Sulfonimidamide Analogs of Oncolytic Sulfonylureas[†,1]

John E. Toth,* Gerald B. Grindey,[‡] William J. Ehlhardt, James E. Ray, George B. Boder, Jesse R. Bewley, Kim K. Klingerman, Susan B. Gates, Sharon M. Rinzel, Richard M. Schultz, Leonard C. Weir, and John F. Worzalla

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

Received September 26, 1996[⊗]

A series of sulfonimidamide analogs of the oncolytic diarylsulfonylureas was synthesized and evaluated for (1) *in vitro* cytotoxicity against CEM cells, (2) *in vivo* antitumor activity against subaxillary implanted 6C3HED lymphosarcoma, and (3) metabolic breakdown to the *o*-sulfate of *p*-chloroaniline. The separated enantiomers of one sulfonimidamide analog displayed very different activities in the *in vivo* screening model. In general, several analogs demonstrated excellent growth inhibitory activity in the 6C3HED model when dosed orally or intraperitoneally. A correlative structure−activity relationship to the oncolytic sulfonylureas was not apparent.

A substantial effort in these laboratories has been directed to the discovery of oncolytic agents demonstrating growth inhibitory activities in murine-based solid tumor models and displaying novel modes of action.[2−5] This approach, which relies on the empirical development of a structure−activity relationship (SAR), has been coupled to extensive focused preclinical pharmacology, metabolism, and toxicology studies and has provided the foundation for the clinical studies of the antimetabolite gemcitabine, the antifolates DDATHF and LY231514, and a lead oncolytic diarylsulfonylurea LY181984 (Figure 1), from whose study sulofenur was derived.[6]

These diarylsulfonylureas display broad spectrum antitumor activity against syngeneic and human xenograft tumors carried in mice through a thoroughly investigated but as yet unidentified mechanism of action.[7,8] Phase I studies of sulofenur defined the dose-limiting toxicity of this agent as methemoglobenemia and hemolytic anemia, non-life-threatening toxicities more commonly associated with aniline metabolism rather than nonspecific cytotoxicity.[9−14] The unpredictable onset of these toxicities, however, complicated the clinical study of sulofenur. Recently published sulofenur metabolism studies identified *p*-chloroaniline and its *o*-sulfate **65** as urinary metabolites in mice, rats, monkeys, and humans, providing direct evidence for the *in vivo* liberation of *p*-chloroaniline from sulofenur.[12,14]

Recent SAR studies limited to the exploration of the diaryl domains of the sulfonylurea structure have been reported.[15,16] In approaching the challenge of identifying other clinical candidates, however, our efforts turned toward the synthesis and study of analogs in which one of the sulfonamide oxygen atoms had been replaced by a nitrogen atom. The resulting sulfonimidamide structures possessed another nitrogen terminus from which the SAR could be explored, in addition to creating a stereogenic sulfur center. This paper describes the synthesis, metabolism, and antitumor activity of sulfonimidamide analogs of the oncolytic sulfonylureas.

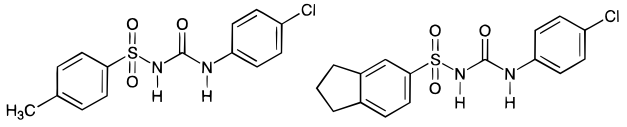


Figure 1. Oncolytic diarylsulfonylureas.

Chemistry

The synthesis of sulfonimidamide analogs of the hypoglycemic agent tolbutamide[17,18] and the sulfonylurea herbicides[19] has previously been reported. Our synthetic efforts, which were briefly reported in a recent publication,[20] are detailed here. These sulfonimidamide analogs listed in Table 1 were synthesized as depicted in Scheme 1.

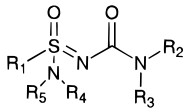
The requisite arylsulfinyl chlorides **6** were synthesized by one of the following methods: (A) alkali metal sulfinate salts **1** were purchased or synthesized by the reduction of the corresponding sulfonyl chloride;[21] these in turn were converted to the sulfinyl chloride with excess thionyl chloride;[22] (B) treatment of an aryl sulfide **2** or disulfide **3** with sulfuryl chloride;[23−25] the sulfides and disulfides were commercially available or synthesized via the oxidation/Pummerer rearrangement/alkaline hydrolysis of appropriately substituted thioanisoles **4**[26] or via the Newman−Kwart reaction of appropriately substituted phenols;[27] (C) sulfide **2** was converted to the sulfenyl chloride **5**[28] which was converted, through the sulfenyl isocyanate **7**, to the sulfenylurea **8** and oxidized to the sulfinylurea **9**.

A noteworthy improvement over procedures previously published for the synthesis of the key sulfinylureas **9** involved the conversion of sulfinyl chlorides **6** to sulfinyl isocyanates **7**, with silver cyanate in ether, as detailed by Jähnchen and Westphal.[29] Simple filtration of the precipitated silver salts followed by treatment of the ether solution of the sulfinyl isocyanates **7** with amine often resulted in the precipitation of analytically pure sulfinylureas **9**. Chlorination of the sulfinylureas **9** with either *N*-chlorobenzotriazole or *tert*-butyl hypochlorite provided the intermediate sulfonimidoyl chlorides **10**, which were reacted with an excess of an amine at low temperature in THF. Some primary and secondary amines used produced a mixture of the desired sulfonimidamide analog **11** and a rearranged sulfon-

[†] Dedicated to the memory of Gerry Grindey.
[‡] Deceased November 16, 1993.
[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1997.

S0022-2623(96)00673-5 CCC: $14.00

Table 1. *In Vitro* Cytotoxicity and *in Vivo* Antitumor Activity of Compounds **13**−**64**



