15}H_{16}N_2O_3S$[e]	300	0	>20	
122	4-CH_3	CH_2Ph-4-Cl	A	PhMe	94		$C_{15}H_{15}ClN_2O_3S$	300	56	>20	
123	4-CH_3	CH_2CH_2Ph	A	PhMe	91		$C_{16}H_{18}N_2O_3S$	300	24	>20	

Arylsulfonylalkylureas



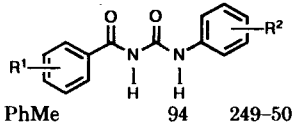
124	5-indanyl	CH_2CH_2Ph	C	PhMe	80		$C_{18}H_{20}N_2O_3S$	300	0	>20
125	2-naphthyl	CH_2CH_2Ph	C	PhMe	83		$C_{19}H_{18}N_2O_3S$	300	0	>20

Phenylsulfonylarylureas



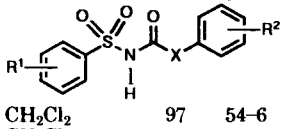
126	4-CH_3	1-naphthyl	A	PhMe	19[g]	130–1	$C_{18}H_{16}N_2O_3S$[e]	300	0	>20
127	4-CH_3	2-naphthyl	A	PhMe	89	180–1	$C_{18}H_{16}N_2O_3S$	300	5	28.0
128	4-CH_3	2-pyridyl	A	CH_2Cl_2	84	144–6	$C_{13}H_{13}N_3O_3S$[e]	300	2	>20
129	4-CH_3	3-pyridyl	A	CH_2Cl_2	97		$C_{13}H_{13}N_3O_3S$	300	1	>20
130	4-CH_3	4-pyridyl	A	CH_2Cl_2	14[n]	199–200 dec	$C_{13}H_{13}N_3O_3S$	300	24	>20
131	4-CH_3	(5-Cl)-pyrid-2-yl	A	MeCN	88		$C_{13}H_{12}ClN_3O_3S$	300	43	>20
132	4-CH_3	pyrimid-2-yl	A	DMF/CH_2Cl_2	81	271 dec	$C_{12}H_{12}N_4O_3S$	300	0	>10
133	4-CH_3	4,6-Cl_2-pyrimid-2-yl	A	DMF/CH_2Cl_2	81	195 dec	$C_{12}H_{10}Cl_2N_4O_3S$	300	0	>20
134	4-CH_3	4,6-$(CH_3)_2$-pyrimid-2-yl	A	CH_2Cl_2	48	221 dec	$C_{14}H_{16}N_4O_3S$	300	0	>20
135	4-CH_3	pyrazin-2-yl	A	CH_2Cl_2/MeCN	94		$C_{12}H_{12}N_4O_3S$	300	0	>20
136	4-CH_3	5-*t*-Bu-isoxazol-3-yl	A	PhMe	77	98–101	$C_{15}H_{19}N_3O_4S$[e]	300	5	nt
137	4-CH_3	1,2,4-triazol-3-yl	A	DMF/THF	93	250–3	$C_{10}H_{11}N_5O_3S$	300	0	>20
138	4-CH_3	1,3,4-thiadiazol-2-yl	A	DMF/CH_2Cl_2	71[o]	229 dec	$C_{10}H_{10}N_4O_3S_2$	300	16	>20

Diphenylacylureas



139	H	4-Cl	A	PhMe	94	249–50	$C_{14}H_{11}ClN_2O_2$[e]	300	7	>20
								300[j]	0[j]	
140	2,6-diF	4-Cl (diflubenzuron)						300	6	>20
								1600[j]	33[j]	

Other Linkage Analogues



141	4-CH_3	4-Cl, X = O	A	CH_2Cl_2	97	54–6	$C_{14}H_{12}ClNO_4S$	300	43	>20
142	4-CH_3	4-Cl, X = S	A	CH_2Cl_2	74	152–3	$C_{14}H_{12}ClNO_3S_2$	150	33	0.9

[a] Elemental analyses (C, H, N, S) for all new compounds were within ±0.4% of theoretical values, except where sulfur was not analyzed (footnote e), and as follows: **26**, C calcd 59.19, found 58.56; **47**, S calcd 8.59, found 9.05; **63**, S calcd 9.75, found 9.26. Acceptable analyses (±0.4%) were found for additional elements for the following compounds: Cl: **33**, **36**, **58**, **60**, **68**, **87**, **139**, 141, 142; I: 15; F: **60**. [b] Daily oral dosing for 8 days. [c] Concentration which inhibited growth of CCRF-CEM cells grown in culture for 72 h to 50% of control growth. [d] (Maximum reduction in blood glucose in mg/dL relative to predosing glucose level)/(time in hours at which maximum reduction occurred). [e] Sulfur not analyzed. [f] Average of two experiments. [g] After recrystallization from PhMe/MeCN. [h] See Experimental Section. [i] After recrystallization from PhMe. [j] ip dosing, daily for 8 days. [k] After recrystallization from THF/hexane. [l] After HPLC (see Experimental Section). [m] After recrystallization from hexane/CH_2Cl_2. [n] After two cycles of treatment per footnote o. [o] After dissolution in 1 N NaOH, filtration, and reprecipitation with 1 N HCl. [p] nt = not tested.

Table IV. Aromatic Substituent Parameters Used in Quantitative Structure–Activity Analysis

