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Synthesis and Antiviral/Antitumor Evaluation of 2-Amino- and 2-Carboxamido-3-arylsulfonylthiophenes and Related Compounds as a New Class of Diarylsulfones

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Abstract—Based on general SARs previously described for anti-HIV-1 diarylsulfone derivatives, a series of 2-amino- and 2-carboxamido-3-arylsulfonylthiophenes has been prepared and evaluated as potential antiviral and antitumor agents. In cell culture, some of the 2-aminothiophenes exhibited moderate and selective activity against HIV-1, with 2-amino-3-(2-nitrophenylsulfonyl)thiophene (**7e**) being most attractive ($EC_{50} = 3.8\,\mu g/mL$, $CC_{50} = > 100\,\mu g/mL$). In broad-spectrum antiviral assays, the 3-arylsulfonyl-2-(trifluoroacetamido)thiophenes (**8c–g**) and 2-acetamido-3-arylsulfonyl-5-nitrothiophenes (**9f–g**) proved considerably active ($IC_{50} = 0.1–10\,\mu g/mL$) against human cytomegalovirus (CMV) and/or varicella zoster virus (VZV). Based on the activity of the trifluoroacetamides, ring-modified furan, *N*-(substituted)pyrrole, phenyl, and 3,4-thiophene analogues were prepared, and these compounds were also active against CMV and/or VZV, with the notable exception of the 3,4-thiophene derivative. In contrast to other amines, the 2-aminopyrrole precursors (**13a–d**) also exhibited potent activity against CMV. Unfortunately, most of these compounds displayed significant cytotoxicity against human fibroblasts, the cells supporting CMV and VZV replication, and thus selectivity indices were low. The most notable exception to this was the naphthyl-substituted aminopyrrole **13d**, which exhibited both potent ($IC_{50} = 0.3\,\mu g/mL$) and selective ($CC_{50} = > 50\,\mu g/mL$) activity against CMV. Finally, thiophene aryl amides **8i–k** displayed moderate in vitro activity against certain leukemia, breast, and colon cancer cell lines.

Introduction

Appropriately substituted diarylsulfone derivatives have recently emerged as a new chemical class of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). The first examples of these compounds were described in 1993 by the National Cancer Institute (NCI),[1] resulting in the identification of nitrophenyl phenyl sulfone (NPPS) (**1**, Fig. 1) as lead compound with activity against HIV-1 in the low micromolar range. Shortly afterwards, Merck Research Laboratories introduced the indole-based diarylsulfone L-737,126 (**2**),[2] a highly potent and selective NNRTI with anti-HIV-1 activity in the low *nanomolar* range ($IC_{95} = 3\,nM$). In comparison to the three NNRTIs currently approved for the treatment of HIV infection,[3–6] L-737,126 is more potent than nevirapine ($IC_{95} = 50\,nM$) and delavirdine ($IC_{95} = 37\,nM$) and is essentially equipotent to efavirenz ($IC_{95} = 1.7\,nM$). Subsequent structural modification of L-737,126 with the aim of improving oral bioavailabilty resulted in the identification of several highly potent 2-heterocyclic indole derivatives, with the 2-imidazoyl derivative **3** being equipotent to the parent carboxamide while having "improved physiochemical properties".[7] Later, Artico et al. introduced the pyrrolyl aryl sulfones as a new group of diarylsulfones, with amino ester **4** being representative of a number of derivatives with activity at sub-micromolar concentrations.[8,9] Finally, NCI and others have recently detailed the potent and selective anti-HIV-1 activity of several (*N*-methylamino)phenyl- and tetrahydroquinoline-substituted diarylsulfones, with compound **5** being the most potent NNRTI of the series.[10]

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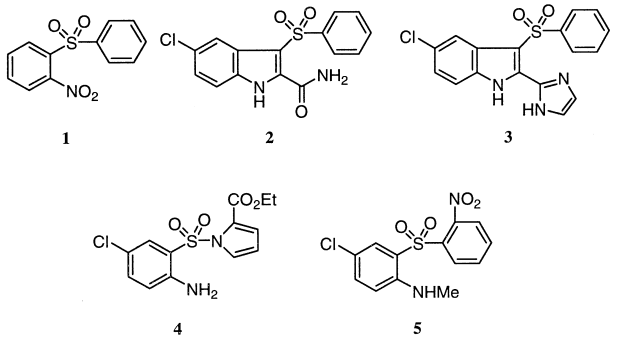


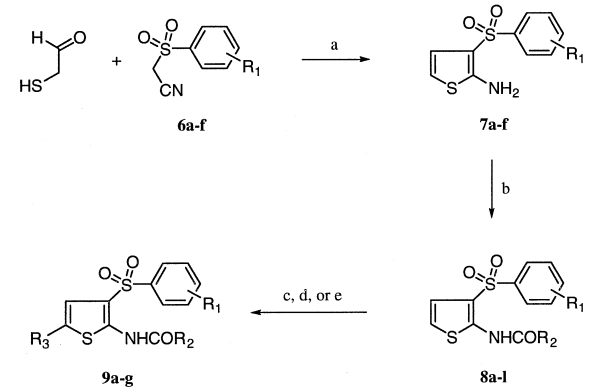
Figure 1. Chemical structures of HIV-active diarylsulfones.

Based on our continued interest in amino heterocycles, and in efforts to expand upon the general SAR of the diarylsulfone class of HIV inhibitors,[8,9] we have initiated a research program directed at the synthesis and anti-HIV evaluation of various heterocyclic-based diarylsulfones containing an amine or amine derivative as the apparently required H-bonding *ortho*-substituent. At the same time, we have also been interested in evaluating these compounds in broad-screen antiviral and antitumor assays, an area of screening that appears to have been very little explored for diarylsulfones. Our initial efforts have focused primarily on 2-amino-3-(arylsulfonyl)thiophenes, as well as a diverse collection of the corresponding carboxamides. Based on the potent antiviral activity exhibited by some of the thiophenes (vide infra), ring-modified furan, *N*-(substituted)pyrrole, phenyl, and 3,4-thiophene derivatives have also been investigated. In this paper, we report on the synthesis and biological evaluation of these new diarylsulfones, and show that certain compounds in this series possess significant activity against HIV-1, CMV, and/or VZV, while others are active against certain human tumor cell lines.

Results and Discussion

Chemistry

The various 2-amino-3-(arylsulfonyl)thiophenes (**7a**–**f**) were prepared by base-catalyzed condensation of an appropriately substituted (arylsulfonyl)acetonitrile (**6a**–**f**) with the dimer of α-mercaptoacetaldehyde (1,4-dithiane-2,5-diol) under typical Gewald conditions[11] (Scheme 1). While 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was employed as catalyst in most instances, triethylamine was used to prepare *ortho*-substituted derivatives **7e**–**f**, as the more basic DBU gave mixtures in these cases, apparently due to reaction of the produced amine with the *ortho* substituent. Subsequent reaction of the 2-aminothiophenes with a carboxylic acid chloride or anhydride in acetonitrile solution using pyridine as base gave the various carboxamides **8a**–**m**. Compounds containing a halogen or nitro group at the 5-position of the thiophene ring (**9a**–**g**) were then prepared by reaction of the appropriate carboxamide with either *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), iodine/silver nitrate,[12] or acetyl nitrate. Finally, tricyclic sulfone **10** was obtained by cyclization



Compd	R_1
6, 7a	H
b	4-Cl
c	4-F
d	4-CH_3
e	2-NO_2
f	2-CO_2Me

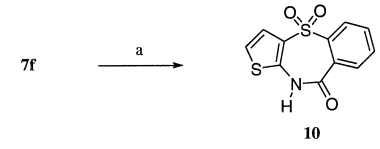
Compd	R_1	R_2	R_3
9a	4-Cl	CH_3	Br
b	4-Cl	CF_3	Br
c	2-CO_2Me	H	Br
d	2-NO_2	CH_3	Cl
e	4-Cl	CF_3	I
f	4-Cl	CH_3	NO_2
g	4-F	CH_3	NO_2

Compd	R_1	R_2
8a	2-NO_2	CH_3
b	4-Cl	CH_3
c	H	CF_3
d	4-Cl	CF_3
e	4-F	CF_3
f	4-CH_3	CF_3
g	2-CO_2Me	CF_3
h	4-Cl	$CF_2CF_2CF_3$
i	H	3-C_5H_4N
j	H	C_6H_5
k	4-CH_3	C_6H_5
l	H	CH_2CO_2Me
m	2-CO_2Me	H