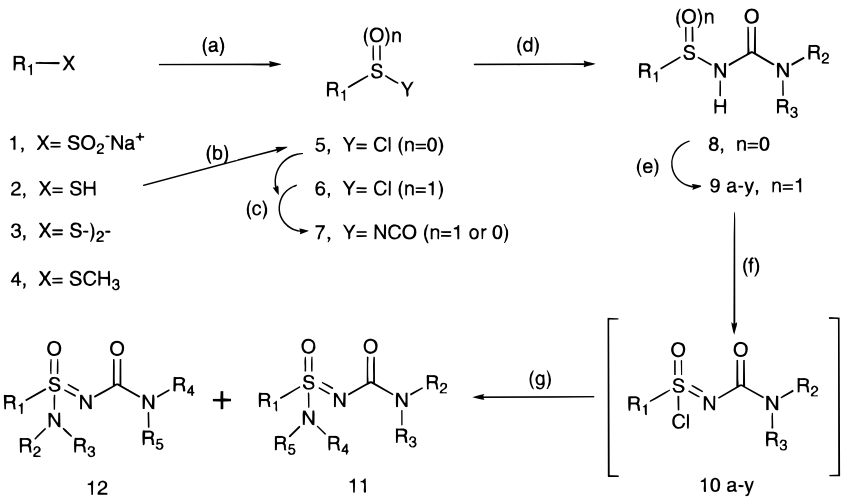
compound	R_1	R_4	R_5	R_2	R_3	molecular formula[a]	6C3HED Lymphosarcoma[b] daily dose, mg/kg	6C3HED Lymphosarcoma[b] % inhibition	CEM[c] IC_{50}, μg/mL
LY181984							150[e]	93	8.9[d]
sulofenur							150	91	11.2[d]
13	phenyl	H	H	H	*p*-Cl-phenyl	$C_{13}H_{12}Cl_1N_3O_2S_1$	300	0	>20
14	*p*-tolyl	H	H	H	*p*-Cl-phenyl	$C_{14}H_{14}Cl_1N_3O_2S_1$	300[e]	89	>20
							150[f]	92	
							50	95	
15(−)[g]	*p*-tolyl	H	H	H	*p*-Cl-phenyl	$C_{14}H_{14}Cl_1N_3O_2S_1$	150[h]	100	>20
16(+)[i]	*p*-tolyl	H	H	H	*p*-Cl-phenyl	$C_{14}H_{14}Cl_1N_3O_2S_1$	150	5	>20
17	*p*-tolyl	H	acetyl	H	*p*-Cl-phenyl	$C_{16}H_{16}Cl_1N_3O_3S_1$	300	84	>20
18	*p*-tolyl	H	methyl	H	*p*-Cl-phenyl	$C_{15}H_{16}Cl_1N_3O_2S_1$	150[e]	93	>20
19	*p*-tolyl	methyl	acetyl	H	*p*-Cl-phenyl	$C_{17}H_{18}Cl_1N_3O_3S_1$	150	98	9.6
20	*p*-tolyl	methyl	acetyl	acetyl	*p*-Cl-phenyl	$C_{19}H_{20}Cl_1N_3O_4S_1$	150	83	5.6
21	*p*-tolyl	H	benzyl	H	*p*-Cl-phenyl	$C_{21}H_{20}Cl_1N_3O_2S_1$	300	87	8.7
22	*p*-tolyl	H	H	methyl	*p*-Cl-phenyl	$C_{15}H_{16}Cl_1N_3O_2S_1$	150	83	>20
23	*p*-tolyl	methyl	methyl	H	*p*-Cl-phenyl	$C_{16}H_{18}Cl_1N_3O_2S_1$	300	63	>20
24	*p*-tolyl	H	methyl	methyl	*p*-Cl-phenyl	$C_{16}H_{18}Cl_1N_3O_2S_1$	150	91	>20
25	*p*-tolyl	H	ethyl	H	*p*-Cl-phenyl	$C_{16}H_{18}Cl_1N_3O_2S_1$	150	87	13.8
26	*p*-tolyl	H	phenethyl	H	*p*-Cl-phenyl	$C_{22}H_{22}Cl_1N_3O_2S_1$	300	48	5.3
27	*p*-tolyl	H	*n*-propyl	H	*p*-Cl-phenyl	$C_{17}H_{20}Cl_1N_3O_2S_1$	300[e]	69	10.9
28	*p*-tolyl	H	allyl	H	*p*-Cl-phenyl	$C_{17}H_{18}Cl_1N_3O_2S_1$	300	45	10.0
29	*p*-tolyl	H	iso-propyl	H	*p*-Cl-phenyl	$C_{17}H_{20}Cl_1N_3O_2S_1$	75	86	1.4
30	*p*-tolyl	H	*n*-butyl	H	*p*-Cl-phenyl	$C_{18}H_{22}Cl_1N_3O_2S_1$	150	88	0.4
31	*p*-tolyl	acetyl	*n*-butyl	H	*p*-Cl-phenyl	$C_{20}H_{24}Cl_1N_3O_3S_1$	300	53	12.5
32	*p*-tolyl	acetyl	*n*-butyl	acetyl	*p*-Cl-phenyl	$C_{22}H_{26}Cl_1N_3O_4S_1$	300	10	2.9
33	*p*-tolyl	H	iso-butyl	H	*p*-Cl-phenyl	$C_{18}H_{22}Cl_1N_3O_2S_1$	75	85	0.7
34	*p*-tolyl	H	$(CH_2)_2OH$	H	*p*-Cl-phenyl	$C_{16}H_{18}Cl_1N_3O_3S_1$	300[e]	60	>20
35	*p*-tolyl	H	$(CH_2)_3OH$	H	*p*-Cl-phenyl	$C_{17}H_{20}Cl_1N_3O_3S_1$	300	89	>20
36	*p*-tolyl	H	phenyl	H	*p*-Cl-phenyl	$C_{20}H_{18}Cl_1N_3O_2S_1$	300[e]	5	7.0
37	*p*-($AcOCH_2$)phenyl	H	H	H	*p*-Cl-phenyl	$C_{16}H_{16}Cl_1N_3O_4S_1$	50	87	>20
38	*p*-($HOCH_2$)phenyl	H	H	H	*p*-Cl-phenyl	$C_{14}H_{14}Cl_1N_3O_3S_1$	75	99	>20
39	*p*-formylphenyl	H	H	H	*p*-Cl-phenyl	$C_{14}H_{12}Cl_1N_3O_3S_1$	150[f]	80	5.6
40	*p*-(CO_2Me)phenyl	H	H	H	*p*-Cl-phenyl	$C_{15}H_{14}Cl_1N_3O_4S_1$	300	0	>20
41	*p*-(CO_2H)phenyl	H	H	H	*p*-Cl-phenyl	$C_{14}H_{12}Cl_1N_3O_4S_1$	243[f]	0	nd
42	*p*-ethylphenyl	H	H	H	*p*-Cl-phenyl	$C_{15}H_{16}Cl_1N_3O_2S_1$	25	91	>20
43	*p*-(t-Bu)phenyl	H	H	H	*p*-Cl-phenyl	$C_{17}H_{20}ClN_3O_2S_1$	300	11	1.7
44	3,4-dimethylphenyl	H	H	H	*p*-Cl-phenyl	$C_{15}H_{16}Cl_1N_3O_2S_1$	4.0[j]	97	>20
45	3,4-dimethylphenyl	H	methyl	H	*p*-Cl-phenyl	$C_{16}H_{18}Cl_1N_3O_2S_1$	25[e]	98	16.2
46	3,5-dimethylphenyl	H	H	H	*p*-Cl-phenyl	$C_{15}H_{16}Cl_1N_3O_2S_1$	200	77	20.0
47	3,4,5-trimethylphenyl	H	H	H	*p*-Cl-phenyl	$C_{16}H_{18}Cl_1N_3O_2S_1$	19[k]	95	12.7
48	3,5-dimethyl-4-Cl-phenyl	H	H	H	*p*-Cl-phenyl	$C_{15}H_{15}Cl_2N_3O_2S_1$	300	0	6.2
49	5-indanyl	H	H	H	*p*-Cl-phenyl	$C_{16}H_{16}Cl_1N_3O_2S_1$	150[f]	86	>20
50	5-indanyl	H	methyl	H	*p*-Cl-phenyl	$C_{17}H_{18}Cl_1N_3O_2S_1$	150	75	10.8
51	*p*-chlorophenyl	H	H	H	*p*-Cl-phenyl	$C_{13}H_{11}Cl_2N_3O_2S_1$	50	80	12.3
52	*p*-bromophenyl	H	H	H	*p*-Cl-phenyl	$C_{13}H_{11}Br_1Cl_1N_3O_2S_1$	150	89	10.6
53	*p*-(CF_3)phenyl	H	H	H	*p*-Cl-phenyl	$C_{14}H_{11}F_3Cl_1N_3O_2S_1$	150	tox[l]	15.2
54	*p*-tolyl	H	H	H	phenyl	$C_{14}H_{15}N_3O_2S_1$	150	0	>20
55	*p*-tolyl	H	H	H	3,4-Cl_2phenyl	$C_{14}H_{13}Cl_2N_3O_2S$	300	14	>20
56	*p*-tolyl	H	H	H	4-Br-phenyl	$C_{14}H_{13}Br_1N_2O_2S_1$	150	100	>20
57	*p*-tolyl	H	H	H	4-CF_3-phenyl	$C_{15}H_{14}F_3N_3O_2S_1$	600	2	>20
58	*p*-tolyl	H	H	H	4-F-phenyl	$C_{14}H_{14}F_1N_3O_2S_1$	300	0	>20
59	*p*-tolyl	H	H	H	4-benzyloxyphenyl	$C_{21}H_{21}N_3O_3S_1$	300	5	>20
60	*p*-tolyl	H	H	H	4-hydroxyphenyl	$C_{14}H_{15}N_3O_3S_1$	300[f]	11	>20
61	*p*-tolyl	H	H	H	4-methoxyphenyl	$C_{15}H_{17}N_3O_3S_1$	300	0	>20
62	*p*-tolyl	H	H	H	4-methylphenyl	$C_{15}H_{17}N_3O_2S_1$	300[e]	40	>20
63	*p*-tolyl	H	H	H	*n*-butyl	$C_{12}H_{19}N_3O_2S_1$	300[f]	12	>20
64	*n*-butyl	H	methyl	H	*p*-Cl-phenyl	$C_{12}H_{18}Cl_1N_3O_2S_1$	300[f]	7	>20

[a] Elemental analyses (C, H, N) for all new compounds were within ±0.4% of theoretical values. [b] Lowest dose which produced >80% tumor growth inhibition, or the highest dose tested; dosed po, BID×8 unless otherwise noted. [c] Concentration which inhibited the growth of CCRF-CEM cells grown in culture for 72 h to 50% of control growth. [d] See ref 2. [e] Dosed po, daily×8. [f] Dosed ip, daily×8. [g] (−)-Enantiomer of **14**. [h] At 75 mg/kg, po, BID×8, 100% tumor growth inhibition with 60% lethality. [i] (+)-Enantiomer of **14**. [j] Dosed ip, BID×8. [k] Dosed po, days 1, 3, 5, 7. [l] At 25 mg/kg, po, BID×8, 100% lethality.

imidamide **12**, the origin of which has been discussed elsewhere.[20] In those cases the yield of the desired product **11** was increased by conducting the reaction at low temperature and with excess amine. This synthetic approach was limited, in general, because the reaction of **10** with many secondary amines produced only the rearranged sulfonimidamides **12**. Another minor complication associated with this synthetic plan arose during the chlorination reaction (**9** → **10**). When R_2 or R_3 contained competitively reactive electrophillic sites, e.g. when R_2 = phenyl, a contaminating ring chlorinated product was produced.