compound set			substituent							partial
1	2	3	pattern	π	σ	σ^+	σ^-	F	R	VDW vol[a]
24			4-SO_2NH_2	−1.82	0.57	0.57[b]	0.94	0.41	0.19	44.3
23			4-SO_2Me	−1.63	0.72	0.72[b]	0.78	0.54	0.22	50.5
20			4-CN	−0.57	0.66	0.66	1.00	0.51	0.19	17.2
		73	4-CO_2Me	−0.01	0.45	0.49	0.64	0.33	0.15	44.7
21			4-CO_2Et	0.51	0.45	0.48	0.64	0.33	0.15	61.7
22			4-CO_2-*n*-Bu	1.62	0.45[c]	0.48[c]	0.67	0.33[c]	0.15[c]	95.8
		92	4-COMe	−0.55	0.50	0.50[b]	0.87	0.32	0.20	35.3
25		*70*	4-NO_2	−0.28	0.78	0.79	1.17	0.67	0.16	22.8
6			4-OH	−0.67	−0.37	−0.92	−0.37	0.29	−0.64	8.1
10		*68*	4-OMe	−0.02	−0.27	−0.78	−0.14	0.26	−0.51	25.5
		95	4-OEt	0.51[d]	−0.24	−0.81	−0.28	0.22	−0.44	42.5
13		96	4-OPh	2.08	−0.03	−0.50	−0.10	0.34	−0.35	81.0
12			4-OCH_2Ph	1.66	−0.23	−0.66	−0.23[b]	0.24[e]	−0.45[e]	98.0
9			4-OCH_2CF_3	1.21[d]	0.02[b]	0.02[b]	0.02[b]	0.26[e]	−0.22[e]	57.4
8			4-OCF_2H	0.31	0.18	0.18[b]	0.11	0.35	−0.14	35.4
7			4-OCF_3	1.04	0.35	0.35[b]	0.27	0.38	0.00	40.3
11			4-SMe	0.61	0.00	−0.60	0.21	0.20	−0.18	35.6
		93	4-NH_2	−1.23	−0.66	−1.30	−0.15	0.02	−0.68	11.0
		94	4-NHAc	−0.97	0.00	−0.60	−0.46	0.28	−0.26	47.6
14			4-NMe_2	0.18	−0.72	−1.70	−0.12	0.10	−0.92	46.0
2		*17*	4-Me	0.56	−0.17	−0.31	−0.17	−0.04	−0.13	16.9
		87	4-Et	1.02	−0.15	−0.30	−0.19	−0.05	−0.10	33.9
		88	4-*n*-Pr	1.55	−0.13	−0.29	−0.06	−0.06	−0.08	51.0
		89	4-*i*-Pr	1.53	−0.15	−0.28	−0.09	−0.05	−0.10	50.9
3			4-*n*-Bu	2.13	−0.16	−0.29	−0.12	−0.06	−0.13	68.0
		90	4-*t*-Bu	1.98	−0.20	−0.26	−0.13	−0.07	−0.13	67.4
		91	4-*n*-octyl	4.24[d]	−0.16[b]	−0.30[b]	−0.15[b]			136.1
		86	4-CH_2OH	−1.03	0.00	−0.04	0.08	0.00	0.00	25.2
4			4-CH_2CN	−0.57	0.01	0.16	0.11	0.21[e]	−0.18[e]	34.2
5			4-Ph	1.96	−0.01	−0.18	0.10	0.08	−0.08	72.5
19		*58*	H	0.00	0.00	0.00	0.00	0.00	0.00	0.0
18		*60*	4-F	0.14	0.06	−0.07	0.05	0.43	−0.34	4.7
17		*62*	4-Cl	0.71	0.23	0.11	0.27	0.41	−0.15	13.8
16		*65*	4-Br	0.86	0.23	0.15	0.28	0.44	−0.17	18.2
15			4-I	1.12	0.18	0.14	0.27	0.40	−0.19	24.4
1			4-CF_3	0.88	0.54	0.61	0.65	0.38	0.19	31.7
		79	3-CN	−0.57	0.56	0.56	0.68			17.2
		78	3-OMe	−0.02	0.12	0.05	0.13			25.5
	28		3-OEt	0.51[d]	0.10	0.05[f]	0.12			42.5
	29		3-O-*n*-Pr	1.04[d]	0.10	0.05[f]	0.13[f]			59.5
	30		3-SMe	0.61	0.15	0.16	0.23			35.6
	26	*76*	3-Me	0.56	−0.07	−0.07	−0.03			16.9
	27	*77*	3-Et	1.02	−0.07	−0.06	−0.10			33.9
	31	*75*	3-Cl	0.71	0.37	0.40	0.36			13.8
		80	3-CF_3	0.88	0.43	0.52	0.49			31.7
	114	*110*	3,4-OCH_2O-	−0.05	−0.16	−0.68	(−0.01)[h]			23.4
		111	3,4-OCH_2CH_2O-	−0.12[g]	−0.12	(−0.73)	(−0.01)			39.7
		109	3,4-CH_2CH_2O-	0.01[g]	(−0.34)	−0.98	(−0.17)			31.7
	112	*104*	3,4-$(CH_2)_3$-	1.20	−0.26	−0.41	(−0.20)			39.9
		108	3,4-$(CH_2)_4$-	1.76[d]	−0.48	−0.41	(−0.20)			56.4
	113		3,4-$COCH_2CH_2$-	−0.48[d]	(0.21)	(0.07)[b]	(0.15)			41.5
	127	*101*	3,4-CH=CHCH=CH-	1.32	0.04	−0.14	0.05			43.8
	45	85	3,4-$(OMe)_2$	0.08	−0.12	(−0.73)	(−0.01)			50.8
		83	3,4-Me_2	0.99	−0.30	(−0.38)	(−0.20)			33.7
		84	3,4-Et_2	(2.04)	(−0.22)	(−0.36)	(−0.29)			67.7
	38		3,4-F_2	(0.28)	(0.40)	(0.28)	(0.39)			9.5
	39	*82*	3,4-Cl_2	1.25	0.52	(0.51)	(0.63)			27.7
	40		3-Me, 4-Cl_2	1.29	0.17	(0.04)	(0.24)			30.7
	41		3-Me, 4-Br	(1.42)	(0.16)	(0.08)	(0.25)			35.0
	42		3-NO_2, 4-Cl	0.11	0.90	(0.78)	(1.07)[b]			36.2
	43		3-CF_3, 4-Cl	(1.59)	(0.66)	(0.63)	(0.76)			45.4
	44		3-Cl, 4-OMe	(0.69)	0.27	(−0.38)	(0.22)			39.2
	49		3,5-Me_2	1.07	−0.17	(−0.14)	(−0.06)			33.8
	50		3,5-F_2	(0.28)	(0.68)	(0.70)	(0.68)			9.4
	51		3,5-Cl_2	1.25	0.75	(0.80)	(0.72)			27.6
	52		3,4,5-Cl_3	(2.13)	(0.97)	(0.91)	(0.99)			41.5

[a] In Å^3 relative to hydrogen. Actual volume of benzene = 84.3 Å^3. [b] Estimated by using trends in related substituents. [c] Value for CO_2Et. [d] Estimated from model substituted benzenes by using CLOGP program (Weininger, D.; Leo, A. Medicinal Chemistry Project, Pomona College, Claremont, CA. Implemented at Lilly with an interface for retrieval of structures from MACCS, format conversion, and other functions, by D. B. Boyd (unpublished work)). [e] Calculated from σ_p and σ_m values in this table, by using formulas 2 and 3 in ref 20. [f] Value for OMe. [g] Computed by using measured partition coefficients of substituted benzenes (1,4-benzodioxan, log P = 2.01, Jow, P.; Hansch, C., Pomona College, unpublished work. 2,3-dihydrobenzofuran, log P = 2.14, Pratesi, P.; Grana, E.; Grieco, C.; et al. *Il Farmaco* **1979**, *34*, 580.) [h] Values in parentheses estimated by simple additivity and by employing the distinct values for the meta and para positions in the case of σ and its variants. This approach has previously been found reliable for π, as well as most combinations of substituents for σ.[20]