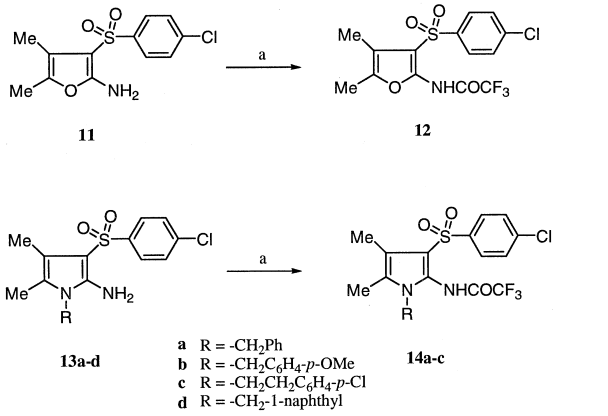
Scheme 1. Reagents and conditions: (a) DBU or TEA, EtOH or MeOH, rt; (b) acid chloride or anhydride, pyridine, MeCN, Δ; (c) NBS or NCS, CH_2Cl_2, Δ; (d) I_2, $AgNO_3$, MeCN, rt; (e) HNO_3, Ac_2O, rt.

of aminothiophene **7f** with potassium *t*-butoxide in refluxing methanol (Scheme 2).

Based on the potent activity exhibited by trifluoroacetamides **8c**–**g** of the above thiophene series (vide infra), certain ring-modified analogues of the chloro-substituted derivative **8d** were prepared. As shown in Scheme 3, the 4,5-dimethylfuran (**12**) and -pyrrole (**14a**–**c**) analogues were prepared by reaction of the appropriate amino heterocycle (**11**[13] or **13a**–**d**[14]) with trifluoroacetic anhydride in the presence of pyridine.[15] As shown in Scheme 4, phenyl-based trifluoroacetamide **17** was similarly obtained from aniline **16**,[16] which, in turn, was prepared by reduction of the nitro derivative **15**[16] with iron/acetic acid. Finally, the 3,4-substituted thiophene analogue **18** and the 3-cyanomethylsulfonyl derivatives **19a**–**b** (Fig. 2) were available as a result of previous work,[17,18] while 5-nitro derivative **19c** was prepared by reaction of **19b** with acetyl nitrate.



Scheme 2. Reagents and conditions: (a) *t*-BuOK, MeOH, Δ.



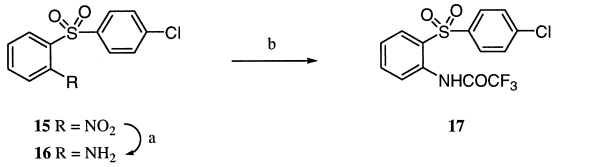
Scheme 3. Reagents and conditions: (a) trifluoroacetic anhydride, pyridine, MeCN, rt.

Ativiral activity

In addition to being evaluated against human immunodeficiency virus type-1 (HIV-1) and type-2 (HIV-2), each compound prepared in this study was also evaluated against human cytomegalovirus (CMV), varicella zoster virus (VZV) (both TK^+ and TK^-), herpes simplex virus type-1 (HSV-1) (both TK^+ and TK^-), herpes simplex virus type-2 (HSV-2), respiratory syncytial virus (RSV), vaccinia, vesicular stomatitis, Coxsackie B4, Sinbis, Reo 1, Punta Toro, and parainfluenza-3 virus.

As shown in Table 1, some of the 2-aminothiophenes (**7a**–**f**) exhibited moderate activity against the cytopathic effects of HIV-1 in human T-lymphocyte (CEM/0) cells. The most potent and selective of these compounds was the *o*-nitro derivative **7e**, which had an EC_{50} of 3.83 μg/mL and CC_{50} of >100 μg/mL. This same compound was much less active against HIV-2, a characteristic which is common to NNRTIs.[1] Although the precise mechanism of action for **7e** remains to be determined, the viral selectivity of **7e**, coupled with its structural similarity to known NNRTIs, suggests that it may also be acting as an inhibitor of RT. In general, the corresponding carboxamides (**8a**–**9g**), including the acetamide (**8a**) of the most potent amine, either exhibited non-selective toxicity or were inactive alltogether. The one exception to this was formamide **8m**, which showed both moderate and selective activity. Finally, the tricyclic sulfone **10** was inactive against HIV-1, although similar tricyclics have been reported to be active in the literature.[19,20]

As shown in Table 2, the 2-aminothiophenes showed only marginal activity against CMV and VZV in human embryonic lung (HEL) cells. However, among the various carboxamides, trifluoroacetamides **8c**–**g** displayed



Scheme 4. Reagents and conditions: (a) Fe, AcOH, H_2O, Δ; (b) trifluoroacetic anhydride, pyridine, MeCN, rt.

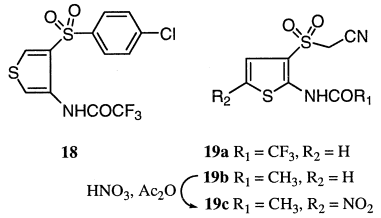


Figure 2. Related follow-up compounds.

significant activity against one or both of these viruses, with the 4-chlorophenylsulfonyl derivative **8d** being the most active in each case ($IC_{50} < 1.0$ μg/mL). As such, compound **8d** was 4- to 5-fold more potent than ganciclovir against CMV, and was either comparable in activity to or about 25-fold more potent than acyclovir against VZV, depending on the TK status (TK^+ or TK^-, respectively) of the virus strain. Unfortunately, the activity of the trifluoroacetamides was only about 5- to 40-fold lower than the cytotoxicity values, and thus the selectivity for the two viruses (CMV, VZV) over host cells was only modest at best. Nevertheless, the inhibitory values for these compounds generally represent a specific antiviral effect.

Other types of carboxamides in the 5-unsubstituted series, that is acetamides, aryl amides, and so forth, were inactive against CMV and VZV. The lack of activity of the acetamides suggests that the acidity of the amide NH

Table 1. Anti-HIV-1 and anti-HIV-2 activity and cytotoxic properties of compounds in human T-lymphocyte (CEM) cells

Compound	Antiviral activity EC_{50} (μg/mL)[a]		Cytotoxicity CC_{50} (μg/mL)[b]
	HIV-1 (III_B)	HIV-2 (ROD)	
7a	23±0.35	32±12	42±22
7b	>20	>20	≥100
7c	>8	>8	40±6.4
7d	12.7±6.7	>20	>100
7e	3.83±2.25	>20	≥100
7f	11.0±1.4	55.0±7.1	ND
8a	>1.6	>1.6	14±5.7
8b	>40	>40	53±11
8c	>8	>8	13±2.1
8d	>1.6	>8	6±4
8e	>1.6	>1.6	3.9±0.6
8f	>8	>8	20±9.9
8g	>20	>20	ND
8h	>8	>8	8.6±6.2
8i	>1.6	>1.6	3.2±2.9
8j	>40	>40	>200
8k	>40	>40	>200
8l	>40	>8	55±2.2
8m	18±0.7	40±0.7	≥ 124
9a	>200	>200	>200
9b	>8	>8	6.9±1.6
9c	>8	>8	12±5.6
9d	>40	>8	>200
9e	>8	>8	5.5±1.6
9f	>0.32	>0.32	2.1±1.2
9g	0.52±0.28	>0.32	>1.6
10	>200	>200	>200

[a]Concentration required to protect CEM cells against the cytopathogenicity of HIV by 50%.
[b]Concentration required to reduce CEM cell viability by 50%. ND, not determined.

may be an important structural feature of the active trifluoroacetamides. This hypothesis is supported by the fact that introduction of a nitro group at the 5-position of the thiophene, thereby considerably increasing the acidity of the amide proton, led to acetamides (**9f–g**) with very potent activity (IC_{50} = 0.06–0.35 μg/mL). Unfortunately, as with the trifluoroacetamides, the activity of these compounds was again not well separated from the cytotoxicity values (CC_{50} = 2–4.4 μg/mL). As to other 5-substituted compounds, we noted that the incorporation of a halogen into lead trifluoroacetamide **8d** led to derivatives (**9b**, **9e**) that were less active than the parent compound, although the opposite was the case with formamide **8m** (compare to **9c**). Finally, the 3-cyanomethylsulfonyl thiophene derivatives (**19a–c**) did not exhibit any appreciable activity against CMV or VZV (data not shown), indicating the importance of the 3-arylsulfonyl moiety in the active compounds.