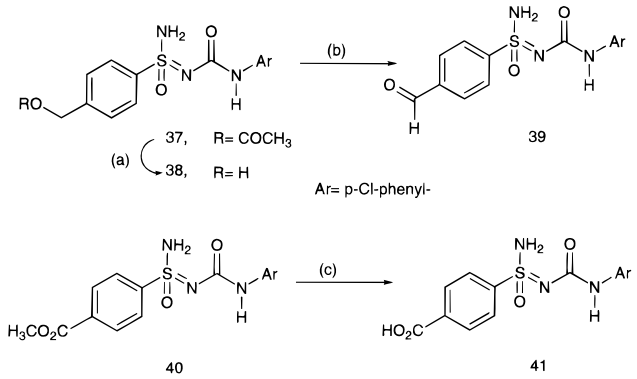
The sulfonimidamide analogs **11** could be acylated under standard conditions. Initial acylation usually

Scheme 1. General Synthesis of Sulfonimidamides[a]



[a] Reagents and conditions: (a) see text; (b) SO_2Cl_2/CCl_4; (c) 1.3 equiv of AgOCN in ether; (d) 1.0 equiv of HNR_2R_3/ether; (e) CH_3CO_3H/THF; (f) 1.05 equiv of *tert*-butyl hypochlorite/THF; (g) excess HNR_4R_5.

Scheme 2. Synthesis of Sulfonimidamide Metabolites[a]



[a] Reagents and conditions: (a) K_2CO_3/aqueous MeOH; (b) MnO_2/THF; (c) NaOH/aqueous THF.

occurred cleanly at the sulfur-bearing nitrogen atom followed by acylation at the phenyl-bearing nitrogen atom. Thus acylation of **30** with 1 equiv of acetic anhydride produced **31** in good yield, while peracylation produced the analog **32**, whose structure was verified by single-crystal X-ray analysis.[30] Chemical resolution of **14** was effected by the reaction of the corresponding sulfonimidoyl chloride with (1*S*,2*R*)-norephedrine to give a chromatographically separable mixture of sulfur diastereomers. Treatment of the separated diastereomers with lead tetraacetate provided the enantiomers of **14**, **15**, and **16**. This preparation is detailed in ref 20.

The potential metabolites of **14** were synthesized as depicted in Scheme 2. Because ceric ammonium nitrate oxidation of **14** did not yield the desired benzylic-oxygenated products cleanly, the requisite functionality was incorporated from 4-(methylthio)benzyl alcohol.[26] Alkaline hydrolysis of the acetoxy sulfonimidamide **37** provided the hydroxy-substituted analog **38**, the major plasma metabolite of **14**. Oxidation of **38** with manganese dioxide gave the aldehyde **39**. Although more thorough oxidation of the alcohol **38** provided the acid **41**, it was more convenient to incorporate the acid oxidation state from the commercially available disulfide, 4,4′-dithiobisbenzoic acid, and synthesize the acid **41** by direct alkaline hydrolysis of the ester **40**.

Biological Evaluation

Our previous experience with the evaluation of sulfonylureas[8] led us to rely most heavily on the demonstrated *in vivo* antitumor activity of these analogs against the 6C3HED Lymphosarcoma (Gardner) implanted in C3H mice. This was augmented by the determination of the *in vitro* cytotoxicity against CCRF-CEM cells. These data are listed in Table 1. Chronologically, **14** was the first analog synthesized and evaluated. In contrast to the excellent activity of the sulfonylurea LY181984 in this model, the analogous sulfonimidamide **14** had lower activity when dosed orally at comparable doses and schedules (89% inhibition for **14** at 300 mg/kg, qd×8 vs 93% inhibition for LY181984 at 150 mg/kg, qd×8). The observation of this level of activity was encouraging, however, because no other linkage isomer of sulfonylurea had demonstrated antitumor activity in this model. Because of the reduced oral activity, **14** was dosed ip in the model. The increased activity demonstrated at comparable doses was accompanied by an increased lethality (1/10 deaths with 92% inhibition at 150 mg/kg and 6/10 deaths with 98% inhibition at 300 mg/kg, both qd×8-ip vs 0/10 deaths with 89% inhibition at 300 mg/kg, qd×8-po). This trend was observed within the entire sulfonimidamide analog series. To investigate the oral absorption of **14** in mice, its plasma level was determined by HPLC after the administration of a single oral dose in mice (see Methods). These results are compared to those plasma levels observed for LY181984 under similar conditions in Figure 2. This study demonstrated significant pharmacokinetic differences between **14** and LY181984.

Plasma levels of **14** were ~10-fold lower than LY181984 after a comparable oral dose, and the half-life of **14** was considerably shorter. In addition, a single, more polar, plasma metabolite of **14** was observed in concentrations similar to the parent. This study suggested that a twice daily oral dosing protocol might exhibit increased antitumor activity, and that was verified by experiment (96% inhibition at 100 mg/kg, bid×8-po). The observation of the polar metabolite directed our synthetic effort to compounds **38**, **39**, and **41**, based on the well-documented oxidative metabolism

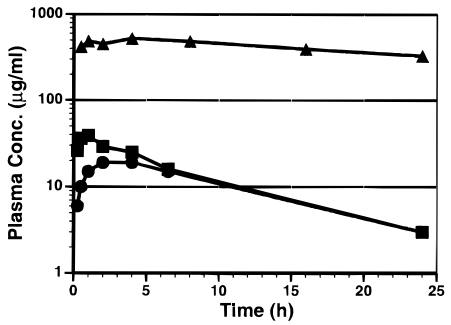


Figure 2. Plasma levels of **14** (■), its metabolite **38** (●), and LY181984 (▲) in C3H mice, following a single 300 mg/kg po dose.

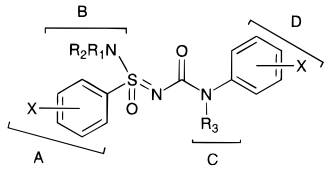


Figure 3. Generalized sulfonimidamide.

of the tolyl group.[31] The cytotoxicity and antitumor activity of these analogs is presented in Table 1.

As in the case of sulfonylureas, no correlation between the *in vitro* cytotoxicity and the *in vivo* antitumor efficacy was observed. In consideration of the limitations (i.e., absorption, distribution, and metabolism) of an empirical *in vivo* SAR study, the following observations relating structure and *in vivo* antitumor activity were made. Reference is made to the following regions of the analog structures as defined in Figure 3.

Compared to the corresponding sulfonylurea LY181984, the sulfonimidamide **14** was not as well orally absorbed, exhibited different mouse pharmacokinetics, and could be dosed (either po or ip) at nontoxic levels that produced significant antitumor activity in the 6C3HED model. It is interesting to note that the antitumor activity of the racemate **14** could be ascribed to the enantiomer **15**. The sulofenur analog **49** also demonstrated good antitumor activity in this model when dosed ip. It was not active when dosed orally. The sulfonimidamide analog **38,** the primary plasma metabolite of **14,** demonstrated excellent antitumor activity (po) while the corresponding sulfonylurea was inactive in this model.[8] The sulfonimidamide **44** demonstrated excellent antitumor activity when dosed ip, and in contrast to most other sulfonimidamide analogs, exhibited significant toxicity (5/8 deaths) when dosed po at the same level. The corresponding sulfonylurea was very active when dosed orally.[8] Other productive substitutions in the A region were limited to nonsterically-demanding alkyl groups and halogen atoms positioned meta or para to the sulfonimidamide function, with superior activity associated with para substitution. In the D region, a para-positioned bromine or chlorine atom was required for superior activity. To summarize for regions A and D, there appeared to be little structural correlation for the preferred route of administration and the *in vivo* antitumor activities between the sulfonylureas and their sulfonimidamide analogs. The only absolute shared structural feature was the necessity of a para-substituted aromatic residue in both the A and D regions.

In region B, the addition of a methyl group to the sulfonimidamide nitrogen atom, as in analog **18**, enhanced antitumor potency (good antitumor activity at half the dose of **14**). Dimethylation of the sulfonimidamide nitrogen atom, as in **23**, was unproductive. Other analogs within the homologous series possessed increased *in vitro* cytotoxicity, but showed no additional *in vivo* antitumor activity enhancement. Phenyl substitution, as in **36**, decreased activity. Acetylation of the sulfonimidamide nitrogen atom of **14** to produce **17**, while lowering the pK_a (from 10.5 for **14** to 5.6 for **17**) also reduced the antitumor activity. Acetylation of the methyl analog **18** to produce **19** increased the *in vitro* cytotoxicity while reducing the antitumor activity. In region C, the diacetyl analog of **18**, **20**, and the methyl analog of **14**, **22**, also showed reduced antitumor activity. Further experiments to determine if these region B and C methyl and acetyl analogs were functioning as prodrugs were not performed.

The clinical studies of sulofenur had demonstrated that a significant route of metabolism involved linkage hydrolysis to release *p*-chloroaniline. The *p*-chloroaniline could be quantitated by the measurement of its oxidation product, 2-amino-5-chlorophenyl sulfate **65** in the urine. Previous work had shown that, in mice, after oral dosing of various substituted sulfonylureas, the urinary excretion of **65** correlated to the degree of methemoglobinemia measured, strongly suggesting, along with other evidence, that the dose-limiting toxicities of sulofenur were caused by the release and metabolism of *p*-chloroaniline.[14] This mouse model was extended to the study of this sulfonimidamide series.