Table V. Results of Cluster Significance Analysis (CSA)

compd set	total compds	active compds	total combinations
1	25	6	177 100
1 + 2	47	9	1 362 649 145
3	35	23	834 451 800

compd set	dimensions	substituent parameters	sample size	no. as tight	p (±95% confidence limit)
1	1	π	177 100	596	0.003 365 3
1	1	σ	177 100	18 046	0.101 90
1	1	σ^+	177 100	10 215	0.057 679
1	1	σ^-	177 100	24 148	0.136 35
1	1	field	177 100	103 589	0.584 92
1	1	resonance	177 100	26 030	0.146 98
1	1	volume	177 100	1 021	0.005 765 1
1	2	π, σ	177 100	1 394	0.007 871 3
1	2	π, σ^+	177 100	412	0.002 326 4
1	2	π, σ^-	177 100	2 881	0.016 268
1	2	π, volume	177 100	29	0.000 163 75
1	2	σ, vol	177 100	529	0.002 987 0
1	2	σ^+, vol	177 100	322	0.001 818 2
1	2	σ^-, vol	177 100	1 439	0.008 125 4
1 + 2	2	π, σ	200 000	913	0.004 565 ± 0.000 295
1 + 2	2	π, σ^+	200 000	440	0.002 200 ± 0.000 205
1 + 2	2	π, volume	200 000	251	0.001 255 ± 0.000 155
1 + 2	2	σ, vol	200 000	327	0.001 635 ± 0.000 177
1 + 2	2	σ^+, vol	200 000	167	0.000 835 ± 0.000 127
3	1	π	400 000	34	0.000 085 ± 0.000 029
3	1	σ	100 000	23 233	0.232 330 ± 0.002 618
3	1	σ^+	100 000	6 934	0.069 340 ± 0.001 575
3	1	σ^-	100 000	23 925	0.239 250 ± 0.002 644
3	1	volume	100 000	5 434	0.054 340 ± 0.001 405
3	2	π, σ^+	100 000	16	0.000 160 ± 0.000 078
3	2	π, volume	100 000	232	0.002 320 ± 0.000 298
3	2	σ^+, vol	100 000	423	0.004 230 ± 0.000 402

substituted systems. In order to arrive at a uniform measure of volume for all patterns involved in the analysis, it was decided to use the aggregate Van der Waals (VDW) volume of all the substituents in a given pattern, relative to an unsubstituted benzene ring.[24] While this measure of volume is inherently devoid of directionality, and so poorly distinguished between similar groups with differing types of branching (e.g. *n*- vs *tert*-butyl), or differing points of substitution by the same groups (e.g. 3,4- and 3,5-dichloro), these limitations are shared to some extent by all volume descriptors which rely on a single parameter. The advantage of the present method was the ability to parmeterize any arbitrarily complex collection of substituents, regardless of their number or points of attachment.

Although several methods of employing aromatic substituent parameters in quantitative structure–activity relationships (QSAR) have been developed, none has achieved universal applicability. The choice of method for analyzing the present system was steered primarily by the nature of the biological data, which was in the form of percent inhibition of tumor growth in an in vivo model, determined for the most part at fixed doses. This placed certain limitations on the ability to discriminate relative degrees of activity, especially at the upper and lower ends of the scale. Thus, all compounds which gave 100% inhibition at some dose were not distinguished, even though their therapeutic indices might be quite different. Similarly, it was found that variability in response was greatest at low degrees of activity, such that most inhibitions in the range 0% to 30–35% could not reliably be said to differ, at least without several replications of the data. These compressions at the ends of the activity scale are a predictable consequence of determining response at fixed doses, rather than determining the dose required for a fixed response.[26] They do, however, make a linear-regression-type treatment of the data problematic. Attention was therefore turned to pattern recognition methods. All three sets of homologues were first segregated into two classes, active or inactive, with activity defined as greater than 60% inhibition in the 6C3HED tumor model. Compounds active by this criterion are designated in Table IV in italics. This classification produced six actives out of a total of 25 compounds in set 1, three actives out of 22 total in set 2, and 23 actives out of 35 total in set 3. Each set was then plotted in a variety of one- and two-dimensional parameter spaces, to produce graphical representations of the sort introduced by Craig.[27] Unfortunately, with each set several choices of parameter axes resulted in obvious clustering of the actives in restricted portions of the plots, such that the best combination could not be confidently selected solely by visual inspection.

(24) Calculated by building various substituted benzenes with MACROMODEL (V1.5: Still, W. C.; et al, Dept. of Chemistry, Columbia Univ., New York, NY), energy minimizing each structure (MM2 force field), and then computing the total volume of the structure with the program VAXVOL.[25] The volume of benzene (84.3 Å^3) was subtracted from each total volume, and the remainder expressed as the partial VDW volume of the substituent or substituent pattern (Table IV). For substituents with significant conformational flexibility (e.g. *n*-alkyl groups), the most extended conformation was used.

(25) VAXVOL is a FORTRAN program written by Bob Hermann (Lilly Research Laboratories) and his assistance in its modification and use is greatly appreciated. VAXVOL converts a structure into a set of overlapping spheres, each centered on an atom and having the Van der Waals radius of that atom (radii adapted from Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441, in angstroms): H 1.2, C 1.7, N 1.55, O 1.52, S 1.8, F 1.47, Cl 1.75, Br 1.85, I 1.98). The structure is then superimposed on a three-dimensional grid having unit resolution of 0.05 A, and its volume derived by counting the grid points which lie within the volume of any sphere.

(26) Martin, Y. C. *Quantitative Drug Design*; Marcel Dekker: New York, 1978; p 118.

(27) Craig, P. N. *J. Med. Chem.* **1971**, *14*, 680.

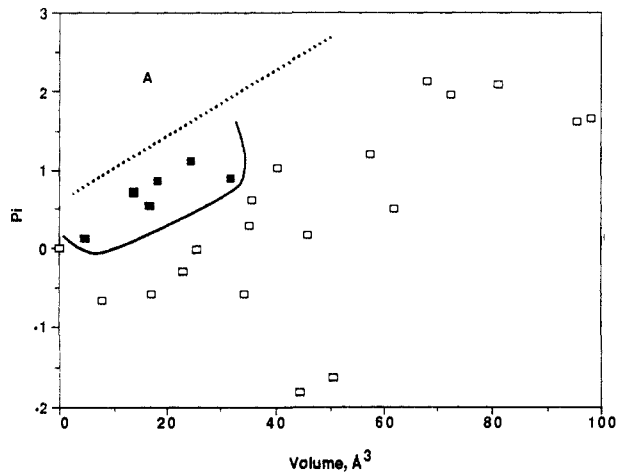


Figure 2. In vivo activity of compound set 1 (ring B 4-monosubstitution) plotted vs π and volume. ■, active; □, inactive.