With the surprising exception of the 3,4-substituted thiophene isomer **18**, each of the ring-modified trifluoroacetamides prepared as follow-up compounds were also active against CMV and/or VZV, although none were more potent than the lead thiophene **8d**. The most potent of these compounds against CMV were the *N*-(substituted)pyrrole derivatives **14a–c**, with IC_{50} values at or below 1.0 μg/mL, followed by furan **12**, and finally phenyl analogue **17**. In contrast to the aminothiophenes and -furan, the aminopyrroles **13a–d** were also quite active against CMV, apparently a result of the pyrrole *N*-substituent. The most potent of these amines was the *N*-(1-naphthylmethyl)-substituted derivative **13d** (IC_{50} = 0.3 μg/mL). In general, the ring-mod-

Table 2. Antiviral activity and cytotoxicity of compounds against human cytomegalovirus (CMV) and varicella-zoster virus (VZV) in human embryonic lung (HEL) cells

Compound	Antiviral activity (IC_{50} (μg/mL)[a])						Cytotoxicity (μg/mL)	
	CMV		TK^+VZV		TK^-VZV		Cell growth	Cell morph.
	AD-169	Davis	OKA	YS	07/1	YS	CC_{50}[b]	MCC[c]
7a	35	32	> 50	> 50	> 50	31	> 50	> 50
7b	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
7c	> 20	20	30.73	32.67	32.09	22.14	> 50	> 50
7d	> 20	30	> 50	> 50	> 50	> 50	> 50	> 50
7e	20	20	> 50	> 50	> 50	> 50	> 50	> 50
7f	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
8a	> 5	> 5	> 50	> 50	> 50	> 50	> 50	41
8b	> 50	> 50	> 50	> 50	> 50	39	> 50	> 50
8c	> 20	> 20	9.58	10.0	9.22	5.83	39	50
8d	0.5	0.5	0.98	0.85	0.96	0.89	19	ND
8e	> 5	> 5	3.41	3.87	3.73	2.49	36	20
8f	3.5	2	> 5	> 5	> 5	> 5	40	ND
8g	12	11	> 50	> 50	> 50	> 50	> 50	> 50
8h	> 0.5	> 0.5	> 0.5	> 0.5	> 0.5	> 0.5	15	2
8i	> 20	> 20	> 50	> 50	> 50	> 50	> 50	ND
8j	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
8k	> 5	> 5	> 5	> 5	> 5	> 5	> 5	ND
8l	> 50	> 50	> 20	> 20	> 20	> 20	> 50	> 50
8m	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
9a	> 50	> 50	> 20	> 20	> 20	> 20	> 50	> 50
9b	> 5	> 2	> 2	> 2	> 2	1.20	34	5
9c	7.5	7.5	11.9	22.1	22.7	10.9	26	50
9d	> 20	> 5	> 5	> 5	> 5	> 5	> 50	20
9e	> 2	> 2	> 2	> 2	> 2	> 2	28	5
9f	0.1	0.1	0.07	0.09	0.06	0.08	4.4	2
9g	0.35	0.35	0.26	0.27	0.27	0.27	2	2
11	> 20	> 20	32	34	31	29	> 50	> 50
12	> 5	10	10.44	13.35	13.77	6.60	50	46
13a	3.1	3.1	9.39	8.20	9.42	8.52	50	20
13b	1.0	0.8	4	> 20	> 5	> 5	15	> 20
13c	0.9	1.0	4.3	> 5	> 5	3.3	13	20
13d	0.3	0.3	1.6	16	> 5	1.2	> 50	> 20
14a	1.0	1.0	8.71	8.08	6.67	3.62	50	31
14b	0.9	0.9	> 5	> 5	> 5	> 5	18	20
14c	0.5	0.6	> 2	> 5	> 5	> 2	50	20
17	10	10	> 50	> 50	> 50	39.2	> 50	> 50
18	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
DHPG[d]	2.22	2.33	—	—	—	—	> 50	> 50
ACV[e]	—	—	0.66	0.90	25.94	21.90	> 50	> 50

[a]Concentration required to reduce virus plaque formation by 50%.
[b]Concentration required to reduce cell growth by 50%.
[c]Minimum cytotoxic concentration that causes a microscopically detectable alteration of normal cell morphology.
[d]DHPG, ganciclovir.
[e]ACV, acyclovir.
ND, not determined.

Table 3. Activity of compounds **8d**, **9b** and **9e** against herpes simplex virus (HSV) and virus in E_6SM cells

Compound	Minimum cytotoxic concentration (μg/mL)[a]	Minimum inhibitory concentration[b]			
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Herpes simplex virus-1 TK-VMW1837	Vaccinia virus
8d	> 400	> 400	> 400	> 400	240
9b	80	9.6	9.6	16	9.6
9e	80	9.6	9.6	9.6	9.6
BVDU	> 400	0.0256	> 400	0.64	1.92
ACG	> 400	0.0768	0.0768	0.64	> 400
DHPG	> 100	0.0038	0.0064	0.032	> 100

[a]Concentration required to cause a microscopically detectable alteration of normal cell morphology.
[b]Concentration required to reduce virus-induced cytopathogenicity by 50%.

ified trifluoroacetamides and aminopyrroles were much less active against VZV. Finally, as with the lead thiophene **8d**, most of the ring-modified compounds showed only modest selectivity for CMV or VZV over host cells (about 5- to 20-fold). The primary exception to this was the naphthyl-substituted aminopyrrole **13d**, which exhibited selectivity indices for CMV of > 67 (MCC) and > 167 (CC_{50}). The positive influence of the naphthyl substituent on the selectivity index in this case remains to be explored/confirmed by additional SAR studies.

When tested against viruses other than HIV, CMV, or VZV, the only compounds to show subtoxic activity were the 5-substituted trifluoroacetamides **9b** and **9e**, which exhibited slight activity against HSV-1, HSV-2, and vaccinia virus (Table 3). Interestingly, the parent trifluoroacetamide **8d** was inactive against these viruses.

Antitumor activity

Several of the aminoheterocycles (**7a**, **11** and **13a**) and carboxamides (**8a–l**) were chosen for evaluation in the NCI in vitro human tumor cell line screen.[21] Of these compounds, aryl amides **8i–k** showed moderate cytotoxic activity, with mean panel GI_{50} values (μM) of 13.2, 51.3, and 72.4, respectively. In general, cytotoxicity was greatest against leukemia, breast, and colon cancer cells, with pyridyl carboxamide **8i** consistently giving low μM inhibition against a variety of these cell lines (Table 4). Interestingly, compounds **8i–k** are somewhat structurally related to a class of antitumor sulfonamides which target the G1 phase of the cell cycle.[22]

Table 4. Activity of aryl amides **8i–k** against various cell lines of leukemia, breast cancer, and colon cancer (GI_{50}, μM)[a]

Panel/Cell line	8i	8j	8k
Leukemia			
K-562	4.37	1.10	1.48
SR	5.25	ND	5.62
MOLT-4	5.31	> 100	> 100
RPMI-8226	7.50	ND	> 100
Breast cancer			
MDA-N	1.02	3.72	3.02
MDA-MB-435	1.86	4.37	3.39
NCI/ADR-RES	3.94	> 100	67.6
MCF7	8.13	> 100	> 100
MDA-MB-231/ATCC	69.2	12.9	4.9
Colon cancer			
COLO 205	3.89	77.6	> 100
KM12	4.62	> 100	ND
HT29	5.62	> 100	> 100
HCT-15	5.13	> 100	7.59
HCT-116	6.61	> 100	> 100
SW-620	5.96	> 100	> 100

[a]GI_{50}, concentration required to inhibit growth of cell line by 50%. Values for **8i** represent the average of duplicate assays; those for **8j–k** represent single assays.
ND, not determined.
Data kindly provided by NCI.