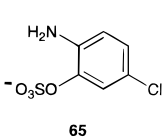
While the cleavage of the sulfonylurea linkage to release *p*-chloroaniline probably occurs by an enzymatic mechanism, it should be noted that acid-catalyzed hydrolysis is also possible. The sulfonamide hydrogen atom in the sulfonylurea structure is weakly acidic (pK_a $\approx$ 6.1), and at a pH $\leq$ pK_a, the sulfonylurea undergoes significant hydrolysis. For example, in 2% acetonitrile/25 mM sodium phosphate buffer at 37 °C, there is observed about 25% decomposition of sulofenur to form *p*-chloroaniline and indan-5-sulfonamide over 24 h at pH = 5.[8,14] In contrast, these diarylsulfonimidamides do not undergo detectable hydrolysis in the pH range of 2−8 over 24 h.[32]

The metabolic breakdown of five sulfonimidamides, as characterized by the urinary excretion of **65**, is listed in Table 2 and compared to LY181984 and sulofenur. For the reasons explained above, the observation of significant amounts of **65** in the urine of mice treated with sulfonimidamides was surprising. One must conclude that this cleavage results from an enzymatic process and that this data provides a credible alternative to the simple chemical hydrolysis mechanism of diarylsulfonylurea cleavage. Even more intriguing was the observation that while both enantiomers of **14** appeared to be equally well absorbed, and formed the major urinary metabolite **41** to an equivalent extent, that enantiomer **15**, possessing antitumor activity, produced greater than 10-fold more **65** than the antitumor inactive enantiomer (**16**).

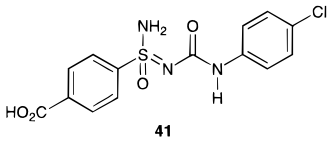
Discussion

The sulfonimidamides exhibit two significantly different molecular properties in comparison to the analogous sulfonylureas. The first is that the sulfonimida-

Table 2. Measurement of Sulfonimidamide Metabolic Cleavage[a]



65



41

compound	pK_a[b]	μmol of **65**	% dose converted to **65**	% dose converted to **41**
sulofenur	6.2	0.37[c]		
LY181984	6.1	1.02[c]		
14	10.5	<0.2		
15(−)		0.58 ± 0.10	4.7 ± 0.8	18 ± 1
16(+)		not detected	<0.3	17 ± 3
18	12.3	1.2		
49	10.8	<0.15[d]		

[a] Groups of two to four mice were given single 100 mg/kg oral doses of each compound, and combined urine was collected 0−24 h; the amount of metabolite **65** excreted into the urine in 24 h per mouse was determined as described in ref 14. [b] Determined in solutions of 2:1 DMF:water. [c] See ref 14. [d] Limited oral absorption.

mides are very weak acids (9 < pK_a < 11) while the sulfonylureas are weak acids (5 < pK_a < 7). As a result, the *in vivo* distribution of ionized vs un-ionized sulfonylurea could be significantly affected by local compartment pH. Indeed, *in vitro* studies have characterized pH-dependent cytotoxicity and accumulation of these sulfonylureas in the pH range 6.0−7.4, that pH range within which the concentrations of both the ionized and un-ionized forms of the sulfonylurea would be expected to be significant.[33−35] In contrast, the sulfonimidamides would circulate and distribute as neutral species. The second relative difference is the hydrolytic stability. Sulfonimidamides, unlike sulfonylureas, would not be expected to undergo simple chemical hydrolysis *in vivo*. Our observations, however, demonstrate that not only is the product of *p*-chloroaniline metabolism, **65**, observed after dosing of sulfonimidamides but it is formed in the same relative magnitude as from sulofenur stereospecifically from one sulfonimidamide enantiomer (**15**) of the racemate (**14**). These data suggest that the cleavage of *p*-chloroaniline from the sulfonimidamide occurs via an enzymatic mechanism similar to that postulated for the cleavage of the sulfonylureas.[14] It is interesting to note that this same enantiomer (**15**) also showed significant 6C3HED antitumor activity, whereas no activity was observed for the enantiomer (**16**) which was not metabolically cleaved. Sulofenur had demonstrated excellent activity, when dosed orally, against the human tumor xenografts MX-1, CX-1, LX-1, GC3, and VRC5 carried in nude mice.[7] Two of the more 6C3HED-active sulfonimidamide analogs, **38** and **44,** exhibited only modest antitumor activity in these models when dosed by either po or ip routes to toxicity, and for that reason, the sulfonimidamide series has not been developed further.

Experimental Section

General Procedure. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were acquired on a GE QE-300 spectrometer at 300 MHz (proton) and 75 MHz (carbon). Heteroatom−proton assignments were made on the basis of D_2O exchange. Coupling constants are reported in Hertz. TLC was performed on silica gel 60 F_{254} plates from E. Merck. Flash chromatography was carried out on EM Science silica gel 60 (230−400 mesh ASTM). All solvents and chemicals were used as purchased without further purification. *tert*-Butyl hypochlorite was obtained from TCI America. Reactions were run under nitrogen.

Biological Methods. *In vivo* antitumor testing procedures,[8] *in vitro* cytotoxicity procedures,[8] and pharmacokinetic methods[12,14] have been described previously.

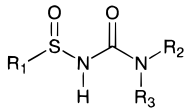
Method A. *N*-[(4-Methylphenyl)sulfinyl]-*N*′-(4-chlorophenyl)urea (9b). A dry 250 mL three-neck round-bottom flask fitted with a mechanical stirrer, addition funnel, and nitrogen line was charged with silver cyanate (20.8 g, 138.6 mmol) and 70 mL of ether. This mixture was cooled to 0 °C and the addition funnel charged with a solution of crude *p*-toluenesulfinyl chloride[22] (16.95 g, 97.05 mmol) in 70 mL of ether; the sulfinyl chloride solution was added dropwise to the cyanate mixture with vigorous stirring over 30 min, keeping the temperature at 0 °C. After the cooling bath was removed and the mixture stirred at room temperature for 2 h, the suspended silver chloride was removed by filtration and the yellow sulfinyl isocyanate solution was transfered to a dry 1 L three-neck flask. A solution of *p*-chloroaniline (11.2 g, 87.8 mmol) in 200 mL of ether was added dropwise to the ice-cold sulfinyl isocyanate solution over 15 min. After the mixture was warmed to room temperature and stirred overnight, the resulting solid was collected by filtration and rinsed with 1 L of ether. Vacuum drying at 40 °C for 4 h gave 20.93 g (77%) of **9b** as a white to light purple solid: mp 163−164 °C; R_f (10/1, EtOAc/HOAc) = 0.63; ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H, C*H*$_3$), 7.33 (d, 2H, J = 8.8, Ar-*H*), 7.41−7.46 (m, 4H, Ar-*H*), 7.63 (d, 2H, J = 8.1, Ar-*H*), 8.83 (s, 1H, N*H*), and 9.56 (s, 1H, SON*H*); ^{13}C NMR (DMSO-d_6) δ 21.3, 120.8, 125.2, 127.0, 129.2, 130.2, 137.9, 141.6, 142.0, and 153.2; IR(KBr) 3274, 3158, 1698, 1247, 1207, 1178, and 1096 cm^{-1}; FDMS(DMSO) *m*/*e* 308, 310 (M^+).

***N*-(Indanylsulfinyl)-*N*′-(4-chlorophenyl)urea (9l).** Indan-5-sulfonyl chloride[36] (10.8 g, 50 mmol) in 75 mL of acetone was treated over 10 min with a solution consisting of $NaHSO_3$ (12.6 g, 100 mmol) and $NaHCO_3$ (8.4 g, 100 mmol) in 150 mL of water. This mixture was heated at reflux (60 °C) for 1 h, during which time it became homogeneous. The cooled reaction mixture was washed with CH_2Cl_2 (1 × 100 mL). Evaporation of the aqueous to dryness under vacuum gave a solid residue which was extracted with CH_3OH (1 × 300 mL). This extract was filtered and evaporated to a volume of about 50 mL. Addition of 200 mL of ether precipitated a solid which was collected by filtration. Vacuum drying yielded 10.1 g (99%) of sodium indan-5-sulfinate: ^{1}H NMR (D_2O) δ 2.05 (m, 2H, C*H*$_2$), 2.88 (m, 4H, 2C*H*$_2$), 7.4 (m, 2H, 2Ar-*H*), and 7.5 (s, 1H, Ar-*H*); FABMS (D_2O) *m*/*e* 227 (M^+), 205 (M + H − Na)$^+$.

Indan-5-sulfinyl chloride (4.2 g, 21.1 mmol) [prepared from sodium indan-5-sulfinate (6.1 g, 29.9 mmol) and thionyl chloride (15 mL, 206 mmol)][22] was reacted, as for **9b**, with silver cyanate (4.4 g, 29.6 mmol) and p-chloroaniline (3.5 g, 27.5 mmol) to provide 4.48 g (45%) of **9l**: mp 140−142 °C; R_f (1/9, MeOH/$CHCl_3$) = 0.68; ^{1}H NMR (DMSO-d_6) δ 2.02−2.1 (m, 2H, C*H*$_2$), 2.89−2.94 (m, 4H, 2C*H*$_2$), 7.32−7.49 (m, 6H, Ar-*H*), 7.60 (s, 1H, Ar-*H*), 8.82 (s, 1H, exchanges with D_2O, N*H*), and 9.53 (s, 1H, exchanges with D_2O, N*H*); IR (KBr) 3425, 3313, 1655, 1547, 1492, 1401, 1089, 820, and 589 cm^{-1}; FDMS (DMSO) *m*/*e* 334, 336 (M^+).

