Sulfonylureas: A New Class of Cancer Chemotherapeutic Agents[1]

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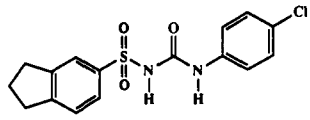
This study summarizes the antitumor properties of a number of sulofenur thiophene analogs against subcutaneously implanted 6C3HED lymphosarcoma with structural modification of the aryl moiety of the sulfonamide portion of the diarylsulfonylureas. The spectrum of activity of *N*-(*p*-chlorophenyl)-*N'*-[(5-methoxy-2-thienyl)sulfonyl]urea in the HXGC3, VRC5, CX-1, and LX-1 cell lines is also presented.

Sulofenur (LY186641) is a novel antineoplastic sulfonylurea that was discovered after the synthesis of numerous analogs and is undergoing clinical evaluation in lung, breast, colon, ovarian, pancreatic, renal, and gastric cancer.[2] This drug candidate has an exceptionally broad spectrum of activity in rodent solid tumors[2] and human tumor xenografts[2b,3] and has displayed some clinical activity.[4] In spite of the numerous efforts to characterize the mechanism of action of this molecule, the biochemistry of this class of agents is not understood.[2b,5] As a result of this, an in vivo (po dosing, daily × 8) structure–activity relationship (SAR) was carried out with mice subcutaneously implanted with the 6C3HED lymphosarcoma cell line in order to arrive at clinically superior agents. This protocol incorporates the oral bioavailability, the metabolic degradation, the pharmacokinetic and pharmacodynamic properties, and the intrinsic activity of the molecule into a single parameter (i.e. percent inhibition of tumor growth). The advantage of this approach is obvious in that these are important attributes of a commercially viable antineoplastic drug. However, the inability to decipher the contributing roles of the above variables to percent inhibition of tumor growth precludes a rational strategy of drug discovery and mandates the use of an empirical in vivo SAR for drug profile optimization.



Sulofenur (LY186641)

Characterization of the antineoplastic properties of these agents in the 6C3HED lymphosarcoma tumor line is arbitrary with regard to discovery of a cancer chemotherapeutic agent based on the biochemical and morphological variability of the cell lines that constitute cancer. Selection of this tumor line for an initial screen is based on the combination of the spectrum of activity of this class of antitumor compounds and the technical facility of working with the relevant cell lines. The shortcoming of this approach was compensated for by the evaluation of the antineoplastic properties of some of these molecules in a number of other in vivo tumor lines.

The thrust of the effort in this area centered on the aryl moiety of the sulfonamide portion of the diarylsulfonylureas. The initial objective was to evaluate the thiophene bioisosterism of this aryl group. The unsubstituted thiophene analog of sulofenur (1) showed only a trace of antitumor activity, although the synthesis of structural analogs of 1 (Scheme I) afforded additional activity (Table I).

Scheme I

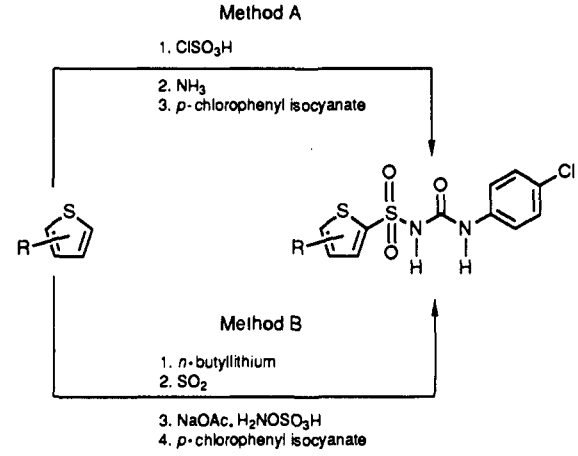
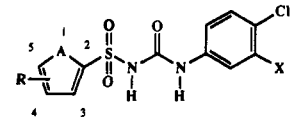


Table I[a]



