2-Sulfonyl-4-chloroanilino Moiety: A Potent Pharmacophore for the Anti-Human Immunodeficiency Virus Type 1 Activity of Pyrrolyl Aryl Sulfones

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The synthesis and the evaluation of cytotoxicity and anti-HIV-1 activity of new aryl pyrrolyl (**8**) and aryl indolyl (**9**) sulfones are reported. Preparation of above sulfones was achieved by reacting arylsulfonyl chlorides with substituted pyrroles and indoles or by condensing sulfonamides with 2,5-dimethoxytetrahydrofuran in glacial acetic acid according to the Clauson−Kaas method. Chemical requisites relevant to the anti-HIV-1 activity of these compounds are both a 2-sulfonyl-4-chloroanilino moiety and an alkoxycarbonyl group at position 2 of the pyrrole ring. The best activity and selectivity were obtained with ethoxycarbonyl and isopropoxycarbonyl substituents. Substitutions at the amino group of the pharmacophore moiety led to inactive products (alkylation) or weakened (acylation) anti-HIV-1 activity. Among test derivatives, 16 compounds showed EC_{50} values ranging between 10 and 1 μM, and five (**8b′**,**d′**,**f′**,**h′**,**j′**) showed EC_{50}s in the sub-micromolar range. The compounds were active against HIV-1, both wild type and AZT-resistant strains, but not against HIV-2. Moreover, in enzyme assays they potently inhibited the HIV-1 recombinant reverse transcriptase, were 10 times less active against enzymes from nevirapine- and TIBO-resistant strains, and were totally inactive against the HIV-2 recombinant enzyme. Interestingly, some compounds (**8r′**−**y′**) were inactive against the recombinant reverse transcriptase while being active in tissue culture.

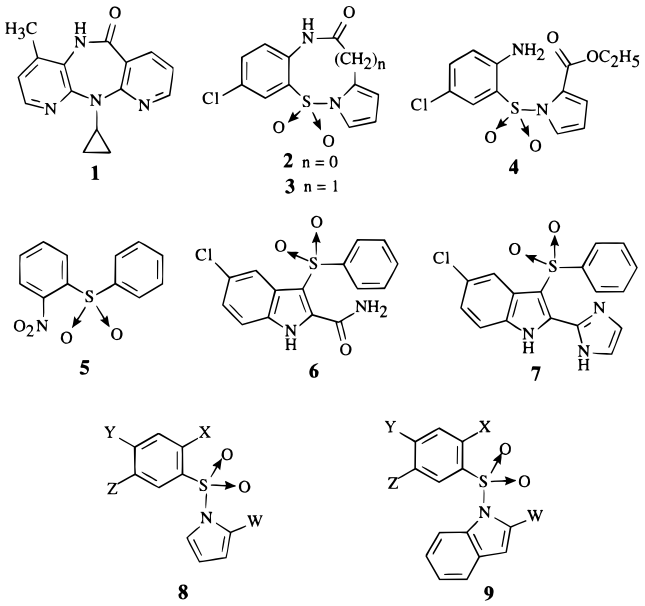
Although various enzymes involved in the replicative cycle of HIV have been selected as targets for the design of new anti-AIDS drugs, the virus-encoded reverse transcriptase (RT) has been one of the most exploited. In addition to nucleoside analogues, new type of inhibitors have been described and referred to as non-nucleoside reverse transcriptase inhibitors (NNRTIs).[1−5] Among them are TIBO,[6] nevirapine,[7] HEPT,[8] BHAP,[9] PETT,[10] DABO,[11−13] α-APA,[14] TSAO,[15,16] and, more recently, oxathiin carboxanilide[17] and dihydroquinoxalinethione S-2720.[18]

The family of tricyclic derivatives related to nevirapine (**1**) has been intensely studied over the past decade, and various 6,7,6- and 6,7,5-membered tricyclic systems have been synthesized and reported active against HIV-1 in the nanomolar range.[19−23]