Conclusions

As a result of this work, several lead compounds or groups of compounds have been identified which exhibit potent chemotherapeutic activity. Of the thiophene series, this includes aminothiophene **7e** (HIV-1), trifluoroacetamides **8c–g**, nitro acetamides **9f–g** (CMV and/or VZV), and pyridyl amide **8i** (leukemia, breast and colon cancers). While the selectivity/specificity of the aminothiophene was satisfactory, the trifluoroacetamides and nitro acetamides exhibited relatively high cytotoxicity towards host cells, and thus their selectivity was low. Of the ring-modified compounds, several trifluoroacetamides (**12**, **14a–c** and **17**) and several *N*-substituted aminopyrroles (**13a–d**) also exhibited potent activity against CMV and/or VZV, while in most cases displaying limited selectivity. Most interestingly, the naphthyl-substituted aminopyrrole **13d** showed both potent and selective activity against CMV. Finally, this work indicates that the broad-screen antiviral/antitumor evaluation of diarylsulfones should continue to be explored, with particular focus on CMV and VZV. Such efforts, along with mechanism of action studies for the more potent compounds of this study, are currently being pursued.

Experimental

Chemistry

Melting points were determined on an Electrothermal apparatus (open capillary) and are uncorrected. The ^1H NMR and mass spectra were obtained using a Brucker AM-300 or WH-400 spectrometer and VG-70 SQ instrument, respectively. Infrared (IR) spectra were determined on a Beckman Acculab 4 spectrophotometer using KBr pellets unless otherwise indicated. Thin layer

chromatography (TLC) was performed on Baker Si250F silica plates. Column chromatography was conducted on Fisher Selecto 60 (230–400 mesh) silica gel. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Reaction temperatures given are indicative of the oil bath. Acetonitrile, pyridine, and triethylamine were distilled from calcium hydride and stored over molecular sieves (4 Å). (Arylsulfonyl)acetonitriles **6b–f** were prepared according to a previous paper,[17] and references contained therein. All other reagents were obtained from Aldrich and used as received.

General procedure for the preparation of 2-amino-3-(arylsulfonyl)thiophenes (7a–f). Example: 2-amino-3-(phenylsulfonyl)thiophene (7a). To a suspension of (phenylsulfonyl)-acetonitrile (2.27 g, 12.5 mmol) and 1,4-dithiane-2,5-diol (1.00 g, 6.57 mmol) in absolute ethanol (15 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.10 g) and the mixture was stirred overnight (16 h) at room temperature. The resulting dark solution was concentrated in vacuo, and the remaining oil was dissolved in a minimum amount of EtOAc and filtered through a short silica plug eluting with hexanes/EtOAc (2/3). Following evaporation of the solvent, the oily solid was crystallized from methanol (20 mL) to give tan crystals (1.95 g, 65%), mp 110–111 °C. ^{1}H NMR ($CDCl_3$) δ 5.52 (br s, 2H), 6.25 (d, 1H), 6.79 (d, 1H), 7.45–7.54 (m, 3H), 7.89–7.91 (m, 2H). IR v 3445 and 3340 (NH_2) cm^{-1}. Anal. calcd for $C_{10}H_9NO_2S_2$: C, 50.19; H, 3.79; N, 5.85; S, 26.79. Found: C, 50.11; H, 3.74; N, 5.81; S, 26.68.

The following aminothiophenes were prepared accordingly.

2-Amino-3-(4-chlorophenylsulfonyl)thiophene (7b). This compound precipitated from the reaction mixture and was isolated by filtration as a tan solid in 82% yield, mp 156–157 °C (MeOH, tan crystals). ^{1}H NMR ($CDCl_3$) δ 5.56 (br s, 2H), 6.27 (d, 1H), 6.77 (d, 1H), 7.44 (d, 2H), 7.82 (d, 2H). IR v 3430 and 3320 (NH_2) cm^{-1}. Anal. calcd for $C_{10}H_8ClNO_2S_2$: C, 43.87; H, 2.95; Cl, 12.95; N, 5.12; S, 23.42. Found: C, 43.81; H, 2.96; Cl, 13.01; N, 5.08; S, 23.35.

2-Amino-3-(4-fluorophenylsulfonyl)thiophene (7c). Trituration of the oily residue following silica gel filtration with diethyl ether/hexanes gave a tan solid (58% yield), mp 104–107 °C. ^{1}H NMR ($CDCl_3$) δ 4.8–5.8 (very br signal, NH_2), 6.26 (d, 1H), 6.76 (d, 1H), 7.11–7.19 (m, 2H), 7.87–7.94 (m, 2H); the amine gave a very broad absorption between 4.8 and 5.8. IR (neat film as oil, NaCl) v 3450 and 3340 (NH_2) cm^{-1}. Anal. calcd for $C_{10}H_8FNO_2S_2$: C, 46.68; H, 3.13; N, 5.44; S, 24.92. Found: C, 46.75; H, 3.19; N, 5.39; S, 25.01.

2-Amino-3-(4-methylphenylsulfonyl)thiophene (7d). Obtained as a tan solid in 74% yield following silica gel filtration; mp 131–132 °C (MeOH, tan crystals). ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 6.37 (d, 1H), 6.75 (d, 1H), 6.95 (s, 2H), 7.36 (d, 2H), 7.79 (d, 2H). IR v 3440 and 3330 (NH_2) cm^{-1}. Anal. calcd for $C_{11}H_{11}NO_2S_2$: C, 52.15; H, 4.38; N, 5.53; S, 25.31. Found: C, 52.04; H, 4.45; N, 5.51; S, 25.43.

2-Amino-3-(2-nitrophenylsulfonyl)thiophene (7e). Prepared using triethylamine in place of DBU; following silica gel filtration, the product was crystallized from EtOAc as a yellow solid in 81% yield, mp 162–163 °C (EtOAc, yellow crystals). ^{1}H NMR ($CDCl_3$) δ 5.63 (br s, 2H), 6.29 (d, 1H), 6.79 (d, 1H), 7.69–7.74 (m, 3H), 8.17–8.19 (m, 1H). IR v 3430 and 3340 (NH_2) cm^{-1}. Anal. calcd for $C_{10}H_8N_2O_4S_2$: C, 42.24; H, 2.84; N, 9.86; S, 22.55. Found: C, 42.33; H, 2.80; N, 9.86; S, 22.49.

2-Amino-3-[(2-methoxycarbonyl)phenylsulfonyl]thiophene (7f). Obtained as an amber colored oil in 83% yield using triethylamine in place of DBU and MeOH as solvent. ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 5.08 (br s, 2H), 6.25 (d, 1H), 6.85 (d, 1H), 7.50–7.60 (m, 3H), 7.93–7.96 (m, 1H). IR v 3465 and 3360 (NH_2), 1725 (CO) cm^{-1}. Anal. calcd for $C_{12}H_{11}NO_4S_2$: C, 48.47; H, 3.73; N, 4.71; S, 21.56. Found: C, 48.30; H, 3.80; N, 4.59; S, 21.38.

2-Acetamido-3-(2-nitrophenylsulfonyl)thiophene (8a). To an ice-chilled solution of **7e** (0.57 g, 2.0 mmol) in acetonitrile (10 mL) was added pyridine (0.174 g, 2.2 mmol) followed by acetyl chloride (0.24 g, 3.0 mmol) and the mixture was heated at 90–100 °C for 30 min. The solution was then poured over ice/water with stirring to give a solid which was collected, rinsed with water. Recrystallization from methanol (10 mL) gave fine olive green crystals (0.49 g, 75%), mp 147–148 °C. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 6.81 (d, 1H), 6.95 (d, 1H), 7.76–7.82 (m, 3H), 8.26 (d, 1H), 10.04 (br s, 1H). IR v 3355 (NH), 1685 (CO) cm^{-1}. Anal. calcd for $C_{12}H_{10}N_2O_5S_2$: C, 44.16; H, 3.09; N, 8.59; S, 19.65. Found: C, 44.15; H, 3.05; N, 8.54; S, 19.65.

The following carboxamides were prepared accordingly.

2-Acetamido-3-(4-chlorophenylsulfonyl)thiophene (8b). Yield 68%; mp 161–161.5 °C (EtOH, tan crystals). ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 6.80 (d, 1H), 6.93 (d, 1H), 7.48 (d, 2H), 7.81 (d, 2H), 10.32 (br s, 1H). IR v 3325 (NH), 1665 (CO) cm^{-1}. Anal. calcd for $C_{12}H_{10}ClNO_3S_2$: C, 45.64; H, 3.19; Cl, 11.23; N, 4.44; S, 20.31. Found: C, 45.57; H, 3.23; Cl, 11.30; N, 4.50; S, 20.44.