entry	R	A	X	percent inhibition[c] 150 mg/kg	300 mg/kg
1	H	S	H	16 ± 27	66 ± 21
2	5-Cl	S	H	58 ± 24	89 ± 15
3[b]	5-CH_3	S	Cl	24 ± 12	61 ± 6
4	5-OCH_3	S	H	93 ± 7	100
5	5-SCH_3	S	H	29 ± 26	62 ± 30
6[b]	5-CH_2CH_3	S	H	57 ± 12	89 ± 10
7	5-OCH_2CH_3	S	H	69 ± 4	96 ± 4
8[b]	5-$(CH_2)_2CH_3$	S	H	38 ± 18	39 ± 12
9	5-$CH(CH_3)_2$	S	H	42 ± 10	63 ± 16
10	5-$O(CH_2)_2CH_3$	S	H	44 ± 20	63 ± 18
11	5-$C(CH_3)_3$	S	H	7 ± 16	10 ± 13
12	5-CH_2CH_3	O	H	57 ± 15	80 ± 5
13	5-CH_2CH_3	NH	H	ND[d]	56 ± 23
14	3-CH_3	S	H	17 ± 21	62 ± 17
15	3-CH_2CH_3	S	H	21 ± 21	25 ± 20
16	4-CH_2CH_3	S	H	55 ± 22	93 ± 7
17	4-OCH_3	S	H	36 ± 14	69 ± 12
18	4,5-Br_2	S	H	25 ± 13	52 ± 18
19	4,5-$(CH_3)_2$	S	H	42 ± 16	73 ± 9
20[b]	5-CH_2CH_3-4-CH_3	S	H	26 ± 16	58 ± 7

[a] Mice (n = 10, except compound 6 and 8 where n = 7 and 5, respectively) dosed po daily × 8 at 150 and 300 mg/kg. [b] Compound tested as its sodium salt. [c] There were no dose-related deaths in this series of compounds, except with compounds 1 and 2 where three and eight of the ten treated mice died at the 300 mg/kg dose, respectively, as a result of drug toxicity. [d] ND = not determined.

Attachment of alkyl substituents to the thiophene ring of 1 resulted in only modest increase in potency as dem-

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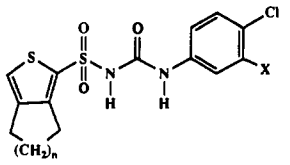
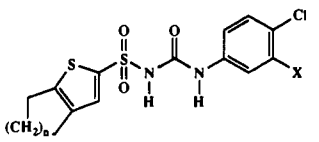
Table II[a]

entry	n	X	percent inhibition[b] 150 mg/kg	300 mg/kg
				
21	1	H	36 ± 21	51 ± 14
22	2	H	0 ± 25	15 ± 10
				
23	1	H	16 ± 21	16 ± 15
24	2	Cl	44 ± 11	

[a] Mice (n = 10) dosed po daily × 8 at 150 and 300 mg/kg, except compound 24 that was dosed at 200 mg/kg. [b] There were no dose-related deaths in this series of compounds.

onstrated by 6 and 15. Evaluation of alkoxy-substituted analogs of 1 resulted in the discovery of 4, which is substantially more potent than 1. Although the 5-(methylthio) analog of 1 (5) was evaluated in this antitumor rodent model, all attempts to synthesize the 5-(methylamino) analog of 1 by reduction of 2-nitro-5-chlorothiophene[6] or acid-catalyzed deprotection of 2-[*N*-[(*tert*-butyloxy)-carbonyl]amino]-5-chlorothiophene[7] failed to provide 2-amino-5-chlorothiophene. The (cyclopenta- and (cyclohexathiophene-ylsulfonyl)ureas 21–24 (Table II) showed only traces of activity when compared to LY186641 in this cell line (91% inhibition of tumor growth at 150 mg/kg).[8]

In the C3H mouse with subcutaneously implanted 6C3HED lymphosarcoma model, 4 was equipotent to sulofenur (po dosing, daily × 8) with an LD_{50} of 450 mg/kg. Figure 1 summarizes the dose–response curve of 4 against a number of other cell lines evaluated in CD1 nu/nu mice with a po dosing schedule of daily × 10 (excluding the 6C3HED lymphosarcoma cell line).

As illustrated in Figure 1, 4 demonstrated substantial efficacy in the HXGC3 and VRC5 (human colon xenografts) cell lines. This prompted evaluation of 4 in the CX-1 (human colon xenograft used by the National Cancer Institute (NCI)) cell line. There was some inhibition (62%) of tumor growth at 600 mg/kg of the CX-1 cell line, but at this dose intensity 70% of the treated animals died as a result of the drug toxicity. At the lowest test doses 4 did not inhibit the tumor growth in the CX-1 cell line. The LX-1 (human lung xenograft used by the NCI) tumor-im-

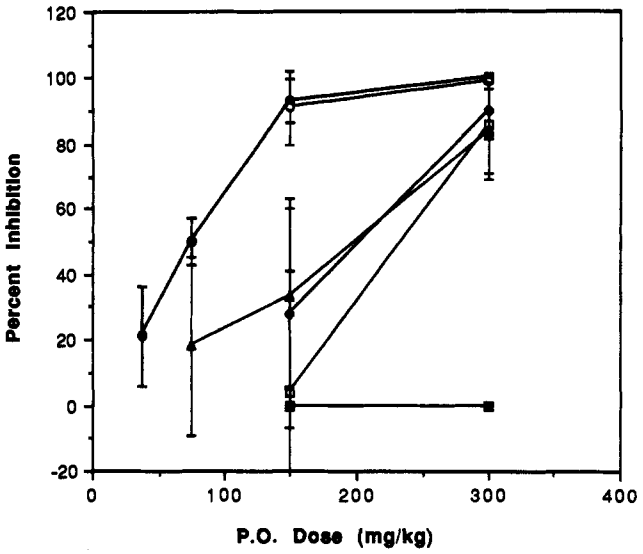


Figure 1. Percent inhibition of growth of cell line vs 4: 6C3HED (●), HXGC3 (□), CX-1 (■), LX-1 (▲), 6C3HED (LY186641) (○), VRC5 (◆).