Method B. *N*-[[4-(Acetoxymethyl)phenyl]sulfinyl]-*N*′-(4-chlorophenyl)urea (9d). A solution of the 4-(hydroxymethyl)phenyl disulfide[37] (2.65 g, 9.52 mmol) in CH_2Cl_2 (75 mL) was treated with catalytic DMAP under nitrogen followed by Et_3N (4.0 mL, 28.6 mmol) and acetic anhydride (2.24 mL, 23.8 mmol). One hour later, the reaction mixture was washed with 1 N HCl solution, water, and brine and dried (Na_2SO_4); filtration followed by evaporation yielded the crude product, which was combined with a similarly prepared lot of crude product [from 1.27 g, 4.56 mmol of 4-(hydroxymethyl)phenyl disulfide] and purified by silica gel flash chromatography (ether/hexane) to provide 4.45 g (87%) of 4-(acetoxymethyl)-phenyl disulfide: mp 52−54 °C; R_f (EtOAc) = 0.69; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, COC*H*$_3$), 5.08 (s, 2H, ArC*H*$_2$-OAc), 7.31 (d, 2H, J = 8.2 Hz, Ar-*H*), and 7.50 (d, 2H, J = 8.3 Hz, Ar-*H*); IR ($CHCl_3$) 3028, 3013, 1735, 1494, 1380, 1362, 1231, 1210,

Table 3. Physical Properties and Method of Synthesis of Sulfinylureas



	substituents				
9	R_1	R_2	R_3	method[a]	molecular formula[b]
a	phenyl	H	*p*-Cl-phenyl	A[c]	$C_{13}H_{11}Cl_1N_2O_2S_1$
b	*p*-tolyl	H	*p*-Cl-phenyl	A[c]	$C_{14}H_{13}Cl_1N_2O_2S_1$
c	*p*-tolyl	Me	*p*-Cl-phenyl	A	$C_{15}H_{15}Cl_1N_2O_2S_1$
d	*p*-($AcOCH_2$)phenyl	H	*p*-Cl-phenyl	B	$C_{16}H_{15}Cl_1N_2O_4S_1$
e	*p*-(CO_2Me)phenyl	H	*p*-Cl-phenyl	B	$C_{15}H_{13}Cl_1N_2O_4S_1$
f	*p*-ethylphenyl	H	*p*-Cl-phenyl	B	$C_{15}H_{15}Cl_1N_2O_2S_1$
g	*p*-(*t*-Bu)phenyl	H	*p*-Cl-phenyl	B	$C_{17}H_{19}Cl_1N_2O_2S_1$
h	3,4-dimethylphenyl	H	*p*-Cl-phenyl	B	$C_{15}H_{15}Cl_1N_2O_2S_1$
i	3,5-dimethylphenyl	H	*p*-Cl-phenyl	C	$C_{15}H_{15}Cl_1N_2O_2S_1$
j	3,4,5-trimethylphenyl	H	*p*-Cl-phenyl	B	$C_{16}H_{17}Cl_1N_2O_2S_1$
k	3,5-dimethyl-4-Cl-phenyl	H	*p*-Cl-phenyl	B	$C_{15}H_{14}Cl_2N_2O_2S_1$
l	5-indanyl	H	*p*-Cl-phenyl	A	$C_{16}H_{15}Cl_1N_2O_2S_1$
m	*p*-Cl-phenyl	H	*p*-Cl-phenyl	B	$C_{13}H_{11}Cl_2N_3O_2S_1$
n	*p*-Br-phenyl	H	*p*-Cl-phenyl	B	$C_{13}H_{11}B_rCl_1N_3O_2S_1$
o	*p*-(CF_3)phenyl	H	*p*-Cl-phenyl	B	$C_{14}H_{10}F_3Cl_1N_2O_2S_1$
p	*p*-tolyl	H	phenyl	A	$C_{14}H_{14}N_2O_2S_1$
q	*p*-tolyl	H	3,4-Cl_2-phenyl	A	$C_{14}H_{12}Cl_2N_2O_2S_1$
r	*p*-tolyl	H	*p*-Br-phenyl	A	$C_{14}H_{13}B_{r1}N_2O_2S_1$
s	*p*-tolyl	H	*p*-CF_3-phenyl	A	$C_{15}H_{13}F_3N_2O_2S_1$
t	*p*-tolyl	H	*p*-F-phenyl	A	$C_{14}H_{13}F_1N_2O_2S_1$[d]
u	*p*-tolyl	H	*p*-(benzyloxy)phenyl	A	$C_{21}H_{20}N_2O_3S_1$
v	*p*-tolyl	H	*p*-(methoxy)phenyl	A	$C_{15}H_{16}N_2O_3S_1$
w	*p*-tolyl	H	*p*-methylphenyl	A	$C_{15}H_{16}N_2O_2S_1$
x	*p*-tolyl	H	*n*-butyl	A	$C_{12}H_{18}N_2O_2S_1$[e]
y	*n*-butyl	H	*p*-Cl-phenyl	B	$C_{11}H_{15}Cl_1N_2O_2S_1$

[a] Method of preparation of sulfinyl chloride (see text). [b] All compounds gave satisfactory C, H, N analyses. [c] Commercially available sodium sulfinate. [d] Characterized by 300 MHz NMR and conversion to **58**. [e] Characterized by 300 MHz NMR and conversion to **63**.

1028, and 1015 cm^{-1}; FDMS (DMSO) 362 (M^+). Anal Calcd for $C_{18}H_{18}O_4S_2$: C, 59.65; H, 5.01. Found: C, 59.90; H, 5.08.

The sulfinyl chloride was prepared from 4-(acetoxymethyl)-phenyl disulfide by the method of Youn and Herrmann[24] and used without purification: IR (film) 1750 and 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H, $COCH_3$), 5.21 (s, 2H, $ArCH_2$-OAc), 7.60 (d, 2H, J = 8.2 Hz, Ar-*H*), and 7.89 (d, 2H, J = 8.3 Hz, Ar-*H*).

As in the preparation of **9b**, 4-(acetoxymethyl)benzenesulfinyl chloride (22.9 mmol), silver cyanate (5.46 g, 36.4 mmol), and *p*-chloroaniline (2.92 g, 22.9 mmol) provided, after vacuum drying at 25 °C, 6.15 g (73.4%) of **9d**: mp 131−133 °C; ^1H NMR (DMSO-d_6) δ 2.07 (s, 3H, CO-CH_3), 5.16 (s, 2H, $ArCH_2$-OAc), 7.34 (d, 2H, J = 8.8 Hz, Ar-*H*), 7.44 (d, 2H, J = 8.8 Hz, Ar-*H*), 7.59 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.75 (d, 2H, J = 8.1 Hz, Ar-*H*), 8.84 (s, 1H, exchanges with D_2O, N-*H*), and 9.67 (s, 1H, exchanges with D_2O, N-*H*); IR (KBr) 3264, 3195, 3130, 1746, 1689, 1668, 1609, 1551, 1495, 1481, 1245, 1225, 1094, 1067, 1028, and 1010 cm^{-1}; FDMS (DMSO) *m*/*e* 366, 368 (M^+).

***N*-[(3,4-Dimethylphenyl)sulfinyl]-*N′*-(4-chlorophenyl)-urea (9h).** According to the method of Youn and Herrmann,[23] a solution of 3,4-dimethylthiophenol (4.79 g, 34.7 mmol) in 120 mL of toluene at −60°C was treated with glacial acetic acid (2.0 mL, 35 mmol), followed by dropwise addition of a solution of sulfuryl chloride (5.75 mL, 69.4 mmol) in 20 mL of toluene. The cooling bath was removed, and after 18 h, additional sulfuryl chloride (2.88 mL, 34.7 mmol) was added to consume the remaining thiol. Evaporation provided 6.6 g (100%) of the crude orange sulfinyl chloride: ^1H NMR ($CDCl_3$) δ 2.34 (s, 6H, $2CH_3$), 7.37 (d, 1H, J = 7.9 Hz, Ar-*H*), 7.62 (d, 1H, J = 7.9 Hz, Ar-*H*), 7.67 (s, 1H, Ar-*H*).