2-Benzamido-3-(phenylsulfonyl)thiophene (8j). Prepared using benzoyl chloride (1.2 equiv). Yield 53%; mp 161–163 °C (MeOH, tan crystals). ^{1}H NMR (DMSO-d_6) δ 7.22–7.26 (dd, 2H), 7.63–7.75 (m, 6H), 7.98 (t, 2H), 8.08 (t, 2H), 11.23 (br s, 1H). IR v 3350 (NH), 1665 (CO) cm^{-1}. Anal. calcd for $C_{17}H_{13}NO_3S_2$: C, 59.46; H, 3.81; N, 4.08; S, 18.67. Found: C, 59.31; H, 3.82; N, 4.03; S, 18.62.

2-Benzamido-3-(4-methylphenylsulfonyl)thiophene (8k). Prepared using benzoyl chloride (1.2 equiv). Yield 49%; mp 199–200 °C (MeOH, fluffy tan needles). ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 6.84 (d, 1H), 7.01 (d, 1H), 7.29 (d, 2H), 7.54–7.63 (m, 3H), 7.79 (d, 2H), 8.02 (d,

2H), 11.41 (br s, 1H). IR v 3350 (NH), 1670 (CO) cm^{-1}. Anal. calcd for $C_{18}H_{15}NO_3S_2 \cdot 0.2H_2O$: C, 59.88; H, 4.30; N, 3.88; S, 17.76. Found: C, 59.55; H, 4.39; N, 3.89; S, 17.82.

2-(Methoxycarbonyl)acetamido-3-(phenylsulfonyl)thiophene (8l). Prepared using methyl malonyl chloride (1.1 equiv). After diluting with ice/water, the resulting oil was extracted into EtOAc and washed with sat. $NaHCO_3$ solution, followed by 1 N HCl, and finally brine. After drying ($MgSO_4$), the organic layer was concentrated to give an orange oil, which was crystallized from a small amount of methanol as a tan solid. Recrystallization from methanol gave tan crystals (yield 46%), mp 102–103 °C. ^1H NMR ($CDCl_3$) δ 3.63 (s, 2H), 3.87 (s, 3H), 6.82 (d, 1H), 7.05 (d, 1H), 7.49–7.60 (m, 3H), 7.94–7.96 (dd, 2H), 11.55 (br s, 1H). IR v 3340 (NH), 1735 (CO), 1685 (CO) cm^{-1}. Anal. calcd for $C_{14}H_{13}NO_5S_2$: C, 49.55; H, 3.86; N, 4.13; S, 18.89. Found: C, 49.60; H, 3.86; N, 4.10; S, 18.96.

3-Phenylsulfonyl-2-(3-pyridylcarboxamido)thiophene (8i). To a solution of **7a** (1.95 g, 8.15 mmol) in acetonitrile (17 mL) was added pyridine (1.64 g, 20.7 mmol) followed by nicotinoyl chloride hydrochloride (1.84 g, 10.3 mmol) and the mixture was stirred overnight (14 h) at room temperature. The resulting suspension was concentrated in vacuo to near dryness, diluted with aq $NaHCO_3$, stirred, and filtered to give a tan solid, which showed two spots on TLC (hexanes/EtOAc, 1/1). The crude product was stirred in methanol (20 mL) and recollected to give the near pure compound. Recrystallization from methanol (220 mL) with concentration to ca. 80 mL after filtering gave tan/colorless needles (1.05 g, 37%), mp 180.5–181.5 °C. ^1H NMR ($CDCl_3$) δ 6.89 (d, 1H), 7.04 (d, 1H), 7.47–7.62 (m, 4H), 7.90 (t, 2H), 8.27–8.30 (m, 1H), 8.85 (m, 1H), 9.27 (s, 1H), 11.55 (br s, 1H). IR v 3330 (NH), 1670 (CO) cm^{-1}. Anal. calcd for $C_{16}H_{12}N_2O_3S_2$: C, 55.80; H, 3.51; N, 8.14; S, 18.62. Found: C, 55.53; H, 3.57; N, 8.07; S, 18.76.

3-Phenylsulfonyl-2-(trifluoroacetamido)thiophene (8c). To an ice-chilled solution of **7a** (0.239 g, 1.0 mmol) in acetonitrile (5 mL) was added pyridine (0.12 g, 1.5 mmol) followed by trifluoroacetic anhydride (0.38 g, 1.8 mmol) and the mixture was stirred overnight at room temperature (16–18 h). The solution was then partially concentrated in vacuo and poured over ice/water to give a tan solid, which was collected, rinsed with water, and air dried (0.30 g, 89%). Recrystallization from methanol/water (8/1) gave tan needles, mp 102–102.5 °C. ^1H NMR ($CDCl_3$) δ 7.01 (d, 1H), 7.06 (d, 1H), 7.52–7.66 (m, 3H), 7.89–7.92 (m, 2H), 11.37 (br s, 1H). IR v 3275 (NH), 1715 (CO) cm^{-1}. Anal. calcd for $C_{12}H_8F_3NO_3S_2$: C, 42.98; H, 2.40; N, 4.18; S, 19.12. Found: C, 43.05; H, 2.35; N, 4.15; S, 18.99.

The following trifluoracetamides and heptafluorobutyramide were prepared accordingly.

3-(4-Chlorophenylsulfonyl)-2-(trifluoroacetamido)thiophene (8d). Yield 78%; mp 130–130.5 °C (MeOH, long colorless needles). ^1H NMR ($CDCl_3$) δ 7.01–7.06 (dd, 2H), 7.52 (d, 2H), 7.83 (d, 2H), 11.29 (br s, 1H). IR v 3280 (NH), 1715 (CO) cm^{-1}. Anal. calcd for $C_{12}H_7ClF_3NO_3S_2$: C, 38.98; H, 1.91; Cl, 9.59; N, 3.79; S, 17.34. Found: C, 38.86; H, 1.86; Cl, 9.61; N, 3.73; S, 17.26.

3-(4-Fluorophenylsulfonyl)-2-(trifluoroacetamido)thiophene (8e). Yield 90%; mp 92–93 °C (cyclohexane, fluffy tan needles). ^1H NMR ($CDCl_3$) δ 7.00–7.05 (dd, 2H), 7.20–7.26 (m, 2H), 7.90–7.95 (m, 2H), 11.31 (br s, 1H). IR v 3280 (NH), 1710 (CO) cm^{-1}. Anal. calcd for $C_{12}H_7F_4NO_3S_2$: C, 40.79; H, 2.00; N, 3.96; S, 18.15. Found: C, 40.85; H, 2.00; N, 3.91; S, 18.24.

3-(4-Methylphenylsulfonyl)-2-(trifluoroacetamido)thiophene (8f). Yield 76%; mp 118–119 °C (MeOH/water, fluffy tan needles). ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 6.98 (d, 1H), 7.04 (d, 1H), 7.33 (d, 2H), 7.77 (d, 2H), 11.37 (br s, 1H). IR v 3280 (NH), 1730 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{10}F_3NO_3S_2$: C, 44.69; H, 2.89; N, 4.01; S, 18.35. Found: C, 44.71; H, 2.92; N, 4.02; S, 18.38.

3-[(2-Methoxycarbonyl)phenylsulfonyl]-2-(trifluoroacetamido)thiophene (8g). Yield 66%; mp 142–143 °C (MeOH/water, tan needles). ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.97 (d, 1H), 7.07 (d, 1H), 7.68–7.71 (m, 3H), 8.20–8.25 (m, 1H), 11.12 (br s, 1H). IR v 3290 (NH), 1740 (ridge), and 1720 (CO) cm^{-1}. Anal. calcd for $C_{14}H_{10}F_3NO_5S_2$: C, 42.75; H, 2.56; N, 3.56; S, 16.30. Found: C, 42.70; H, 2.42; N, 3.59; S, 16.46.