A quantitative assessment of pattern was attained using the statistical algorithm of cluster significance analysis (CSA).[28,29] In CSA, groups of points are randomly selected from the total set of actives and inactives, and the mean squared interpoint distance (MSD) within each trial group compared to that of the true active group. The fraction of trial groups having MSDs less than that of the true active group is expressed as the probability (p value) that the actual clustering was due to random chance alone. Ideally, all possible combinations of points are tested, but as shown at the top of Table V for set 1 + 2 and set 3, the number of trial groups frequently exceeds computational feasibility. In these situations, a sufficiently large random sample is taken so that the uncertainty in the p value obtained is acceptable.

As shown in Table V, compound set 1 was analyzed by CSA in one dimension with respect to the hydrophobicity π, volume (partial VDW volume), and electronic character (σ, σ^-, σ^+, field, resonance) of the ring B 4-substituent of the analogues. Among these, π and volume produced clustering much superior to any electronic parameter, with π being slightly better ($p = 0.0034$). Among the electronic parameters, σ^+ was the best, and the only one whose p value approached statistical significance ($p = 0.058$). In two-dimensional combinations of parameters, it was perhaps not surprising that π and volume together gave by far the best clustering ($p = 0.000\,16$), since they were the two best parameters separately. While it was conceivable this improvement arose artifactually due to colinearity between π and volume, this appeared to be excluded by the modest degree of correlation of the two parameters ($R = 0.525$ for the 25 analogues in set 1). It was interesting that the addition of σ^+ to π in a two-dimensional analysis did not much improve the clustering evident with π alone ($p = 0.0023$ vs 0.0034), whereas some improvement was seen in going from volume alone to volume plus σ^+, enough to perhaps be meaningful ($p = 0.0018$ vs 0.0058). The clustering obtained in set 1 with π and volume as parameter axes is shown graphically in Figure 2. A clean separation of active and inactive regions of parameter space is evident. In addition, since region A of the graph (above the dotted line) is effectively inaccessible to real-world substituents, the active domain is in a sense bounded on that side as well.

(28) McFarland, J. W.; Gans, D. J. *J. Med. Chem.* **1986**, *29*, 505. *Ibid.* **1987**, *30*, 46.
(29) The CSA algorithm was implemented at Lilly in VAX FORTRAN by J. J. Howbert. All parameter axes were normalized to a standard deviation of unity prior to analysis.

Since compound set 2 contained so few actives, it was not analyzed separately, but combined with set 1 to produce the superset designated 1 + 2. This superset was analyzed in several of the same two-dimensional spaces used with set 1, and in no case was the p value obtained improved by more than a factor of 2.2 over set 1, and in the case of π plus volume, the best combination for set 1, the p value was dramatically worse. Because set 2 adds nothing to the quality of clustering already obtained with set 1, it apparently cannot be appropriately coanalyzed with the same descriptors as set 1. The possibility remains that additional parameter scales, or combinations of scales in more than two dimensions, would uncover an enhanced degree of clustering in superset 1 + 2. At present, however, there appear to be fundamental differences between sets 1 and 2 which transcend the physical properties of the substituents per se. This was characterized above as a "positional requirement" for activity, where groups such as chloro are highly active in the 4-position, but become inactive when moved to the 3-position. In this sense, the properties of the substituents seem to be exerted in a spatially localized fashion, rather than being transmitted through the ring. This could indicate the sulfonylureas operate through a stereospecific binding or other drug-target interaction, to which the active substituents make a specific contribution. Other possibilities would include position-dependent influences on overall conformation or orientation at a target, though these seem unlikely given the remoteness of the 4-substituent from other rotatable bonds in the structure.

Initial analysis in one dimension of the ring A analogues in set 3 showed that π was by far the best single descriptor of activity, having a remarkably low p value of 0.000 085. Among other parameters tested singly, only σ^+ and volume produced clustering that even approached significance ($p = 0.069$ and 0.054). The result with π alone could not be improved, and was in fact worsened, when π was taken in combination with σ^+ or volume. The hydrophobicity of the substituents was thus established as the parameter controlling the contribution of ring A to in vivo activity.

In interpreting the findings from CSA on this series, one salient fact emerges, namely the preponderance of hydrophobicity as a determinant of activity. Of two parameter types involved in the best clustering for ring B substituents, one was π, and π was also the only parameter which produced significant clustering with ring A. It is known from considerable experience with QSAR that hydrophobicity is an excellent correlate of partitioning and transport phenomena, such as absorption, systemic distribution, penetration to target tissue, etc. In contrast to these "pretarget" phenomena, the activity of a series at a putative target macromolecule, where highly specific interactions may be involved (e.g. with an enzyme active site), are often determined by a mix of molecular properties, for which other classes of descriptors such as σ and volume may apply. Since the present analysis is based entirely on in vivo data, the dominance of hydrophobicity raises the distinct possibility that a significant portion of the trends seen in the SAR reflect the pharmacokinetic properties of the compounds rather than their intrinsic activity. It will therefore be of great interest and importance, once the mechanism of the series is established, to see whether an in vitro assay for intrinsic activity can be developed, and the extent to which the SAR there correlates with that existing in vivo.

Cell Culture, Hypoglycemic, and Other Activities

Two other biological properties of the series, in vitro cytotoxicity and in vivo hypoglycemic effects, were also

studied extensively (Table III). In vitro cytotoxicity was determined for nearly all analogues, in order to explore possible correlations with in vivo activity, using the human leukemia cell line CCRF-CEM.[30,31] IC_{50}s for inhibition of growth of this line by compounds in this study ranged from 0.9 to greater than 20 μg/mL. This is comparatively nontoxic relative to most clinically effective agents, but may be proportionate with the doses required for good in vivo activity. While all compounds with activity in vivo were noted to give some demonstrable in vitro cytotoxicity (<20 μg/mL), there were also numerous cytotoxic compounds that were devoid of in vivo activity. Unfortunately, this only allows for a prediction of in vitro activity from in vivo activity and not vice versa, and was therefore not useful as a tool that might circumvent some of the labor and material requirements of in vivo evaluation. One possible basis for the partial lack of correlation was the use of a leukemia line for assessing cytotoxicity; the in vivo inactivity of the series in murine leukemia models was noted above.