As in the preparation of **9b**, 3,4-dimethylbenzenesulfinyl chloride (6.6 g, 34.7 mmol), silver cyanate (6.8g, 45 mmol), and *p*-chloroaniline (4.9 g, 38 mmol) gave 9.14 g (82%) of **9h**: mp 129−130 °C; R_f (10/10/2, EtOAc/EE/AcOH) = 0.75; ^1H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.32−7.51 (m, 7H, Ar-*H*), 8.81 (s, 1H, exchanges with D_2O, N*H*), and 9.52 (s, 1H, exchanges with D_2O, N*H*); IR (KBr) 3427, 3319, 3209, 1712, 1701, 1602, 1550, 1492, 1444, 1052, 832, and 661 cm^{-1}; FDMS (DMSO) *m*/*e* 322, 324 (M^+).

***N*-[(3,4,5-Trimethylphenyl)sulfinyl]-*N′*-(4-chlorophenyl)-urea (9j).** A three-neck 1000 mL round-bottom flask, fitted with a mechanical stirrer, thermometer, addition funnel, and nitrogen purge, was charged with 3,4,5-trimethylphenol (35.80 g, 0.26 mol) and 200 mL of DMF. Sodium hydride (60% dispersion in mineral oil, 11.60 g, ∼0.29 mol) was cautiously added in portions with vigorous stirring over 20 min. The resulting mixture was stirred 30 min under nitrogen. *N*,*N*-Dimethylthiocarbamoyl chloride (39.0 g, 0.3 mol), dissolved in 30mL of DMF, was added dropwise to the sodium trimethylphenolate mixture, maintaining an internal temperature of <60 °C. After the addition was complete, the reaction mixture was heated at 90 °C for 40 min and then cooled to room temperature. Following dilution with 300 mL of cold water, the solution was poured into 350 mL of aqueous KOH, stirred briefly, and placed in the refrigerator for 2 h. The resulting solid was isolated by filtration, rinsed with 200 mL of water, and dissolved in ether (500 mL). The organic phase was washed with water (1 × 100 mL) and brine (1 × 100 mL) and dried ($MgSO_4$). Filtration and evaporation gave 62 g of crude product. Recrystallization from 100 mL of MeOH gave 35.8 g of *O*-(3,4,5-trimethylphenyl) *N*,*N*-dimethylthiocarbamate as a light yellow solid (61%): mp 90−91 °C; R_f (3/7, EtOAc/hexane) = 0.45; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 2.30 (s, 6H, $2CH_3$), 3.33 and 3.46 (s, 6H, NCH_3), and 6.74 (s, 2H, Ar-*H*); IR ($CHCl_3$) 2983, 2871, 1535, 1479, 1398, 1304, 1276, 1217, 1179, 1121, 1026, 924, and 867 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 205.4 (25 402) and 250.8 (14 013) nm; FDMS (DMSO) *m*/*e* 223 (M^+). Anal Calcd for $C_{12}H_{17}N_1O_1S_1$: C, 64.54; H, 7.67; N, 6.27. Found: C, 64.77; H, 7.87; N, 6.33.

The *O*-(3,4,5-trimethylphenyl) *N*,*N*-dimethylthiocarbamate (27.40 g, 0.12 mol) was heated neat under nitrogen to a temperature of 290 °C; rearrangement to product was conveniently monitored by TLC (30% EtOAC/hexane) and was complete after 4 h. A small sample was purified by silica gel flash chromatography (3/7, EtOAC/hexane) and recrystallized

from ether/hexane to provide an analytical sample of *S*-(3,4,5-trimethylphenyl) dimethylthiocarbamate: mp 80−81 °C; R_f (3/7, EtOAc/hexane) = 0.25; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H, CH_3), 2.29 (s, 6H, 2CH_3), 3.07 (bs, 6H, NCH_3), and 7.16 (s, 2H, Ar-H); IR ($CHCl_3$) 3011, 2932, 1655, 1474, 1367, 1261, and 1099 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 212.4 (23 432) nm; FDMS (MeOH) *m/e* 223 (M^+). Anal. Calcd for $C_{12}H_{17}N_1O_1S_1$: C, 64.54; H, 7.67; N, 6.27. Found: C, 64.79; H, 7.71; N, 6.10.

The crude *S*-(3,4,5-trimethylphenyl) dimethylthiocarbamate (30 g, 0.13 mol) was dissolved in 350 mL of MeOH and 30 mL of water. Potassium hydroxide (35 g, 0.6 mol) was added, and the mixture was heated at reflux for 3 h. After the mixture was cooled and removing the MeOH removed *in vacuo*, the residue was diluted with water (500 mL) and washed with ether (3 × 100 mL). The aqueous layer was acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 100 mL); the combined organic extract was dried (Na_2SO_4) and evaporated to yield 16.4 g of an orange oil. Vacuum distillation provided 13.3 g (72%) of 3,4,5-trimethylthiophenol as a clear oil: bp 68−70 °C (0.25 mmHg); R_f (3/7, EtOAc/hexane) = 0.63; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H, CH_3), 2.25 (s, 6H, 2CH_3), 3.33 (s, 1H, exchanges with D_2O, S*H*), and 6.97 (s, 2H, Ar-*H*); IR-($CHCl_3$) 3010, 2978, 1589, 1475, 1444, 1379, 1196, 886, and 853 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 212.0 (23 084) and 240.8 (7803) nm; EIMS (MeOH) *m/e* 152 (M^+), 137, 119, 91. Anal. Calcd for $C_9H_{12}S_1$: C, 70.99; H, 7.94. Found: C, 70.89; H, 8.08.

The sulfinyl chloride was prepared from 3,4,5-trimethylthiophenol (10 g, 66 mmol) by the method of Youn and Herrmann[23] and used without purification: ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 2.40 (s, 6H, 2CH_3), and 7.52 (s, 2H, Ar-H).

As in the preparation of **9b,** 3,4,5-trimethylbenzenesulfinyl chloride (13.3 g, 65.7 mmol), silver cyanate (12.8 g, 85.4 mmol), and *p*-chloroaniline (9.2 g, 72 mmol) gave 9.01 g (41%) of **9j**: mp 144−145 °C; R_f (1/9, MeOH/$CHCl_3$) = 0.66; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3H, CH_3), 2.31 (s, 6H, 2CH_3), 7.33 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.36 (s, 2H, Ar-*H*), 7.43 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 8.81 (bs, 1H, exchanges with D_2O, N*H*), and 9.50 (s, 1H, exchanges with D_2O, N*H*); IR (KBr) 3427, 3314, 1655, 1586, 1492, 1470, 1133, 821, and 618 cm^{-1}; FDMS (DMSO) *m/e* 336, 338 (M^+).

Method C. *N*-[(3,5-Dimethylphenyl)sulfinyl]-*N′*-(4-chlorophenyl)urea (9i). As in the preparation of **9b**, 3,5-dimethylbenzenesulfenyl chloride[28] (13.9 g, 80.7 mmol), silver cyanate (16 g, 107 mmol), and *p*-chloroaniline (12.4 g, 97.2 mmol) provided 10.8 g (46%) of crude **8i**. Silica gel flash chromatography (EtOAc/hexane) afforded 1.92 g (8%) of **8i**: mp 180−181 °C; R_f (1/9, MeOH/$CHCl_3$) = 0.74; ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 6H, 2CH_3), 6.79 (s, 1H, Ar-*H*), 6.80 (s, 2H, Ar-*H*), 7.29 (d, 2H, *J* = 8.8Hz, Ar-*H*), 7.48 (d, 2H, *J* = 8.8Hz, Ar-*H*), 8.15 (s, 1H, exchanges with D_2O, N*H*), and 9.11 (s, 1H, exchanges with D_2O, N*H*); IR (KBr) 3268, 1641, 1602, 1551, 1462, 1089, 834, and 681 cm^{-1}; FDMS (DMSO) *m/e* 306, 308 (M^+). Anal. Calcd for $C_{15}H_{15}Cl_1N_2O_1S_1$: C, 58.72; H, 4.93; N, 9.13. Found: C, 58.45; H, 5.13; N, 9.19.

A solution of **8i** (2.53 g, 8.7 mmol) in 50 mL of THF was cooled to 0 °C. Peracetic acid (32%, 1.6 mL, 8.6 mmol) was added dropwise. Two hours later additional peracetic acid (0.2 mL, 1.07 mmol) was added to complete the oxidation. After the mixture was diluted with 150 mL of water and stirred for 30 min, the solid was collected by filtration and rinsed with 100 mL of water to yield, after drying, 2.16 g (81%) of **9i**: mp 114−115 °C; R_f (1/9, MeOH/ $CHCl_3$) = 0.65; ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 6H, 2CH_3), 7.23−7.46 (m, 7H, Ar-*H*), 8.83 (s, 1H, exchanges with D_2O, N*H*), and 9.58 (s, 1H, exchanges with D_2O, N*H*); IR (KBr) 3427, 3313, 1654, 1609, 1550, 1492, 1402, 1136, 1041, 821, and 503 cm^{-1}; FDMS (DMSO) *m/e* 322, 324 (M^+).