3-(4-Chlorophenylsulfonyl)-2-(heptafluorobutyramido)-thiophene (8h). Prepared using heptafluorobutyric anhydride (1.5 equiv). After diluting with ice/water, the resulting gummy solid was extracted into EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica eluting with hexanes/EtOAc (3/1) (R_f 0.54) to give a light-tan solid (yield 60%), mp 105–106 °C (cyclohexane, fluffy white needles). ^1H NMR ($CDCl_3$) δ 7.02–7.07 (dd, 2H), 7.52 (d, 2H), 7.81 (d, 2H), 11.39 (br s, 1H). IR v 3325 (NH), 1715 (CO) cm^{-1}. Anal. calcd for $C_{14}H_7ClF_7NO_3S_2$: C, 35.79; H, 1.50; Cl, 7.55; N, 2.98; S, 13.65. Found: C, 35.85; H, 1.45; Cl, 7.62; N, 3.03; S, 13.73.

2-Formamido-3-[2-(methoxycarbonyl)phenylsulfonyl]thiophene (8m). As in the literature,[9] the formic acetic anhydride reagent was prepared by adding formic acid (95–97%) (0.16 g) to acetic anhydride (0.30 g) followed by stirring at room temperature for 1 h. A solution of **7f** (0.297 g, 1.0 mmol) in acetonitrile (5 mL) was then added to the anhydride and the mixture was stirred overnight at room temperature. Concentration in vacuo gave an oily solid, which was triturated with MeOH/water (1/1, 3–4 mL), collected, and air dried. Recrystallization from MeOH/water (4/1) gave a fluffy tan solid (0.225 g, 69%), mp 116–117 °C. ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.85 (d, 1H), 7.08 (d, 1H), 7.59–7.66 (m, 3H), 8.03–8.06 (m, 1H), 8.56 (s, 1H), 10.41 (br s, 1H). IR v 3250 (NH), 1725 (CO), 1680 and 1650 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{11}NO_5S_2$: C, 47.99; H, 3.41; N, 4.31; S, 19.71. Found: C, 48.08; H, 3.40; N, 4.37; S, 19.64.

2-Acetamido-5-bromo-3-(4-chlorophenylsulfonyl)thiophene (9a). To a solution of **8b** (0.632 g, 2.0 mmol) in dichloromethane (15 mL) was added *N*-bromosuccinimide (NBS) (0.356 g, 2.0 mmol) and the mixture was stirred at gentle reflux with TLC monitoring. After 3–4 h, a small amount of starting material remained, and thus additional NBS (0.018 g, 0.1 mmol) was added and stirring was continued overnight at room temperature. Filtration through silica with EtOAc/hexanes (1/1) followed by concentration gave an oily solid. Recrystallization from ethanol (40 mL) gave light-tan crystals (0.59 g, 75%). A second recrystallization from methanol gave off-white prisms, mp 169–171 °C. ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 6.88 (s, 1H), 7.48 (d, 2H), 7.79 (d, 2H), 10.31 (br s, 1H). IR ν 3325 (NH), 1690 (CO) cm^{-1}. Anal. calcd for $C_{12}H_9BrClNO_3S_2$: C, 36.52; H, 2.30; N, 3.55; S, 16.25. Found: C, 36.58; H, 2.35; N, 3.48; S, 16.31.

Compounds **9b–d** were prepared accordingly with the noted modifications.

5-Bromo-3-(4-chlorophenylsulfonyl)-2-(trifluoroacetamido)thiophene (9b). Reaction of **8d** (0.185, 0.5 mmol) with 1.0 equiv of NBS for 45 min gave the product as a pale-purple solid (yield 85%) after silica gel filtration; mp 148–148.5 °C (MeOH/water, lavender needles). ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 1H), 7.55 (d, 2H), 7.82 (d, 2H), 11.30 (br s, 1H). IR ν 3280 (NH), 1715 (CO) cm^{-1}. Anal. calcd for $C_{12}H_6BrClF_3NO_3S_2$: C, 32.12; H, 1.35; N, 3.12; S, 14.29. Found: C, 32.16; H, 1.36; N, 3.06; S, 14.20.

5-Bromo-2-formamido-3-[2-(methoxycarbonyl)phenylsulfonyl]thiophene (9c). Reaction of **8m** (0.108 g, 0.33 mmol) with 1.0 equiv of NBS for 45 min followed by heating with another 0.15 equiv of NBS for 15 min gave a fluffy orange/tan solid following recrystallization from methanol/water. Yield 47%; mp 131–131.5 °C, with partial melting at 110 °C. ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 7.06 (s, 1H), 7.64–7.69 (m, 3H), 8.05–8.08 (m, 1H), 8.53 (s, 1H), 10.47 (br s, 1H). IR ν 3320 (NH), 1730 (CO), 1680 (ridge), 1665 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{10}BrNO_5S_2$: C, 38.62; H, 2.49; N, 3.46; S, 15.86. Found: C, 38.69; H, 2.46; N, 3.48; S, 15.97.

2-Acetamido-5-chloro-3-(2-nitrophenylsulfonyl)thiophene (9d). Reaction of **8a** (0.16 g, 0.5 mmol) overnight with 1.0 equiv of *N*-chlorosuccinimide (NCS) at gentle reflux gave a 1/1 mixture of product and starting material according to TLC. Addition of another 1.0 equiv of NCS plus a few drops of methanesulfonic acid, followed by continued heating for 3–4 h led to complete reaction. Yield 44%; mp 202–204 °C (MeOH/water, fluffy pale-orange needles). ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 6.77 (s, 1H), 7.80–7.83 (m, 3H), 8.25 (t, 1H), 10.03 (br s, 1H). IR ν 3315 (NH), 1675 (CO) cm^{-1}. Anal. calcd for $C_{12}H_9ClN_2O_5S_2$: C, 39.95; H, 2.51; N, 7.77; S, 17.77. Found: C, 40.12; H, 2.54; N, 7.64; S, 17.71.

3-(4-Chlorophenylsulfonyl)-5-iodo-2-(trifluoroacetamido)-thiophene (9e). To a stirred solution of **8d** (0.074 g, 0.2 mmol) in acetonitrile (3 mL) was added crystalline iodine (0.056 g, 0.22 mmol). After dissolution of the iodine, crystalline silver nitrate (0.041 g, 0.24 mmol) was added causing the formation of a yellow precipitate. After stirring for 20 min, the precipitate was filtered off and the solution was diluted with water to give a tan solid. Recrystallization of the collected product from methanol/water (10/1) gave fluffy light-tan needles (0.056 g, 56%), mp 181–182 °C. ^{1}H NMR ($CDCl_3$) δ 7.16 (s, 1H), 7.55 (d, 2H), 7.82 (d, 2H), 11.32 (br s, 1H). IR ν 3290 (NH), 1715 (CO) cm^{-1}. Anal. calcd for $C_{12}H_6ClF_3INO_3S_2$: C, 29.08; H, 1.22; N, 2.83; S, 12.94. Found: C, 29.10; H, 1.20; N, 2.79; S, 12.87.

2-Acetamido-3-(4-chlorophenylsulfonyl)-5-nitrothiophene (9f). A suspension of **8b** (0.632 g, 2.0 mmol) in acetic anhydride (4 mL) was treated in portions with a chilled mixture of acetyl nitrate (prepared by adding cold HNO_3 (70%) (0.36 g) to cold acetic anhydride (3.0 g)) and stirred at room temperature for 1 h. The resulting solution was poured over ice and stirred for 15 min to give a solid, which was collected, washed with water, and air dried. Recrystallization from methanol (100 mL, followed by partial concentration) gave fluffy peach colored needles (0.515 g, 71%), mp 190–192 °C. ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 7.55 (d, 2H), 7.80 (s, 1H), 7.84 (d, 2H), 10.57 (br s, 1H). IR ν 3315 (NH), 1695 (CO) cm^{-1}. Anal. calcd for $C_{12}H_9ClN_2O_5S_2$: C, 39.95; H, 2.51; N, 7.77; S, 17.77. Found: C, 39.94; H, 2.48; N, 7.75; S, 17.70.

2-Acetamido-3-(4-fluorophenylsulfonyl)-5-nitrothiophene (9g). Reaction of aminothiophene **7c** (0.643 g, 2.5 mmol) with acetyl chloride/pyridine according to the procedure described for the synthesis of **8a** gave 2-acetamido-3-(4-fluorophenylsulfonyl)thiophene as a yellow/brown solid. Subsequent reaction of this acetamide with acetyl nitrate as described above gave the title compound as a yellow/orange solid (0.59 g, 69% overall), mp 187–189 °C (MeOH, gold prisms). ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 7.25–7.30 (m, 2H), 7.81 (s, 1H), 7.94–7.97 (m, 2H), 10.60 (br s, 1H). IR ν 3315 (NH), 1695 (CO) cm^{-1}. Anal. calcd for $C_{12}H_9FN_2O_5S_2$: C, 41.85; H, 2.63; N, 8.14; S, 18.62. Found: C, 41.95; H, 2.58; N, 8.07; S, 18.51.