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planted CD1 nu/nu mouse was responsive to oral dosing of 4 at 150 and 300 mg/kg, but at a dose of 600 mg/kg 90% of the treated mice died.

Phase I clinical urinary metabolite studies demonstrated extensive oxidation of the benzylic carbons of sulofenur. The absence of oxidizable benzylic methylene groups in 4 will substantially alter the metabolic degradation/excretion of this molecule.[9] Experiments designed to elucidate the variables responsible for the toxicity in the maximum-tolerated dose of sulofenur will in parallel to the ongoing mechanistic studies provide a better understanding of this class of novel cancer chemotherapeutic drugs.[10]

Experimental Section

Pharmacology Methods. 6C3HED lymphosarcoma tumor fragments (1–2 mm) were implanted subcutaneously and grown for 1 day in C3H mice. The compound being tested was suspended in 2.5% emulphor and administered po by gavage in 0.5–0.6-mL portions, daily × 8 (animals dosed days 2–9). Percent inhibition of tumor growth is expressed as a ratio of tumor weight (as estimated by the dimensions of the intact tumor when measured by calipers on day 10) of the treated animals versus the untreated control mice (n = 10, except compound 6 where seven mice were used).[11]

Chemical Methods. ^{1}H NMR chemical shifts are reported in ppm downfield from an internal tetramethylsilane standard in the specified deuterated solvent. Elemental analyses were obtained from the Eli Lilly Microanalysis Laboratory and are within 0.4% of the theoretical values unless stated otherwise.

Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and chloroform was distilled from P_2O_5 under nitrogen prior to use. All reactions involving n-BuLi were carried out in oven/flame-dried glassware.

Procedure for the Synthesis of Thiophenes. A solution of 1.6 moles of 88% KOH in 0.6 L of ethylene glycol was heated carefully[12] (80–100 °C), then 0.1 L of 85% hydrazine hydrate and 0.79 moles of ketone/aldehyde were added, and the reaction was refluxed under a Dean–Stark apparatus for 1 h. The upper layer was drained, dried over anhydrous sodium sulfate, and filtered. The substituted thiophene was used as obtained from this procedure. The following substituted thiophenes were synthesized from commercially available starting materials as denoted in parentheses: 3-ethylthiophene (3-acetylthiophene), 2,3-dimethylthiophene (3-methyl-2-thiophenecarboxaldehyde), 2-n-propylthiophene (1-(2-thienyl)-1-propanone), 2-ethyl-3-methylthiophene (2-acetyl-3-methylthiophene), 4,5,6,7-tetrahydrobenzo[b]thiophene (4-keto-4,5,6,7-tetrahydrothianaphthene), and 5,6-dihydro-4H-cyclopenta[b]thiophene (thiaindan-6-one[13]).

Method A for the Synthesis of Thiophenesulfonamide from Thiophene. To a solution of $ClSO_3H$ (81.6 mmol) in 60 mL of anhydrous $CHCl_3$ at −5–0 °C under a drying tube was added a solution of the substituted thiophene (26.7 mmol) dissolved in 20 mL of anhydrous $CHCl_3$. This mixture was stirred at 0 °C for 30 min and then poured over 100 mL of ice–water, and the aqueous layer was extracted with (2 × 50 mL) of $CHCl_3$. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under vacuum. To the residue was added 30 mL of concentrated ammonium hydroxide, and the mixture was stirred at room temperature for 30 min. The ammonia was removed under vacuum and the aqueous layer extracted (3 × 100 mL) with CH_2Cl_2. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography.

Method B for the Synthesis of Thiophenesulfonamide from Thiophene. To a solution (38.5 mmol) of the substituted thiophene in 100 mL of anhydrous THF under a nitrogen atmosphere at −78 °C was added (29.6 mL, 38.5 mmol) a 1.3 M hexanes solution of n-BuLi. The reaction was warmed to 0 °C and stirred for 30 min. Sulfur dioxide gas was bubbled through this mixture for 20 min at 0 °C and the reaction concentrated under vacuum. The residue was dissolved in 100 mL of water, then 304 mmoles of NaOAc and 100 mmoles of H_2NOSO_3H were added to this solution, and the reaction was stirred at room temperature for 1.5 h. This mixture was diluted with 200 mL of water and the aqueous layer extracted (3 × 100 mL) with CH_2Cl_2. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography.