Sulfonimidamides. *N*-[[(4-Chlorophenyl)amino]carbonyl]-*N′*,4-dimethylbenzenesulfonimidamide (18). A flame-dried, 500 mL three-neck round-bottom flask was charged with 200 mL of dry THF and **9b** (6.48 g, 21.0 mmol). *N*-Chlorobenzotriazole (3.39 g, 22.07 mmol) was added in one portion and stirring continued another 25 min. The resulting solution was added dropwise to 100 mL of methylamine at −78 °C over 10 min. The cooling bath was removed and stirring continued at room temperature for 3 h. The reaction solution was concentrated *in vacuo* and the resulting residue dissolved in 350 mL of EtOAc and washed with 1 N HCl solution (1 × 100 mL), water (1 × 100 mL), and brine (1 × 50 mL). After drying (Na_2SO_4), filtration and evaporation gave a foam (10 g). Trituration with warm toluene (120 mL) followed by cooling gave a white crystalline product which was collected by filtration, rinsed with chilled toluene (20 mL), and vacuum-dried to yield 3.89 g (55%) of the product: mp 79−81 °C; R_f (1/9, MeOH/ $CHCl_3$) = 0.69; ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H, CH_3), 2.40 (d, 3H, *J* = 4.9 Hz, NCH_3), 7.20 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.40 (d, 2H, *J* = 8.1 Hz, Ar-*H*), 7.47 (d obscuring N*H*, 3H, *J* = 8.8 Hz, 1H exchanges with D_2O, Ar-*H* + N*H*), 7.72 (d, 2H, *J* = 8.2 Hz, Ar-*H*), and 9.33 (s, 1H, exchanges with D_2O, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.4, 28.1, 120.0, 125.4, 127.7, 128.6, 130.0, 136.3, 140.0, 143.4, and 156.8; IR (KBr) 3357, 1630, 1592, 1526, 1399, 1278, 1232, 1121, 1090, 1082, 1011, 927, 829, 774, and 687 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 204.6 (37 504), 254.6 (27 729) nm; FDMS (DMSO) *m/e* 337, 339 (M^+).

***N*-[[(4-Chlorophenyl)amino]carbonyl]-*N′*-acetyl-*N′*,4-dimethylbenzenesulfonimidamide (19).** A slurry of **18** (5.1 g, 15.1 mmol) in 120 mL of CH_2Cl_2 was treated with Et_3N (4.2 mL, 30 mmol) and DMAP (30 mg, 0.25 mmol), followed by acetic anhydride (1.62 mL, 16.7 mmol) dropwise. After being stirried for 1 h, the reaction solution was washed with 1 N aqueous HCl (1 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL); drying (Na_2SO_4), filtration, and evaporation gave 5.4 g of a white solid. Silica gel flash chromatography (2/3, EtOAc/hexane) afforded 3.32 g of **19** and a small amount of **20**. Recrystallization from EtOAc/hexane yielded 2.6 g (45%) of **19**: mp 150−151 °C; R_f (1/1, EtOAc/hexanes) = 0.40; ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, Ar-CH_3), 2.41 (s, 3H, OAc), 3.28 (s, 3H, N-CH_3), 7.28 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.45 (d, 2H, *J* = 8.1 Hz, Ar-*H*), 7.54 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.98 (d, 2H, *J* = 8.1 Hz, Ar-*H*), and 9.74 (s, 1H, exchanges with D_2O, N*H*); IR-($CHCl_3$) 3450, 1702, 1664, 1590, 1510, 1399, 1268, and 1121 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 204.8 (41 076) and 259.0 (24 346) nm; FDMS (DMSO) *m/e* 379, 381 (M^+).

***N*-Acetyl-*N*-[[(4-chlorophenyl)amino]carbonyl]-*N′*-acetyl-*N′*,4-dimethylbenzenesulfonimidamide (20).** In a manner similar to the synthesis of **19**, **18** (3.38 g, 10 mmol), Et_3N (7 mL, 50 mmol), DMAP (100 mg, 0.8 mmol), and acetic anhydride (3.4 mL, 35 mmol) in 75 mL of CH_2Cl_2 gave a yellow solid, 3.06 g. Recrystallization from 100 mL of EtOAc/hexane (3/7) yielded **20** as a white solid, 2.33 g (55%): mp 138−139 °C; R_f (1/1, EtOAc/hexane) = 0.27; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, Ar-CH_3), 2.41 (s, 3H, OAc), 2.67 (s, 3H, OAc), 3.28 (s, 3H, N-CH_3), 7.17−7.22 (m, 4H, Ar-*H*), 7.34 (d, 2H, *J* = 8.4 Hz, Ar-*H*), and 7.45 (d, 2H, *J* = 8.6 Hz, Ar-*H*); IR ($CHCl_3$) 1702, 1492, 1371, 1256, 1149, 1093, 1015 and 926 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 203.4 (36 566), 223.6 (23 490), and 238.6 (20 158) nm; FDMS (DMSO) *m/e* 421, 423 (M^+).

***N*-[[(4-Chlorophenyl)amino]carbonyl]-*N′*,*N′*-4-trimethylbenzenesulfonimidamide (23).** In a manner similar to the synthesis of **18**, **14** (6.2 g, 20 mmol) was reacted with *N*-chlorobenzotriazole (3.2 g, 21 mmol) and dimethylamine (10 mL, 151 mmol) at −20 °C. Recrystallization of the crude product from 100 mL of warm toluene gave 4.2 g (59%) of **23**: mp 183−184 °C; R_f (1/9, MeOH/$CHCl_3$) = 0.80; ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 2.66 (s, 6H, 2CH_3), 7.23 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.44 (d, 2H, *J* = 8.2 Hz, Ar-*H*), 7.51 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.72 (d, 2H, *J* = 8.2 Hz, Ar-*H*), and 9.50 (bs, 1H, exchanges with D_2O, N*H*); IR (KBr) 3285, 1630, 1536, 1284, 1127, and 958 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 205.0 (37 973), 255.0 (28 328) nm; FDMS (DMSO) *m/e* 351, 353 (M^+).

***N*-[[(4-Chlorophenyl)amino]carbonyl]-*N′*-(2-hydroxyethyl)-4-methylbenzenesulfonimidamide (34).** In a manner similar to the synthesis of **18**, **14** (3.08 g, 10.0 mmol), *N*-chlorobenzotriazole (1.54 g, 10.0 mmol), and ethanolamine (1.95 mL, 32.3 mmol) gave 6.0 g of a foam. Purification by silica gel flash chromatography (EtOAc/hexane) followed by recrystallization from toluene gave 1.48 g (40%) of **34**: mp 112.5−114 °C; R_f (EtOAc) = 0.43; ^{1}H NMR (DMSO-d_6) δ 2.79−2.88 (m, 2H, CH_2N), 3.32 (s, 3H, Ar-CH_3), 3.35−3.41 (m, 2H, CH_2OH), 4.70 (t, 1H, *J* = 5.5 Hz, exchanges with D_2O, CH_2OH), 7.21 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.40 (d, 2H, *J* = 8.1 Hz, Ar-*H*), 7.48 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.65 (t, 1H, *J* = 5.9

Hz, exchanges with D_2O, CH_2NH), 7.75 (d, 2H, J = 8.1 Hz, Ar-*H*), and 9.33 (s, 1H, exchanges with D_2O, N*H*); IR ($CHCl_3$) 1634, 1591, 1510, 1398, 1305, 1274, 1230, 1123, 1092, 1047 and 830 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 204 (38 740), 223 (16 076), 255 (28 541), 311.8 (629) nm; FDMS (DMSO) *m/e* 367, 369 (M^+).

***N*-[[(4-Chlorophenyl)amino]carbonyl]-*N*′-phenyl-4-methylbenzenesulfonimidamide (36).** In a manner similar to the synthesis of **18**, **14** (6.2 g, 20 mmol), *N*-chlorobenzotriazole (3.2 g, 21 mmol), and aniline (2.0 g, 21 mmol) gave the crude **36** as a foam (10.6 g). Silica gel flash chromatography (1/9, MeOH/$CHCl_3$), followed by recrystallization from 75 mL of warm toluene, gave 4.8 g (59%) of the **36** as a white solid: mp 160−161.5 °C; R_f(1/9, MeOH/$CHCl_3$) = 0.77; ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 7.00−7.26 (m, 7H, Ar-*H*), 7.35 (d, 2H, J = 8.2 Hz, Ar-*H*), 7.53 (d, 2H, J = 8.8 Hz, Ar-*H*), 7.75 (d, 2H, J = 8.2 Hz, Ar-*H*), 9.46 (bs, 1H, exchanges with D_2O, N*H*), and 10.30 (bs, 1H, exchanges with D_2O, N*H*); ^{13}C NMR (DMSO-d_6) δ 21.3, 120.2, 121.1, 124.5, 125.7, 127.7, 128.8, 129.5, 130.0, 136.9, 137.9, 139.9, 143.8, and 156.2; IR (KBr) 3353, 3166, 1637, 1590, 1495, 1398, 1287, 1214, 1124, and 685 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 205.8 (44 356), 255.2 (34 798) nm; FDMS (DMSO) *m/e* 399, 401 (M^+).