It was anticipated that some members of the series would additionally produce hypoglycemia, due to their structural similarity to well-known clinical hypoglycemic sulfonylureas such as tolbutamide, chlorpropamide, acetohexamide, etc. Although these marketed hypoglycemics generally contain a saturated alkyl group in place of the ring B phenyl in the present series, there are ample reports in the literature for hypoglycemic effects among *N*-(phenylsulfonyl)-*N'*-phenylureas,[15] including several specific compounds of this series.[32] Accordingly, a selection of 27 analogues were tested for their ability to lower blood glucose in normal fed rats (see Experimental Section). These included most of the highly active antitumor compounds, along with some inactive ones (Table III). While several compounds produced robust hypoglycemic responses, there was no apparent correlation with antitumor activity. All possible patterns of activity were seen, e.g. good antitumor and hypoglycemic activity together, hypoglycemic activity but no antitumor activity, etc. Tolbutamide (**120**) was representative of this latter class, inducing pronounced hypoglycemia consistent with its known clinical profile, yet lacking antitumor activity. Since there were also several compounds which showed the opposite pattern of activity (e.g. **104**), it was felt that a definitive segregation of the hypoglycemic and antitumor structure–activity relationships had been achieved. In addition to alleviating concerns that the two effects might prove inseparable (e.g. due to an underlying common mechanism of action), this provided candidates for eventual clinical trial lacking a side-effect considered highly undesirable in cancer patients.

Another well-known class of sulfonylureas with biological actions are the herbicides exemplified by chlorsulfuron and sulfometuron methyl, in which ring B is typically a pyrimidine or triazine instead of phenyl. These act through inhibition of acetolactate synthase, the first enzyme specific to branched chain amino acid biosynthesis.[33] While this specific pathway is found primarily in plants and unicellular organisms, rather than animals, it suggests the present series may inhibit protein synthesis via some related pathway. Possible effects on amino acid and protein biosynthesis were explored by several means. Several antitumor analogues (**17**, **59**, **66**, **99**, **101**) assayed for inhibition of amino acid biosynthesis in *E. coli*[34] were found to be inactive. There was also no evidence of inhibition of protein synthesis by compounds **1**, **17**, and **104** in mammalian cell culture systems, at doses (10–50 μg/mL) which were clearly in the cytotoxic range.[35] It was also of interest that compounds containing a ring B pyrimidine substituted in the manner usually associated with excellent herbicidal activity (**133**, **134**) were devoid of antitumor effects. Although additional studies are in order, at present no data has been generated to support protein synthesis as the target of the antitumor sulfonylureas nor is there any suggestion of crossover between antitumor and herbicidal structure–activity relationships.

Compounds **1**, **17**, and **104** likewise failed to inhibit synthesis of RNA and DNA in cell culture at cytotoxic doses, or to exhibit toxicity in any specific portion of the cell cycle.[35] The mechanism of action of the series thus appears not to involve interference with macromolecular biosynthesis or polynucleotide function, a distinct departure from the great majority of oncolytics.

To complete the profile provided by the antitumor and hypoglycemic evaluations, several of the most promising antitumor compounds were subjected to two-week pilot toxicology in rats.[4b,5a,36] Very little acute toxicity was noted, and all were generally well tolerated for the duration of the study. In particular, none of this series produced myelosuppression, unlike the majority of existing clinical agents. This property is of great potential interest for combination protocols, where it is highly desirable that the agents combined have distinct and nonadditive dose-limiting toxicities. At the end of two weeks of dosing at high levels, however, it was discovered that a subset of the analogues produced varying degrees of liver and bile duct toxicity, including **17** (LY181984), which was therefore dropped from consideration for further development. In subsequent SAR work, compound **104** (LY186641) was identified as having antitumor efficacy and spectrum at least equivalent to **17**. It also was lacking in hypoglycemic effects or hepatic or bile duct toxicity and was tolerated overall at higher doses than any other analogues in two-week studies. LY186641 has accordingly been advanced into Phase I clinical trials, where the profile of safety generated in rodents and other species[36] appears to have been confirmed in man.[6]

Experimental Section

Chemistry. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a JEOL FX-90Q (90 MHz), Bruker WM-270 (270 MHz), or GE QE-300 (300 MHz) spectrometer. DMSO-d_6 was employed as NMR solvent and chemical shift values are reported in parts per million (δ) relative to Me_4Si. UV spectra were recorded on a Varian 219 instrument. Mass spectra were recorded in EI mode on a CEC 21-110 instrument or in FD mode on a Varian MAT 731 instrument. IR spectra were recorded on a Nicolet 10-MX/DX FTIR spectrophotometer, with samples in KBr pellets or in $CHCl_3$ solution. C, H, N elemental analyses were performed with a CEC Model 240XA instrument. Analyses for sulfur and chlorine employed a Metrohm Impulsomat

(30) Foley, G. E.; Lazarus, H.; Forbes, S.; Uzman, B. G.; Boone, B. A.; McCarthy, R. E. *Cancer* **1965**, *18*, 522.
(31) Grindey, G. B.; Wang, M. C.; Kinahan, J. *J. Mol. Pharmacol.* **1979**, *16*, 601.
(32) Reference 15b: **19**; ref 15c: **2**, **10**, **14**, **16–19**, **57–59**, **62–63**; ref 15d: **62**, **69**.
(33) Chaleff, R. S.; Mauvais, C. J. *Science* **1984**, *224*, 1443. LaRossa, R. A.; Schloss, J. V. *J. Biol. Chem.* **1984**, *259*, 8753.
(34) Somers, P., Lilly Research Laboratories, Unpublished data. Specific assays included inhibition of glutamine synthetase, shikimate synthesis, and branched chain amino acid biosynthesis.
(35) Boder, G. B.; Beasley, F. W.; Grindey, G. B. *Proc. Am. Assoc. Cancer Res.* **1989**, *30*, 554. Boder, G., Lilly Research Laboratories, Unpublished data.
(36) Todd, G. C. Unpublished data.

E473 automated titrator following combustion. All new products and intermediates had analytical results within ±0.4% of theoretical values. Compounds **109** and **116** were preparatively purified by HPLC on a Waters Prep LC/System 500A system using silica cartridges and EtOAc (**116**) or a hexane → 1:1 (EtOAc + 1% HOAc)/hexane gradient (**109**) as eluent. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates from E. Merck, thickness 0.25 mm with UV indicator dye, using the indicated solvent mixture as eluent. Solvents were removed with a rotary evaporator and reduced pressure. THF was dried by distillation from sodium/benzophenone, and DMF by storage over 4-Å molecular sieves. All reaction and workup steps were at room temperature unless otherwise noted.