Procedure for the Synthesis of Sulfonylurea from Sulfonamide. To a solution of 7.2 mmol of the sulfonamide dissolved in 10 mL of acetone was added 1 N aqueous NaOH (7.2 mL, 7.2 mmol) and the mixture was stirred at room temperature for 10 min. A solution of the aryl isocyanate (7.2 mmol) dissolved in 10 mL of acetone was added dropwise to this mixture. The reaction was stirred overnight and then acidified with 1 N aqueous HCl (7.2 mL, 7.2 mmol). The precipitated N-aryl-N'-(thienylsulfonyl)urea was filtered under vacuum and purified by flash chromatography.

The sodium salt of three sulfonylureas (3, 6, and 8) precipitated out of the reaction mixture after the corresponding sulfonamide had reacted with the aryl isocyanate. These products were obtained by filtration of the reaction mixture without addition of HCl. The solid was washed with water and acetone and dried (40–50 °C) in a vacuum oven to obtain pure product.

N-(4-Chlorophenyl)-N'-(2-thienylsulfonyl)urea (1). Synthesized from 2-thiophenesulfonamide as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.88 (bs, 1 H), 9.07 (s, 1 H), 8.04 (d, J = 4 Hz, 1 H), 7.84 (d, J = 4 Hz, 1 H), 7.45 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 7.23 (dd, J = 4, 4 Hz, 1 H); ^{13}C NMR (CD_3SOCD_3) δ 149.3, 140.3, 137.0, 134.1, 133.7, 128.6, 127.4, 127.0, 120.7; MS (FAB) m/z 317 (M^+). Anal. ($C_{11}H_9ClN_2O_3S_2$) C, H, N.

N-(4-Chlorophenyl)-N'-[(5-chloro-2-thienyl)sulfonyl]urea (2). Synthesized from 5-chloro-2-thiophenesulfonamide as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 9.09 (s, 1 H), 7.63 (d, J = 4 Hz, 1 H), 7.46 (d, J = 9 Hz, 2 H), 7.32 (d, J = 9 Hz, 2 H), 7.24 (d, J = 4 Hz, 1 H); ^{13}C NMR (CD_3SOCD_3) δ 149.5, 138.5, 136.9, 136.2, 133.4, 128.7, 127.5, 127.1, 120.8; MS (FAB) m/z 351 (M^+). Anal. ($C_{11}H_8Cl_2N_2O_3S_2$) C, H, N.

N-(3,4-Dichlorophenyl)-N'-[(5-methyl-2-thienyl)sulfonyl]urea, Sodium Salt (3). Synthesized from 5-methyl-2-thiophenesulfonamide (prepared from 2-methylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.92 (s, 1 H), 7.94 (d, J = 3 Hz, 1 H), 7.34 (d, J = 3 Hz, 1 H), 7.33 (s, 1 H), 7.22 (d, J = 6 Hz, 1 H), 6.68 (d, J = 6 Hz, 1 H), 2.42 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 158.3, 145.9, 142.5, 141.9, 130.5, 129.9, 128.3, 124.3, 120.7, 118.3, 117.4, 14.9; MS (FAB) m/z 387 (M^+). Anal. ($C_{12}H_9Cl_2N_2NaO_3S_2$) C, H, N.

N-(4-Chlorophenyl)-N'-[(5-methoxy-2-thienyl)sulfonyl]urea (4). Synthesized from 5-methoxy-2-thiophenesulfonamide (prepared from 2-methoxythiophene[14] by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.93 (s, 1 H), 7.47 (d, J = 4 Hz, 1 H), 7.46 (d, J = 9 Hz, 2 H), 7.30 (d, J = 9 Hz, 2 H), 6.39 (d, J = 4 Hz, 1 H), 3.95 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 170.9, 151.0, 137.9, 132.1, 128.5, 126.0, 120.2, 104.4, 60.7; MS (FAB) m/z 347 (M^+). Anal. ($C_{12}H_{11}ClN_2O_4S_2$) C, H, N.