Acknowledgment. The authors wish to express their appreciation for the analytical and spectral services provided by the Physical Chemistry Department at the Lilly Research Laboratories and for quantities of **9b** provided by Bennie Foster, Dave Hunden, and Elizabeth Aaron.

Supporting Information Available: Tables listing final atomic coordinates for compound **32**, equivalent isotropic displacement parameters, anisotropic displacement parameters for non-hydrogen atoms, bond angles, and bond lengths (9 pages). Ordering information is given on any current masthead page.

References

(1) Presented, in part, at the ACCR Special Conference on Novel Strategies Against Resistant Cancers, November 17−21, 1995, Ft. Myers, FL. Poster A24.
(2) Grindey G. B. Current Status of Cancer Drug Development: Failure or Limited Success? *Cancer Cells* **1990**, *2* (6), 163−71.
(3) Grindey, G. B.; Boder, G. B.; Harper, R. W.; Howbert, J. J.; Poore, G. A.; Reider, B. J.; Shaw, W. N.; Todd, G. C. Identification of diarylsulfonylureas as novel antitumor agents. *Proc. Am. Assoc. Cancer Res.* **1986**, *27*, 277.
(4) Grindey, G. B.; Boder, G. B.; Grossman, C. S.; Howbert, J. J.; Poore, G. A.; Shaw, W. N.; Todd, G. C.; Worzalla, J. F. Further development of diarylsulfonylureas as novel anticancer drugs. *Proc. Am. Assoc. Cancer Res.* **1987**, *28*, 309.
(5) Grindey, G. B. Identification of diarylsulfonylureas as novel anticancer drugs. *Proc. Am. Assoc. Cancer Res.* **1988**, *29*, 535.
(6) Pearce, H. L. Anticancer drug development at Lilly Research Laboratories. *Ann. Oncol.* **1995**, *6* (Suppl. 1), S55−62.
(7) Howbert, J. J. Sulofenur. *Drugs Future* **1991**, *16* (6), 517−20.
(8) Howbert, J. J.; Grossman, C. S.; Crowell, T. A.; Rieder, B. J.; Harper, R. W.; Kramer, K. E.; Tao, E. V.; Aikens, J.; Poore, G. A.; Rinzel, S. M.; Grindey, G. B.; Shaw, W. N.; Todd, G. C. Novel Agents Against Solid Tumors: The Diarylsulfonylureas. Synthesis, Activities, and Analysis of Quantitative Structure-Activity Relationships. *J. Med. Chem.* **1990**, *33*, 2393−407.
(9) 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. Clinical Pharmacology of a novel diarylsulfonylurea anticancer agent. *J. Clin. Oncol.* **1989**, *7*, 1733−40.
(10) Hainsworth, J. D.; Hande, K. R.; Satterlee, W. G.; Kuttesch, J.; Johnson, D. H.; Grindey, G. B.; Jackson, L. E.; Greco, F. A. Phase I Clinical Study of N-[(4-chlorophenyl)-amino]carbonyl-2,3-dihydro-1H-indene-5-sulfonamide (LY186641). *Cancer Res.* **1989**, *49*, 5217−20.
(11) Brown, T.; O'Rourke, T.; Craig, J.; Havlin, K.; Kuhn, J.; Cagnola, J.; Hamilton, M.; Grindey, G. B.; Satterlee, W.; Von Hoff, D. Orally administered LY186641: A phase I clinical and pharmacologic study on a daily X 21 schedule. *Proc. Am. Soc. Clin. Oncol.* **1989**, *8*, 70.
(12) Ehlhardt, W. J. Metabolism and disposition of the anticancer agent sulofenur in rat, mouse, monkey and human. *Drug Metab. Dispos.* **1991**, *19* (2), 370−5.
(13) Ehlhardt, W. J.; Howbert, J. J. Metabolism and disposition of p-chloroaniline in rat, mouse and monkey. *Drug Metab. Dispos.* **1991**, *19* (2), 366−9.
(14) Ehlhardt, W. J.; Woodland, J. M.; Worzalla, J. F.; Bewley, J. R.; Grindey, G. B.; Todd, G. C.; Toth, J. E.; Howbert, J. J. Comparison of metabolism and toxicity to the structure of the anticancer agent sulofenur and related sulfonylureas. *Chem. Res. Toxicol.* **1992**, *5* (5), 667−73.
(15) Mohamadi, F.; Spees, M. M.; Grindey, G. B. Sulfonylureas: A new Class of Cancer Therapeutic Agents. *J. Med. Chem.* **1992**, *35*, 3012−16.
(16) Mohamadi, F.; Spees, M. M.; Grindey, G. B. Antineoplastic Bicyclicsulfonylureas. *Bioorg. Med. Chem. Lett.* **1992**, *2* (9), 987−92.
(17) Johnson, C. R.; Jonsson, E. U.; Bacon, C. C. Preparation and Reactions of Sulfonimidoyl Chlorides. *J. Org. Chem.* **1979**, *44*, 2055−61.
(18) Johnson, C. R.; Wambsgans, A. Sulfonimidoyl Chlorides by Oxidation of Sulfinamides with tert-Butyl Hypochlorite. *J. Org. Chem.* **1979**, *44*, 2278−80.
(19) Hillemann, C. L. Herbicidal Pyrimidines. US Patent 4,666,506, 1987 (DuPont).
(20) Toth, J. E.; Ray, J.; Deeter, J. Synthesis and Resolution of Sulfonimidamide Analogs of Sulfonylureas. *J. Org. Chem.* **1993**, *58*, 3469−72.
(21) Field, L.; Lee, C. Sulfinic Acids and Related Compounds: 24. Monothioquinone S,S-Dioxides and Their Relation to Convergent Syntheses Involving Hydroxyarenesulfonyl Chlorides. *J. Org. Chem.* **1990**, *55*, 2558−63.
(22) Kurzer, F. p-Toluenesulfonyl Chloride. *Organic Syntheses*; John Wiley & Sons, Inc.: New York, 1963; Collect. Vol. IV, pp 937−9.
(23) Youn, J.-H.; Hermann, R. Direct Conversion of Thiols to Sulfinyl Chlorides by Sulfuryl Chloride. *Synthesis* **1987**, 72−3.
(24) Youn, J.-H.; Hermann, R. A Simple and Efficient Preparation of Sulfinyl Chlorides from Disulfides and Sulfuryl Chloride. *Tetrahedron Lett.* **1986**, *27*, 1493−4.
(25) Kee, M.-L.; Douglass, I. B. The Synthesis of Sulfinyl Chlorides. A Review. *Org. Prep. Proc.* **1970**, *2* (3), 235−44.
(26) Young, R. N.; Gauthier, J. Y.; Coombs, W. The Methyl Group as A Protecting Group for Arylthiols: A Mild and Efficient Method for the Conversion of Methyl Aryl Sulfides to Arylthiols. *Tetrahedron Lett.* **1984**, *25* (17), 1753−56.
(27) Newman, M. S.; Karnes, H. A. The Conversion of Phenols to Thiophenols via Dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31*, 3980−84.
(28) Harpp, D. N.;Friedlander, B. T.,Smith, R. A. The Synthesis of Thiocyanates from Sulfenyl Chlorides and Trimethylsilyl Cyanide. *Synthesis* **1979**, 181−2.
(29) Jähnchen, G.; Westphal, G. Zur Darstellung von p-Toluolsulfinylisocyanat. (The Preparation of p-Toluenesulfinylisocyanate.) *Z. Chem.* **1969**, *8*, 305.
(30) X-ray data has been filed with the Cambridge Crystallographic Data Center.
(31) Thomas, R. C.; Ikeda, G. J. The metabolism of tolbutamide in man and in the rat. *J. Med. Chem.* **1966**, *9*, 507−10.
(32) William J. Ehlhardt, John E. Toth. Unpublished results.
(33) Tannock, I.; Lee, C.; Thakar, J.; Houghton, P. pH-Dependent activity of the diarylsulfonylurea N-(5-indanylsulphonyl)-N′-(4-chlorophenyl)-urea. *Cell. Pharmacol.* **1995**, *2*, 193−8.
(34) Sosinski, J.; Chapin, C.; Thakar, J. H.; Houghton, P. J. Influence of Extracellular pH on the Accumulation and Cytotoxicity of N-(4-Methylphenylsulfonyl)-N′-(4-chlorophenyl)urea in Human Cell Lines. *Cancer Commun.* **1991**, *3* (12), 373−81.
(35) Rockwell S.; Grindey, G. B. Diarylsulfonylureas and Radiotherapy I. In Vitro Studies with N-(5-Indanylsulfonyl)-N′-(4-chlorophenyl)-urea (Sulofenur). *Cancer Commun.* **1991**, *3* (4), 103−8.
(36) Tao, E. V.; Aikens, J. Indane sulfonyl chloride: Eur. Pat. Appl. EP 254,577, 1988.
(37) Grice, R.; Owen, L. N. Cytotoxic Compounds. Part IV. Substituted Benzyl Halides. *J. Chem. Soc.* **1963**, 1947−54.

JM960673L