Method A. *N*-[(4-Methylphenyl)sulfonyl]-*N'*-(4-methylphenyl)urea (2). 4-Toluenesulfonyl isocyanate (34.9 g, 0.177 mol) was quickly transferred with a Mohr pipet to a nitrogen-flushed flask and 310 mL of PhMe added to produce a solution. 4-Toluidine (19.07 g, 0.178 mol) was added as a solution in 110 mL PhMe over 8 min with stirring; considerable warming was noted. Within 2 min following the end of addition a white precipitate began to form. The mixture was stirred overnight and then the solid was collected, washed with 2 × 60 mL of PhMe, and dried in vacuo at 60 °C to give 49.4 g (92%) of white powder: mp 153–155 °C; ^{1}H NMR δ 2.21 (s, 3 H), 2.38 (s, 3 H), 7.06 (d, 2 H), 7.21 (d, 2 H), 7.42 (d, 2 H), 7.84 (d, 2 H), 8.70 (s, 1 H), 10.52 (br s, 1 H); MS 304 (M^+); UV λ_{max} (EtOH) 243 (ε 20 700); IR (KBr) (cm^{-1}) 3300, 3239, 1689, 1529, 1449, 1343, 1168, 1042, 736, 669. Anal. ($C_{15}H_{16}N_2O_3S$) C, H, N, S.

***N*-[(4-Methylphenyl)sulfonyl]-*N'*-(1,2,4-triazol-3-yl)urea (137).** A solution of 4-toluenesulfonyl isocyanate (26.09 g, 0.1323 mol) in 50 mL of dry THF was added over 10 min with stirring to a solution of 3-amino-1,2,4-triazole (11.63 g, 0.1383 mol, 1.05 equiv) in 150 mL of dry DMF; some warming was noted. [CAUTION: DMF reacts at an appreciable rate with sulfonyl isocyanates and is not suitable for initial solution of these reactants.] After 4 h, the resulting solution was treated dropwise with 200 mL of H_2O, producing a massive white precipitate. After a further 2 h stirring, the solid was collected, washed with 2 × 75 mL of H_2O, and dried in vacuo at 65 °C to afford 34.67 g (93%) of white solid: mp 250–253 °C; ^{1}H NMR δ 2.40 (s, 3 H), 7.43 (d, 2 H), 7.86 (d, 2 H), 8.19 (v br, 1 H), 10.10 (v br, 1 H); MS 281 (M^+); UV λ_{max} (EtOH) 229 (ε 20 400), 274 (ε 447); IR (KBr) (cm^{-1}) 3146, 1711, 1552, 1495, 1482, 1466, 1446, 1351, 1307, 1251, 1162, 1091, 913, 806, 732, 685. Anal. ($C_{10}H_{11}N_5O_3S$) C, H, N, S.

4-Chlorophenyl *N*-[(4-Methylphenyl)sulfonyl]carbamate (141). A solution of 4-toluenesulfonyl isocyanate (35.7 g, 0.181 mol) in 300 mL of CH_2Cl_2 was treated with a solution of 4-chlorophenol (23.7 g, 0.184 mol, 1.02 equiv) in 100 mL of CH_2Cl_2 over 8 min. The resulting solution was stirred at room temperature for 65 h and heated to reflux for 2.7 h and then the solvent was removed in vacuo, leaving a viscous oil. Trituration with 40 mL petroleum ether induced conversion to a crystalline solid, which was collected, washed 3 times with petroleum ether, and dried in vacuo to provide 57.0 g (97%) of white powder: mp 54–56 °C; MS 197 (fragment $C_7H_7SO_2NCO^+$); UV λ_{max} (95% EtOH) 226 (ε 23 750), 274 (ε 1360); IR (KBr) (cm^{-1}) 1765, 1491, 1426, 1353, 1210, 1200, 1160, 1088, 905, 675. Anal. ($C_{14}H_{12}ClNO_4S$) C, H, N, S, Cl. The ^{1}H NMR was complex, containing two sets of signals, suggestive of decomposition or a mixture of tautomers, however, the product was essentially homogeneous by TLC (1:1 hexane/EtOAc + 0.5% HOAc), and the presence of an intact sulfonyl–carbamate linkage was indicated by the MS and analysis.

***S*-4-Chlorophenyl *N*-[(4-Methylphenyl)sulfonyl]thiocarbamate (142).** A solution of 4-toluenesulfonyl isocyanate (25.2 g, 0.128 mol) in 200 mL of CH_2Cl_2 was treated with a solution of 4-chlorothiophenol (18.6 g, 0.129 mol, 1.01 equiv) in 100 mL of CH_2Cl_2 over 10 min. The resulting solution was stirred at room temperature for 18.5 h and heated to reflux for 1.7 h and then the solvent was removed to give a solid, which was washed three times with petroleum ether and dried in vacuo, giving 32.3 g (74%) of white powder having a faint thiol-like odor: mp 152–153 °C; MS 197 (fragment $C_7H_7SO_2NCO^+$); UV λ_{max} (95% EtOH) 229 (ε 18 810), 273 (ε 1450); IR (KBr) (cm^{-1}) 3235, 1724, 1439, 1353, 1170, 1109, 1075, 1014, 876, 671. Anal. ($C_{14}H_{12}ClNO_3S_2$) C, H, N, S, Cl. As for **141**, the ^{1}H NMR showed two or more sets of signals, suggesting decomposition or a mixture of tautomers. However, the product was again essentially homogeneous by TLC (1:1 hexane/EtOAc + 0.5% HOAc), with the existence of an intact sulfonyl–thiocarbamate linkage supported by the MS and analysis.

***N*-Benzoyl-*N'*-(4-chlorophenyl)urea (139).** Benzoyl isocyanate (3.74 g, 25.4 mmol) was dissolved in 100 mL of PhMe and filtered under nitrogen to remove a small quantity of insoluble material, and then 4-chloroaniline (3.32 g, 26.0 mmol, 1.02 equiv) was added neat and mixture heated at 86 °C for 1.3 h. After the mixture was cooled to room temperature and allowed to stand, the resulting precipitate was collected, washed with 2 × 20 mL of PhMe, and dried in vacuo at 65 °C to afford 6.59 g (94.4%) white crystalline solid: mp 249–250 °C; ^{1}H NMR δ 7.4–7.7 (m, 7 H), 8.04 (d, 2 H), 10.88 (s, 1 H), 11.09 (s, 1 H); MS 274 (M^+); UV λ_{max} (EtOH) 238 (ε 20 250), 258 (ε 16 720); IR (KBr) (cm^{-1}) 1702, 1673, 1597, 1557, 1505, 1492, 1474, 1272, 1227, 826. Anal. ($C_{14}H_{11}ClN_2O_2$) C, H, N, Cl.