N-(4-Chlorophenyl)-N'-[[5-(methylthio)-2-thienyl]sulfonyl]urea (5). Synthesized from 5-(methylthio)-2-thiophenesulfonamide (prepared from 2-(methylthio)thiophene

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by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 9.18 (s, 1 H), 7.69 (d, J = 4 Hz, 1 H), 7.44 (d, J = 9 Hz, 2 H), 7.35 (d, J = 9 Hz, 2 H), 7.13 (d, J = 4 Hz, 1 H), 2.64 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 150.4, 148.7, 138.8, 137.9, 135.3, 129.6, 127.9, 127.6, 121.6, 20.0; MS (FAB) m/z 363 (M^+). Anal. ($C_{12}H_{11}ClN_2O_3S_3$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(5-ethyl-2-thienyl)sulfonyl]urea, Sodium Salt (6).** Synthesized from 5-ethyl-2-thiophenesulfonamide (prepared from 2-ethylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.68 (s, 1 H), 7.52 (d, J = 9 Hz, 2 H), 7.24 (d, J = 4 Hz, 1 H), 7.14 (d, J = 9 Hz, 2 H), 6.68 (d, J = 4 Hz, 1 H), 2.76 (q, J = 9 Hz, 2 H), 1.12 (t, J = 9 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 158.8, 149.0, 145.8, 141.1, 127.83, 127.79, 123.0, 122.4, 118.8, 22.7, 15.7; MS (FD) m/z 344 (M^+ - Na). Anal. ($C_{13}H_{12}ClN_2NaO_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(5-ethoxy-2-thienyl)sulfonyl]urea (7).** Synthesized from 5-ethoxy-2-thiophenesulfonamide (prepared from 2-ethoxythiophene[12] by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.94 (s, 1 H), 7.46 (d, J = 9 Hz, 2 H), 7.40 (d, J = 6 Hz, 1 H), 7.28 (d, J = 9 Hz, 2 H), 6.36 (d, J = 6 Hz, 1 H), 4.18 (q, J = 9 Hz, 2 H), 1.36 (t, J = 9 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 169.6, 152.1, 138.2, 128.4, 126.6, 125.8, 120.1, 104.8, 104.5, 69.7, 14.3; MS (FD) m/z 361 (M^+ - 1). Anal. ($C_{13}H_{13}ClN_2O_4S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(5-*n*-propyl-2-thienyl)sulfonyl]urea, Sodium Salt (8).** Synthesized from 5-*n*-propyl-2-thiophenesulfonamide (prepared from 2-*n*-propylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.72 (s, 1 H), 7.54 (d, J = 9 Hz, 2 H), 7.25 (d, J = 4 Hz, 1 H), 7.14 (d, J = 9 Hz, 2 H), 6.68 (d, J = 4 Hz, 1 H), 2.72 (t, J = 8 Hz, 2 H), 1.60 (sext, J = 8 Hz, 2 H), 0.92 (t, J = 8 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 158.9, 147.2, 145.9, 141.1, 127.8, 123.1, 118.8, 31.3, 24.2, 13.4. Anal. ($C_{14}H_{14}ClN_2NaO_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(5-*i*-propyl-2-thienyl)sulfonyl]urea (9).** Synthesized from 5-*i*-propyl-2-thiophenesulfonamide (prepared from 2-*i*-propylthiophene[15] by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.86 (s, 1 H), 7.52 (d, J = 4 Hz, 1 H), 7.30 (d, J = 9 Hz, 2 H), 7.22 (d, J = 9 Hz, 2 H), 6.68 (d, J = 4 Hz, 1 H), 3.10 (hept, J = 6 Hz, 1 H), 1.18 (d, J = 6 Hz, 6 H); MS (FD) m/z 359 (M^+). Anal. ($C_{14}H_{15}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(5-*n*-propoxy-2-thienyl)sulfonyl]urea (10).** Synthesized from 5-*n*-propoxy-2-thiophenesulfonamide (prepared from 2-*n*-propoxythiophene[12] by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.66 (bs, 1 H), 8.99 (s, 1 H), 7.54 (d, J = 4 Hz, 1 H), 7.44 (d, J = 9 Hz, 2 H), 7.35 (d, J = 9 Hz, 2 H), 6.44 (d, J = 4 Hz, 1 H), 4.11 (t, J = 8 Hz, 2 H), 1.76 (sext, J = 8 Hz, 2 H), 0.96 (t, J = 8 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 171.2, 149.4, 137.0, 133.8, 128.6, 126.8, 123.7, 120.6, 105.3, 75.5, 21.7, 10.0; MS (FAB) m/z 375 (M^+). Anal. ($C_{14}H_{15}ClN_2O_4S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(5-*tert*-butyl-2-thienyl)sulfonyl]urea (11).** Synthesized from 5-*tert*-butyl-2-thiophenesulfonamide (prepared from 2-*tert*-butylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.84 (bs, 1 H), 9.04 (s, 1 H), 7.66 (d, J = 4 Hz, 1 H), 7.44 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 7.02 (d, J = 4 Hz, 1 H), 1.38 (s, 9 H); ^{13}C NMR (CD_3SOCD_3) δ 165.1, 149.2, 137.0, 136.2, 133.8, 128.7, 126.9, 122.6, 120.6, 38.6, 34.8; MS (FAB) m/z 373 (M^+). Anal. ($C_{15}H_{17}ClN_2O_3S_2$) H, N, C: calcd, 48.31; found, 47.84.