Thieno[3,2-*b*][1,4]benzothiazepin-9(10*H*)-one 4,4-dioxide (10). To a solution of aminothiophene **7f** (0.297 g, 1.0 mmol) in methanol (5 mL) was added potassium *t*-butoxide (0.135 g, 1.2 mmol) and the mixture was heated at 60–65 °C for 1.5 h. After concentration, the residue was dissolved in a minimum amount of water and extracted with EtOAc. The aqueous layer was acidified with concentrated HCl/ice to give a tan solid, which was collected, rinsed with water, and air dried (0.15 g, 57%). Recrystallization from methanol (50 mL, with concentration by half after filtering) gave fluffy tan needles, mp 313–315 °C. ^{1}H NMR (DMSO-d_6) δ 7.20 (d, 1H), 7.35 (d, 1H), 7.86–8.00 (m, 4H), 11.99 (br s, 1H). IR ν 3180 (NH), 1645 (CO) cm^{-1}. Anal. calcd for $C_{11}H_7NO_3S_2$: C, 49.80; H, 2.66; N, 5.28; S, 24.17. Found: C, 49.88; H, 2.66; N, 5.28; S, 24.08.

3-(4-Chlorophenylsulfonyl)-4,5-dimethyl-2-(trifluoroacetamido)furan (12). Prepared according to the synthesis of **8c** using aminofuran **11** (0.286 g, 1.0 mmol). Yield

60%; mp 118–119 °C (MeOH/water, fluffy tan scales). ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.19 (s, 3H), 7.52 (d, 2H), 7.79 (d, 2H), 10.03 (br s, 1H). IR v 3320 (NH), 1735 (CO) cm^{-1}. Anal. calcd for $C_{14}H_{11}ClF_3NO_4S$: C, 44.04; H, 2.91; N, 3.67; S, 8.40. Found: C, 44.16; H, 2.88; N, 3.58; S, 8.31.

New compounds **13b**–**13d** were prepared according to a general literature procedure.[14]

2-Amino-3-(4-chlorophenylsulfonyl)-1-(4-methoxybenzyl)-4,5-dimethylpyrrole (13b). Yield 61%; mp 135–136 °C (MeOH, yellow crystals). ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 6H), 3.75 (s, 3H), 4.60 (br s, 2H), 4.81 (s, 2H), 6.80–7.80 (m, 8H). IR v 3440 and 3330 (NH_2) cm^{-1}. Anal. calcd for $C_{20}H_{21}ClN_2O_3S$: C, 59.32; H, 5.23; N, 6.92; S, 7.92. Found: C, 59.35; H, 5.23; N, 6.87; S, 7.93.

2-Amino-1-[2-(4-chlorophenyl)ethyl]-3-(4-chlorophenylsulfonyl)-4,5-dimethylpyrrole (13c). Yield 31%; mp 146–147 °C (MeOH, tan crystals). ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 6H), 2.85 (t, 2H), 3.38 (t, 2H), 4.20 (br s, 2H), 6.90–7.69 (m, 8H). IR v 3440 and 3360 (NH_2) cm^{-1}. Anal. calcd for $C_{20}H_{20}Cl_2N_2O_2S$: C, 56.74; H, 4.76; N, 6.62; S, 7.57. Found: C, 56.60; H, 4.71; N, 6.67; S, 7.51.

2-Amino-3-(4-chlorophenylsulfonyl)-4,5-dimethyl-1-(1-naphthylmethyl)pyrrole (13d). Yield 71%; mp 205–206 °C dec (MeOH, off-white fluffy solid). ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H), 2.00 (s, 3H), 5.15 (s, 2H), 7.39–8.00 (m, 11H). IR v 3440 and 3350 (NH_2) cm^{-1}. Anal. calcd for $C_{23}H_{21}ClN_2O_2S$: C, 65.00; H, 4.98; N, 6.59; S, 7.55. Found: C, 65.03; H, 5.00; N, 6.52; S, 7.50.

Compounds **14a**–**c** were prepared according to the synthesis of **8c** using the appropriate aminopyrrole.

1-Benzyl-3-(4-chlorophenylsulfonyl)-4,5-dimethyl-2-(trifluoroacetamido)pyrrole (14a). Yield 83%; mp 192–194 °C (MeOH/water, fluffy white needles). ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.07 (s, 3H), 4.94 (s, 2H), 6.89 (d, 2H), 7.27–7.31 (m, 3H), 7.44 (d, 2H), 7.74 (d, 2H), 8.42 (s, 1H). IR v 3235 (NH), 1740 (CO) cm^{-1}. Anal. calcd for $C_{21}H_{18}ClF_3N_2O_3S$: C, 53.56; H, 3.85; N, 5.95; S, 6.81. Found: C, 53.66; H, 3.85; N, 5.94; S, 6.88.

3-(4-Chlorophenylsulfonyl)-1-(4-methoxybenzyl)-4,5-dimethyl-2-(trifluoroacetamido)pyrrole (14b). Yield 98%; mp 203–204 °C (MeOH, fluffy white crystals). ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.05 (s, 3H), 3.75 (s, 3H), 4.87 (s, 2H), 6.80–6.99 (m, 4H), 7.40–7.68 (dd, 4H), 8.46 (s, 1H). IR v 3240 (NH), 1740 (CO) cm^{-1}. Anal. calcd for $C_{22}H_{20}ClF_3N_2O_4S$: C, 52.75; H, 4.02; N, 5.59; S, 6.40. Found: C, 52.87; H, 4.06; N, 5.57; S, 6.43.

1-[2-(4-Chlorophenyl)ethyl]-3-(4-chlorophenylsulfonyl)-4,5-dimethyl-2-(trifluoroacetamido)pyrrole (14c). Yield 61%; mp 208–210 °C (MeOH, fluffy white solid). ^{1}H NMR (DMSO-d_6) δ 1.95 (s, 6H), 2.85 (t, 2H), 3.91 (t, 2H), 7.20–7.90 (m, 8H), 11.45 (s, 1H). IR v 3200 (NH), 1735 (CO) cm^{-1}. Anal. calcd for $C_{22}H_{19}Cl_2F_3N_2O_3S$: C, 50.87; H, 3.69; N, 5.40; S, 6.17. Found: C, 51.04; H, 3.61; N, 5.34; S, 6.11.

2-(4-Chlorophenylsulfonyl)aniline (16). A gently refluxing solution of 4-chlorophenyl 2-nitrophenyl sulfone (**15**)[16] (1.49 g, 5.0 mmol) in acetic acid (25 mL) and water (2 mL) was treated in two portions with iron powder (1.50 g). After stirring vigorously for 1 h at 100–110 °C, the solution was poured over ice/water to give a pale-pink solid, which was collected and rinsed with water. Recrystallization from methanol (25 mL) gave off-white crystals (1.03 g, 81%), mp 134–135 °C, lit[15] mp 134–135 °C. ^{1}H NMR ($CDCl_3$) δ 4.43 (br s, 2H), 6.66 (d, 1H), 6.78 (t, 1H), 7.29 (t, 1H), 7.43 (d, 2H), 7.79 (d, 1H), 7.85 (d, 2H). IR v 3450 and 3355 (NH_2) cm^{-1}.

2′-(4-Chlorophenylsulfonyl)trifluoroacetanilide (17). To an ice chilled solution of aniline **16** (0.254 g, 1.0 mmol) and pyridine (0.09 g, 1.14 mmol) in acetonitrile (5 mL) was added trifluoroacetic anhydride (0.25 g, 1.2 mmol) and the mixture was stirred at room temperature. After stirring 30 min, the resulting suspension was diluted with water (5 mL) and the product was collected. Recrystallization from MeOH/water (10/1, 15–20 mL) gave white fluffy needles (0.23 g, 63%), mp 153–154 °C. ^{1}H NMR ($CDCl_3$) δ 7.36–7.41 (t, 1H), 7.49 (d, 2H), 7.63–7.68 (t, 1H), 7.77 (d, 2H), 8.06 (d, 1H), 8.38 (d, 1H); NH was not observed. IR v 3315 (NH), 1730 (CO) cm^{-1}. Anal. calcd for $C_{14}H_9ClF_3NO_3S$: C, 46.23; H, 2.49; N, 3.85; S, 8.82. Found: C, 46.22; H, 2.53; N, 3.78; S, 8.93.