Method B. *N*-[(3-Methylphenyl)sulfonyl]-*N'*-(4-chlorophenyl)urea (76). A solution of 3-toluenesulfonamide (97.22 g, 0.5678 mol) in 285 mL of acetone was treated with 570 mL of 1.00 N aqueous NaOH (1.00 equiv), and then a solution of 4-chlorophenyl isocyanate (96.35 g, 0.6274 mol, 1.10 equiv) in 285 mL of acetone was added over 17 min with stirring. A white precipitate (*N,N'*-bis(4-chlorophenyl)urea) appeared shortly after the end of the addition. The mixture was stirred 16.5 h, filtered, and then treated with 580 mL of 1.00 N aqueous HCl (0.580 mol, 1.02 equiv). The resulting precipitate was stirred another 0.5 h, collected, washed twice with H_2O, and dried in vacuo at 65 °C to provide 170.49 g (92.4%) of fine white powder. This was recrystallized from 2.3 L of boiling toluene to give 148.24 g (80.4%) of fluffy white needles: mp 171–173 °C; ^{1}H NMR δ 2.40 (s, 3 H), 7.34 (AB q, 4 H), 7.50 (br d, 2 H) 7.76 (br s, 2 H), 9.00 (s, 1 H), ca. 10.1 (v br, 1 H); MS 324 (M^+); UV λ_{max} (EtOH) 250 (ε 24 260); IR (KBr) (cm^{-1}) 3341, 3240, 1711, 1598, 1533, 1458, 1332, 1154, 1040, 700, 682. Anal. ($C_{14}H_{13}ClN_2O_3S$) C, H, N.

[With method B, certain sulfonamides came out of solution upon treatment with NaOH. Solution was usually readily restored by addition of more H_2O and/or acetone, prior to addition of the isocyanate.]

***N*-[(4-Methylphenyl)sulfonyl]-*N'*-(4-chlorophenyl)thiourea (99).** A solution of 4-toluenesulfonamide (10.42 g, 60.9 mmol) in 30 mL of acetone was treated with 62 mL of 1.00 N aqueous NaOH (1.02 equiv) and a solution of 4-chlorophenyl isothiocyanate (10.46 g, 61.7 mmol, 1.01 equiv) in 40 mL of acetone, and then the mixture was heated to reflux for 4.7 h. After the mixture was cooled in an ice bath and a small quantity of solid was filtered off, the filtrate was treated with 62 mL of 1.00 N aqueous HCl (1.02 equiv) and further diluted with 150 mL of H_2O, and the precipitate was collected and washed with 2 × 50 mL of H_2O. Recrystallization from 150 mL of boiling absolute EtOH gave 5.19 g (25%) light brown needles: mp 184–185 °C dec; ^{1}H NMR δ 2.42 (s, 3 H), 7.45 (m, 6 H), 7.86 (m, 2 H), 10.28 (br s, 1 H); MS 341 ($M + 1^+$); UV λ_{max} (EtOH) 257 (ε 14 470), 291 (ε 14 750); IR (KBr) (cm^{-1}) 3292, 1518, 1489, 1478, 1402, 1383, 1182, 1152, 1084, 812. Anal. ($C_{14}H_{13}ClN_2O_2S_2$) C, H, N, S.

***N*-Methyl-*N*-[(4-methylphenyl)sulfonyl]-*N'*-(4-chlorophenyl)urea (97).** *N*-Methyl-4-toluenesulfonamide (12.83 g, 69.3 mmol) and 4-chlorophenyl isocyanate (10.7 g, 69.8 mmol, 1.01 equiv) were suspended with stirring in 300 mL of PhMe, and Et_3N (14.5 mL, 104 mmol, 1.50 equiv) was added over 5 min. The mixture was heated to reflux for 3.5 h and cooled to room temperature, and a small amount of remaining undissolved solid was filtered off. The filtrate spontaneously generated a precipitate, which was collected, washed twice with PhMe, and dried in vacuo at 60 °C to give 6.68 g (28%) fine white needles: mp 123–124 °C; ^{1}H NMR δ 2.40 (s, 3 H), 3.16 (s, 3 H), 7.35–7.55 (m, 6 H), 7.80 (d, 2 H), 9.72 (s, 1 H); MS 338 (M^+); UV λ_{max} (EtOH) 234 (ε 21 050); IR (KBr) (cm^{-1}) 3350, 1711, 1598, 1547, 1493, 1351, 1151, 951, 826, 668. Anal. ($C_{15}H_{15}ClN_2O_3S$) C, H, N, S. Removal of solvent from the filtrate of the first crop gave a solid, which after washing with 2 × 50 mL of petroleum ether and drying provided a second crop of 15.71 g of **97**, similar in appearance to the first crop and with acceptable analysis, but showing traces of Et_3N and *N*-methyl-4-toluenesulfonamide by NMR. Combined yield both crops was 22.38 g (95%).

Method C. *N*-(5-Indansulfonyl)-*N'*-(4-bromophenyl)urea (105). A mixture of 5-indansulfonamide (20.18 g, 0.1023 mol) and

finely pulverized K_2CO_3 (15.66 g, 0.1133 mol, 1.11 equiv) in 300 mL of 2-butanone was stirred and heated to reflux for 30 min. Ethyl chloroformate (11.96 g, 0.1102 mol, 1.08 equiv) was added neat to the refluxing mixture through the top of the condenser over 3 min and heating continued for another 3 h. The resulting thick paste was cooled to room temperature, poured into 700 mL of H_2O, and washed with 2 × 200 mL of EtOAc. The combined organic phases were extracted with 300 mL of H_2O, then the aqueous phases combined and acidified with 250 mL of 1.0 N aqueous HCl. This was extracted with 500 mL of EtOAc, and the organic phase washed with 500 mL of H_2O and 500 mL of brine, then evaporated to leave 21.84 g of light brown solid. Recrystallization from 50 mL of boiling toluene provided 14.79 g (53.7%) of ethyl *N*-(5-indansulfonyl)carbamate as a white crystalline solid: mp 123–126 °C; ^{1}H NMR δ 1.08 (t, 3 H), 2.04 (m, 2 H), 2.92 (t, 4 H), 3.98 (q, 2 H), 7.32–7.68 (m, 3 H).