***N*-(4-Chlorophenyl)-*N'*-[(5-ethyl-2-furanyl)sulfonyl]urea (12).** Synthesized from 5-ethyl-2-thiophenesulfonamide (prepared from 2-ethylfuran by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 9.01 (s, 1 H), 7.42 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 7.22 (d, J = 4 Hz, 1 H), 6.38 (d, J = 4 Hz, 1 H), 2.71 (q, J = 9 Hz, 2 H), 1.20 (t, J = 9 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 162.2, 148.8, 145.3, 136.9, 128.6, 127.0, 120.7, 119.3, 106.8, 20.8, 11.4; MS (FAB) m/z 329 (M^+). Anal. ($C_{13}H_{13}ClN_2O_4S$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(5-ethyl-2-pyrrolyl)sulfonyl]urea (13).** Synthesized from 2-ethylpyrrole:[16] ^{1}H NMR (CD_3SOCD_3) δ 10.38 (s, 1 H), 8.80 (s, 1 H), 7.34 (d, J = 9 Hz, 2 H), 7.26 (d, J = 9 Hz, 2 H), 6.62 (d, J = 3 Hz, 1 H), 5.90 (d, J = 3 Hz, 1 H), 2.56 (q, J = 9 Hz, 2 H), t (t, J = 9 Hz, 3 H); MS (FAB) m/z 328 (M^+). Anal. ($C_{13}H_{14}ClN_3O_3S$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(3-methyl-2-thienyl)sulfonyl]urea (14).** Synthesized from 3-methyl-2-thiophenesulfonamide (prepared from 3-methylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.86 (s, 1 H), 7.88 (d, J = 6 Hz, 1 H), 7.40 (d, J = 9 Hz, 2 H), 7.32 (d, J = 9 Hz, 2 H), 7.06 (d, J = 6 Hz, 1 H), 2.48 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 149.1, 143.4, 136.9, 133.6, 131.8, 131.4, 128.6, 126.9, 120.6, 14.5; MS (FAB) m/z 330 (M^+). Anal. ($C_{12}H_{11}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(3-ethyl-2-thienyl)sulfonyl]urea (15).** Synthesized from 3-ethyl-2-thiophenesulfonamide (prepared from 3-ethylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.66 (bs, 1 H), 8.86 (s, 1 H), 7.90 (d, J = 6 Hz, 1 H), 7.49 (d, J = 9 Hz, 2 H), 7.36 (d, J = 9 Hz, 2 H), 7.14 (d, J = 6 Hz, 1 H), 2.94 (q, J = 9 Hz, 2 H), 1.10 (t, J = 9 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 149.3, 149.1, 136.9, 133.3, 132.2, 129.7, 128.7, 126.9, 120.6, 21.4, 14.5; MS (FAB) m/z 345 (M^+). Anal. ($C_{13}H_{13}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(4-ethyl-2-thienyl)sulfonyl]urea (16).** Synthesized from 4-ethyl-2-thiophenesulfonamide (prepared from 3-ethylthiophene by method B with lithium 2,2,6,6-tetramethylpiperidide) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.56 (bs, 1 H), 9.00 (s, 1 H), 7.70 (d, J = 2 Hz, 1 H), 7.64 (d, J = 2 Hz, 1 H), 7.44 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 2.64 (q, J = 8 Hz, 2 H), 1.18 (t, J = 8 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 149.2, 144.3, 139.8, 137.0, 134.0, 128.7, 128.2, 127.0, 120.7, 22.7, 14.4; MS (FAB) m/z 345 (M^+). Anal. ($C_{13}H_{13}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(4-methoxy-2-thienyl)sulfonyl]urea (17).** Synthesized from 4-methoxy-2-thiophenesulfonamide (prepared from 3-methoxythiophene[12] by method B) as outline above:[17] ^{1}H NMR (CD_3SOCD_3) δ 10.40 (bs, 1 H), 9.06 (s, 1 H), 7.46 (d, J = 2 Hz, 1 H), 7.44 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 7.12 (d, J = 2 Hz, 1 H), 3.78 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 156.5, 149.2, 138.9, 136.9, 128.7, 127.0, 124.2, 120.7, 106.3, 57.7; MS (FAB) m/z 347 (M^+). Anal. ($C_{12}H_{11}ClN_2O_4S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(2,3-dibromo-5-thienyl)sulfonyl]urea (18).** Synthesized from 2,3-dibromo-5-thiophenesulfonamide as outlined above: ^{1}H NMR (CD_3SOCD_3) 9.26 (s, 1 H), 7.80 (s, 1 H), 7.45 (d, J = 9 Hz, 2 H) and 7.35 (d, J = 9 Hz, 2 H); ^{13}C NMR (CD_3SOCD_3) δ 149.4, 141.5, 136.8, 134.7, 128.7, 127.1, 120.8, 119.5, 113.9; MS (FAB) m/z 475 (M^+). Anal. ($C_{11}H_7Br_2ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(2,3-dimethyl-5-thienyl)sulfonyl]urea (19).** Synthesized from 2,3-dimethyl-5-thiophenesulfonamide (prepared from 2,3-dimethylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) 8.82 (s, 1 H), 7.46 (d, J = 9 Hz, 2 H), 7.43 (s, 1 H), 7.28 (d, J = 9 Hz, 2 H), 2.34 (s, 3 H), 2.10 (s, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 151.7, 140.1, 138.1, 134.6, 133.2, 128.4, 125.9, 120.1, 120.0, 13.1, 12.9; MS (FAB) m/z 345 (M^+). Anal. ($C_{13}H_{13}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[(2-ethyl-3-methyl-5-thienyl)sulfonyl]urea, Sodium Salt (20).** Synthesized from 2-ethyl-3-methyl-5-thiophenesulfonamide (prepared from 2-ethyl-3-methylthiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) 8.70 (s, 1 H), 7.72 (d, J = 8 Hz, 2 H), 7.16 (s, 1 H), 7.14 (d, J = 8 Hz, 2 H), 2.68 (q, J = 9 Hz, 2 H), 2.04 (s, 3 H), 1.16 (t, J = 9 Hz, 3 H); ^{13}C NMR (CD_3SOCD_3) δ 158.9, 143.5, 142.3, 141.1, 130.68, 130.66, 127.8, 123.1, 118.8, 20.7, 15.4, 13.1; MS (FAB) m/z 381 (M^+). Anal. ($C_{14}H_{14}ClN_2NaO_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-(5,6-dihydro-4*H*-cyclopenta[*c*]thiophene-yl-2-sulfonyl)urea (21).** Synthesized from 5,6-dihydro-4*H*-cyclopenta[c]thiophene-2-sulfonamide (prepared from 5,6-dihydro-4*H*-cyclopenta[c]thiophene[6] by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 8.88 (s, 1 H), 7.44 (d, J = 9 Hz,