2-Acetamido-3-cyanomethylsulfonyl-5-nitrothiophene (19c). This compound was prepared from acetamide **19b** (0.244 g) using the nitration procedure described above for **9f**. Yield 48%; mp 225–226 °C (MeOH, fluffy yellow needles). ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H), 5.34 (s, 2H), 8.16 (s, 1H), 11.08 (br s, 1H). IR v 3310 (NH), 2250 (CN), 1690 (CO) cm^{-1}. Anal. calcd for $C_8H_7N_3O_5S_2$: C, 33.21; H, 2.44; N, 14.53; S, 22.17. Found: C, 33.28; H, 2.40; N, 14.37; S, 22.34.

Virology

Cells. Human embryonic lung (HEL) fibroblasts and E_6SM cells were grown in minimum essential medium (MEM) and human lymphoblast (CEM) cells were grown in RPMI-1640 medium, supplemented with 10% inactivated fetal calf serum (FCS), 1% L-glutamine and 0.3% sodium bicarbonate.

Viruses. The laboratory wild-type VZV strains OKA and YS, the thymidine kinase-deficient VZV strains 07-1 and YS-R, HSV-1 (KOS), HSV-2 (G), the thymidine kinase-deficient HSV-1 strains B-2006 and VMW 1837, cytomegalovirus strains Davis and AD-169, and human immunodeficiency virus type 1 (strain III_B) and type 2 (strain ROD) were used in the virus inhibition assays.

Antiviral assays. The procedures of the antiviral assays were as described before.[23–26] Confluent HEL cells grown in 96-well microtiter plates were inoculated with VZV at an input of 20 PFU (plaque forming units) per well, with CMV at an input of 100 PFU per well, or with HSV at 100 $CCID_{50}$ (50% cell culture infective doses) per well. After a 1 to 2-h incubation period,

residual virus was removed and the infected cells were further incubated with MEM (supplemented with 2% inactivated FCS, 1% L-glutamine and 0.3% sodium bicarbonate) containing varying concentrations of the compounds. Antiviral activity was expressed as EC_{50} (50% effective concentration), or concentration required to reduce viral plaque formation after 5 days (VZV) or virus-induced cytopathicity (CMV after 7 days and HSV, VV after 3 days) by 50% compared to the untreated control. For the HIV assays, 4×10^5 CEM cells per mL were infected with HIV-1 or HIV-2 at ~100 $CCID_{50}$ (50% cell culture infective dose) per mL of cell suspension. Then 100 μL of the infected cell suspension was transferred to microtiter plate wells and mixed with 100 μL of the appropriate dilutions of test compounds. After 4 days, giant cell formation (CEM) was recorded microscopically in the HIV-infected cell cultures. The 50% effective concentration (EC_{50}) and 50% cytotoxic concentration (CC_{50}) of the test compounds were defined as the compound concentrations required to inhibit virus-induced cytopathicity (CEM) by 50% or to reduce by 50% the number of viable cells in mock-infected cell cultures, respectively. The other viruses were assayed as described before.

Cytotoxicity assays. Confluent monolayers of HEL cells as well as growing HEL cells in 96-well microtiter plates were treated with different concentrations of the experimental drugs. Cell cultures were incubated for 3 (growing cells) or 5 (confluent cells) days. At the indicated time, the cells were trypsinized and the cell number was determined using a Coulter counter. The 50% cytostatic concentration (CC_{50}) was defined as the compound concentration required to reduce the cell number by 50%.

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References and Notes

1. McMahon, J. B.; Gulakowski, R. J.; Weislow, O. S.; Schultz, R. J.; Narayanan, V. L.; Clanton, D. J.; Pedemonte, R.; Wassmundt, F. W.; Buckheit, R. W., Jr.; Decker, W. D.; White, E. L.; Bader, J. P.; Boyd, M. R. *Antimicrob. Agents Chemother*. **1993**, *37*, 754.
2. Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem*. **1993**, *36*, 1291.
3. (a) *Antiviral Agents Bulletin* **1998**, *11*, 289. (b) Cited activity obtained from: Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *J. Med. Chem*. **2000**, *43*, 2019.
4. Richman, D.; Rosenthal, A. S.; Skoog, M.; Eckner, R. J.; Chou, T.-C.; Sabo, J. P.; Merluzzi, V. *J. Antimicrob. Agents Chemother*. **1991**, *35*, 305.
5. Dueweke, T. J.; Poppe, S. M.; Romero, D. L.; Swaney, S. M.; So, A. G.; Downey, K. M.; Althaus, I. W.; Reusser, F.; Busso, M.; Resnick, L.; Mayers, D. L.; Lane, J.; Aristoff, P. A.; Thomas, R. C.; Tarpley, W. G. *Antimicrob. Agents Chemother*. **1993**, *37*, 1127.
6. Young, S. D.; Britcher, S. F.; Tran, L. E.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother*. **1995**, *39*, 2602.
7. Young, S. D.; Amblard, M. C.; Britcher, S. F.; Grey, V. E.; Tran, L. O.; Lumma, W. C.; Huff, J. R.; Schleif, W. A.; Emini, E. E.; O'Brien, J. A.; Pettibone, D. J. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 491.
8. Artico, M.; Silvestri, R.; Stefancich, G.; Massa, S.; Pagnozzi, E.; Musu, D.; Scintu, F.; Pinna, E.; Tinti, E.; La Colla, P. *Arch. Pharm. (Weinheim)* **1995**, *328*, 223.
9. Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; La Colla, P. *J. Med. Chem*. **1996**, *39*, 522.
10. Buckheit, Jr., R. W.; Fliakas-Boltz, V.; Russell, J. D.; Snow, M.; Pallansch, L. A.; Yang, S. S.; Bader, J. P.; Khan, T. N.; Zanger, M. *Antiviral Chem. Chemother*. **1996**, *7*, 243.
11. Gewald, K. *Chem. Ber*. **1965**, *98*, 3571.
12. Merkushev, E. B. *Synthesis* **1988**, 923.
13. Ross, J. R.; Sowell, J. W., Sr. *J. Heterocycl. Chem*. **1987**, *24*, 757.
14. Mattson, R. J.; Wang, L.-C.; Sowell, J. W., Sr. *J. Heterocyclic Chem*. **1980**, *17*, 1793.
15. The trifluoroacetamide of aminopyrrole **13d** was not prepared at this time.
16. Cadogan, J. I. G.; Done, J. N.; Lunn, G.; Lim, P. K. K. *J. Chem. Soc., Perkins Trans 1* **1976**, 1749
17. Stephens, C. E.; Price, M. B.; Sowell, J. W., Sr. *J. Heterocycl. Chem*. **1999**, *36*, 659.
18. Stephens, C. E.; Sowell, J. W., Sr. *J. Heterocycl. Chem*. **1998**, *35*, 927.
19. Artico, M.; Stefancich, G.; Silvestri, R.; Massa, S.; Pagnozzi, E.; Loi, A. G.; Musu, D.; Doa, M.; Scano, P.; La Colla, P. *Med. Chem. Res*. **1994**, *4*, 283.
20. Artico, M.; Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Massa, S.; Loi, A. G.; Putzolu, M.; Corrias, S.; Spiga, M. G.; La Colla, P. *Bioorg. Med. Chem*. **1996**, *4*, 837.
21. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst*. **1991**, *93*, 757.
22. Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. *J. Med. Chem*. **1999**, *42*, 3789.
23. De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. *J. Infect. Dis*. **1980**, *141*, 563.
24. De Clercq, E.; Holý, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. *Nature* **1986**, *323*, 464.
25. De Clercq, E.; Sakuma, T.; Baba, M.; Pauwels, R.; Balzarini, J.; Rosenberg, I.; Holý, A. *Antiviral Res*. **1987**, *8*, 261.
26. Balzarini, J.; Pérez-Pérez, M. J.; San-Félix, A.; Schols, D.; Perno, C.-F.; Vandamme, A. M.; Camarasa, M. J.; De Clercq, E. *Proc. Natl. Acad. Sci. U.S.A*. **1992**, *89*, 4392.