A solution of ethyl *N*-(5-indansulfonyl)carbamate (2.50 g, 9.28 mmol) and 4-bromoaniline (1.69 g, 9.82 mmol, 1.06 equiv) in 20 mL PhMe was heated to reflux under nitrogen for 7.5 h. After the solution stood overnight at room temperature, the resulting precipitate was collected, washed twice with PhMe, and dried in vacuo at 65 °C to afford 3.06 g (83%) of a white solid: mp 168–171 °C dec; ^{1}H NMR δ 2.06 (pentet, 2 H), 2.94 (m, 4 H), 7.3–7.8 (m, 7 H), 8.95 (s, 1 H), ca. 10.7 (v br, 1 H); MS 396, 394 (M^+s for Br isotopes); UV λ_{max} (EtOH) 253 (ϵ 26 200); IR ($CHCl_3$) (cm^{-1}) 1718, 1701, 1600, 1542, 1491, 1399, 1388, 1145. Anal. ($C_{16}H_{15}BrN_2O_3S$) C, H, N, S.

***N*-[(4-Methylphenyl)sulfonyl]-*N'*-(4-hydroxyphenyl)urea (6).** A solution of **12** (8.35 g, 21.1 mmol) in 84 mL of THF was catalytically hydrogenated using 8 g of 5% Pd/C on a Parr shaker (60 psi H_2) for 15 min at room temperature (uptake 100% of theoretical). The catalyst was filtered off, the solvent removed in vacuo, and the resulting foam triturated with MeOH/CH_2Cl_2 to produce a solid. This was washed several times with CH_2Cl_2 and dried in vacuo at 40 °C to give 5.68 g (88%) of a fine white solid: mp 179–180 °C dec; ^{1}H NMR δ 2.40 (s, 3 H), 6.66 (d, 2 H), 7.11 (d, 2 H), 7.41 (d, 2 H), 7.83 (d, 2 H), 8.49 (s, 1 H), 9.18 (br s, 1 H), 10.45 (v br, 1 H); MS 307 ($M + 1^+$); UV λ_{max} (EtOH) 228 (ϵ 17 450), 243 (ϵ 17 600); IR (KBr) (cm^{-1}) 3478, 3374, 1659, 1529, 1521, 1328, 1211, 1150, 1095, 1056. Anal. ($C_{14}H_{14}N_2O_4S$) C, H, N, S.

Pharmacology. Activity against in Vivo Syngeneic Rodent Tumors. Both solid and ascites tumors were passaged serially. For solid tumors, excised tumor tissue was minced into fragments approximately 1–2 mm on a side, and then individual pieces were implanted sc via trochar into a subaxillary site on syngeneic recipient animals (C3H, C57BL/6, Balb/C, or DBA/2 mice; Holtz-Holtz rats). Ascites tumors were implanted ip as an inoculum of 1 × 10^6 cells into DBA/2 mice. Control groups and each dose level of treated groups consisted of 7–10 animals, selected at random from the pool of implanted animals. Treatment of tumor-bearing animals was initiated the day following implantation, except as noted in Table II where dosing was delayed for 3 days. Compounds were generally dosed daily for 10 days, except for the 6C3HED model, which was dosed for only 8 days. Compounds were prepared for dosing by suspension in 2.5% Emulphor in 0.9% saline, and dosed in a total volume of 0.5 mL. Oral administration was by gavage with use of an 18-gauge needle, and ip injections employed a 23-gauge needle. The route, frequency, and duration of dosing for preliminary studies (Table I) were as noted. All results in Table II were obtained with oral dosing, with modifications from a daily × 10 schedule as noted. All results in Table III were obtained in the 6C3HED model with daily oral dosing for 8 days, except where dosing was ip, as noted, for compounds **99**, **139**, and **140**. In the solid tumor models, tumor growth at the end of the dosing period was extensive but not life-threatening, so that any deaths among the treatment group were recorded as drug-related toxicity, unless a clear-cut alternative explanation existed (e.g. trapping under cage cover). The width (W) and length (L) of subcutaneously growing tumors was measured, without excision, using calipers connected to a microcomputer for automatic recording of data (Worzalla, J. F.; Bewley, J. R.; Grindey, G. B. *Invest. New Drugs*, in press), and converted to tumor volume (V) using the formula $V = LW^2/2$. One day after the final dose, percent inhibition of growth was determined by comparing the tumor volume in treated groups to that of controls. For ascites models, percent increase in life span (ILS) was derived from comparison of mean life span for treated and control groups.

Cytotoxicity toward CCRF-CEM Cells in Vitro. CCRF-CEM cells, a human leukemia cell line,[30] were grown as previously described.[31] Dose–response curves were generated for various compounds to determine the concentration required for 50% inhibition of growth (IC_{50}). Cluster plates were prepared in duplicate with the compound at various concentrations. Test compounds were dissolved initially in DMSO at a concentration of 4 mg/mL and further diluted with solvent to the desired concentration. Cells in Roswell Park Memorial Institute 1640 media supplemented with 10% dialyzed fetal bovine serum, 16 mM HEPES, and 8 mM MOPS buffers were added to the well at a final concentration of 4.8 × 10^4 cells/well in a total volume of 2.0 mL. After 72 h of incubation (95% air, 5% CO_2), cell numbers were determined on a ZBI Coulter counter. Cell number for indicated controls at the end of incubation was usually (4–6) × 10^5 cells/well.

Effects on Blood Glucose in Normal Fed Rats. The potential hypoglycemic activity was determined in fed male Sprague-Dawley rats (Charles River Laboratories) weighing 175–200 g. The test compound was suspended in 5% acacia and administered by oral gavage at a dose of 200 mg/kg. The concentration of the compound was adjusted such that 0.25 mL per 100 g body weight administered orally gave the desired dose on a body weight basis. Blood glucose levels were determined on blood samples (0.1 mL) taken from the tail immediately prior to and at 1, 2, 3, and 5 h following administration of compound. Glucose was determined by an enzymatic procedure utilizing glucose oxidase and peroxidase coupled with a chromogenic oxygen acceptor (Sigma Chemical Co.). Each compound was run in a group of four fed rats. The predosing glucose level was in the range 90–100 mg/dL. The hypoglycemic effect was judged by the change in glucose levels (expressed as mg/dL) from the predosing level. In this way each rat acted as its own control. Acetohexamide and tolbutamide, used as positive controls in this system, produced a fall in blood glucose of 50 mg/dL or more at 2 h, lasting for at least 5 h.

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