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(16) E. I. Du Pont de Nemours and Company Herbicidal Sulfonamides. U.S. Patent 4,368,067. January 11, 1983.

(17) In order to circumvent formation of 4-methoxy-5-thiophenesulfonamide with this protocol, the 5 position was protected by a trimethylsilyl group that was removed with tetrabutylammonium fluoride after functionalization of the 2 position.

2 H), 7.24 (d, J = 9 Hz, 2 H), 7.21 (s, 1 H), 2.82 (t, J = 9 Hz, 2 H), 2.60 (t, J = 9 Hz, 2 H), 2.30 (quint, J = 9 Hz, 2 H); MS (FAB) m/z 356 ($M^+ - 1$). Anal. ($C_{14}H_{13}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-(4,5,6,7-tetrahydrobenzo[*c*]thiophene-yl-2-sulfonyl)urea (22).** Synthesized from 4,5,6,7-tetrahydrobenzo[c]thiophene-2-sulfonamide (prepared from 4,5,6,7-tetrahydrobenzo[c]thiophene[6] by method B) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.78 (bs, 1 H), 8.84 (s, 1 H), 7.54 (s, 1 H), 7.42 (d, J = 9 Hz, 2 H), 7.32 (d, J = 9 Hz, 2 H), 2.94 (m, 2 H), 2.64 (m, 2 H), 1.68 (m, 4 H); ^{13}C NMR (CD_3SOCD_3) δ 149.5, 143.1, 139.1, 137.2, 132.5, 128.6, 126.7, 126.6, 120.5, 25.7, 24.9, 22.0, 21.8; MS (FAB) m/z 371 (M^+). Anal. ($C_{15}H_{15}ClN_2O_3S_2$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-(5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-yl-2-sulfonyl)urea (23).** Synthesized from 5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-2-sulfonamide (prepared from 5,6-dihydro-4*H*-cyclopenta[*b*]thiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 10.52 (bs, 1 H), 8.99 (s, 1 H), 7.57 (s, 1 H), 7.46 (d, J = 9 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 2.93 (t, J = 7 Hz, 2 H), 2.72 (t, J = 7 Hz, 2 H), 2.38 (quint, J = 7 Hz, 2 H); ^{13}C NMR δ 150.8, 149.2, 146.0, 140.8, 137.0, 128.8, 128.6, 126.9, 120.6, 29.0, 28.5, 27.6; MS (FAB) m/z 357 (M^+). Anal. ($C_{14}H_{13}ClN_2O_3S_2$) H, N, C: calcd, 47.12; found, 48.91.

***N*-(3,4-Dichlorophenyl)-*N'*-(4,5,6,7-tetrahydrobenzo[*b*]thiophene-yl-2-sulfonyl)urea (24).** Synthesized from 4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-sulfonamide (prepared from 4,5,6,7-tetrahydrobenzo[*b*]thiophene by method A) as outlined above: ^{1}H NMR (CD_3SOCD_3) δ 9.18 (s, 1 H), 7.76 (d, J = 2 Hz, 1 H), 7.54 (d, J = 9 Hz, 1 H), 7.44 (s, 1 H), 7.30 (dd, J = 2, 9 Hz, 1 H), 2.76 (m, 2 H), 2.56 (m, 2 H), 1.74 (m, 4 H); ^{13}C NMR (CD_3SOCD_3) δ 141.4, 140.1, 134.8, 131.8, 130.8, 130.42, 130.39, 130.3, 123.0, 119.4, 118.5, 24.8, 24.5, 22.7, 22.0; MS (FAB) m/z 404 ($M^+ - 1$). Anal. ($C_{15}H_{14}Cl_2N_2O_3S_2$) C, H, N.

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Side-Chain Derivatives of Biologically Active Nucleosides. 1. Side-Chain Analogs of 3'-Azido-3'-deoxythymidine (AZT)[1]

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Starting from 3-*O*-mesyl-1,2-*O*-isopropylidene-α-D-allofuranose (**9**) the anomeric mixtures of the requisite carbohydrates 1,2-di-*O*-acetyl-6-*O*-benzoyl-5-deoxy-3-*O*-mesyl-D-allofuranoses **17Aα/β**, 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-D-allofuranoses **17Bα/β**, and 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*O*-mesyl-L-talofuranoses **17Cα/β** were synthesized. 1,2-Di-*O*-acetyl-5-*O*-benzoyl-6-deoxy-3-*O*-mesyl-D-allofuranoses **17Dα/β** and the corresponding L-talofuranoses **17Eα/β** were obtained from 6-deoxy-3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-allofuranose (**12**) and the corresponding β-L-talofuranose **13**. Coupling of these sugar derivatives with thymine gave the β-nucleoside derivatives **18A–E**. Treatment of compounds **18A–E** with DBU produced the corresponding 2,3'-anhydro nucleosides **19A–E** with a free 2'-OH group. After deoxygenation of 2'-*O*-[[(4-methylphenyl)oxy]thiocarbonyl] compounds **20A–E** with tributyltin hydride the 2,3'-anhydro bridge of the 2'-deoxynucleosides **21A–E** was opened with LiN_3 to produce the protected 3'-azido-2,3'-dideoxynucleoside derivatives **22A–G**. Saponification with $NaOCH_3$ gave 1-(3'-azido-2',3',5'-trideoxy-β-D-allofuranosyl)thymine (**2**; homo-AZT), the 5'-*C*-(hydroxymethyl) derivatives of AZT 1-(3'-azido-2',3'-dideoxy-β-D-allofuranosyl)thymine (**3**) and 1-(3'-azido-2',3'-dideoxy-α-L-talofuranosyl)thymine (**4**), and the 5'-*C*-methyl derivatives of AZT 1-(3'-azido-2',3',6'-trideoxy-β-D-allofuranosyl)thymine (**5**) and 1-(3'-azido-2',3',6'-trideoxy-α-L-talofuranosyl)thymine (**6**). Compounds **2–6** were evaluated for their inhibitory effect on human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) replication in MT-4 cells and found inactive at subtoxic concentrations. Compounds **2–4** and **6** are not effective against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), vaccinia virus (VV), and vesicular stomatitis virus (VSV) at 400 μg/mL. **5** is slightly active against HSV-1, HSV-2, and VV at 150, 300, and 300 μg/mL, respectively.

Introduction

3'-Azido-3'-deoxythymidine (1; AZT) has been reported to be of marked benefit in the treatment of AIDS and AIDS-related complex.[2] The triphosphate analog inhibits the utilization of dTTP by reverse transcriptase and may be incorporated in the terminal position of DNA, thereby preventing elongation.[3,4] During long term treatment, AZT is significantly toxic to men.[5] The major drawbacks of AZT are (a) the low V_{max} (0.3% compared to the natural substrate thymidine monophosphate) for the introduction of the second phosphate residue by thymidylate kinase which results in the accumulation of AZT monophosphate;[3] (b) the short half-life in the body necessitates frequent

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