Efforts in this direction have led us to design and test some new tricyclic systems (**2** and **3**) containing a pyrrole ring condensed with benzothiadiazepine and benzothiadiazocine moieties in the S-dioxide state.[24−31] During these studies we have found that compounds in which the sulfone is not part of a ring, such as derivative **4**, were as active as, if not more active than, the related cyclic counterparts. Therefore, we decided to synthesize new pyrrolyl aryl sulfones as a further development of our previous studies on pyrrole analogues[32] of the nitrophenyl phenyl sulfone **5** (NPPS).[33]

NPPS was selected in 1993 as a potent member of a new emerging class of NNRTI agents, the diaryl sulfones, after a large-scale drug-screening program pursued by the National Cancer Institute. In the same year a preliminary communication from Merck Research Laboratories accounted for the high activity of 5-chloro-3-(phenylsulfonyl)indole-2-carboxamide (L-737,126,**6**), a novel specific inhibitor of the HIV-1 RT.[34] More details on the synthesis and activity of indole 3-sulfones have been published recently, and structure−activity relationship (SAR) studies clearly demonstrated that the presence of carboxamide is crucial for the anti-HIV activity. Subsequently, optimization of the indole-containing compound L-737,126 has led to potent inhibitors, *e.g.*, derivative **7**,[35] with equivalent anti-HIV-1 RT activity but improved physicochemical properties.

The importance of the diaryl sulfone moiety for the



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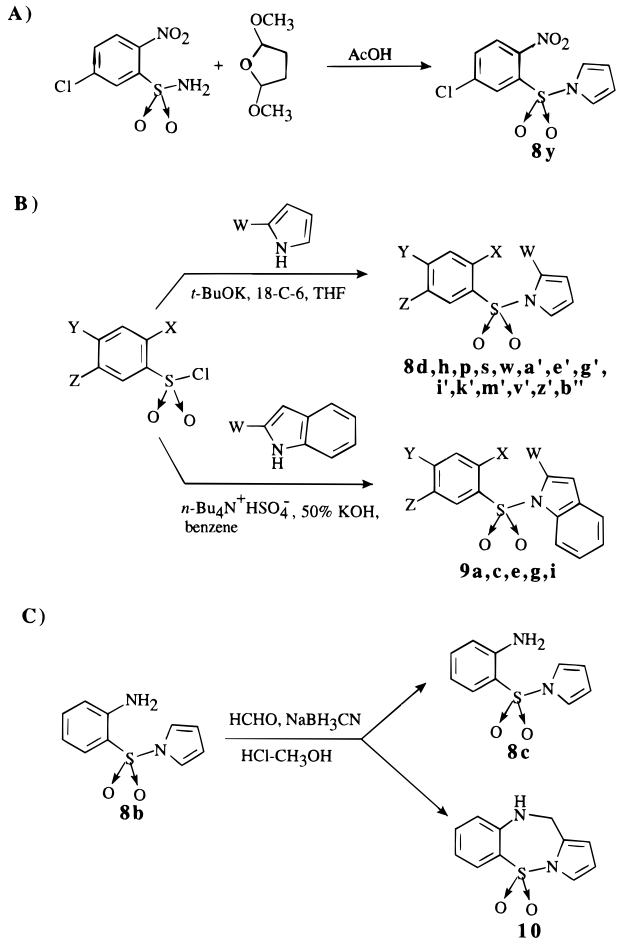
Scheme 1



design of new potential anti-HIV-1 agents is now confirmed by the present study on novel pyrrolyl aryl sulfones and related indole sulfones, represented by general formulas **8** and **9**.

Chemistry

Compounds **8a**,**b** were prepared according to literature.[36] Compounds **8f**,**g**,[24] **8j**,**k**,**m**,**n**,**v**,**c′**,**d′**,[31] and **8q**,**u**[32] were described by us in previous works.

1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole (**8y**) was prepared by refluxing 5-chloro-2-nitrobenzenesulfonamide[37] with 2,5-dimethoxytetrahydrofuran in glacial acetic acid according to the Clauson−Kaas procedure[38] (Scheme 1, A). Similarly 1-[(2-chloro-5-nitrophenyl)sulfonyl]-1*H*-pyrrole (**8x′**) was obtained starting from 2-chloro-5-nitrobenzenesulfonamide.[39]

Nitroaryl pyrrolyl sulfones **8d**,**h**,**p**,**s**,**w**,**a′**,**e′**,**g′**,**i′**,**k′**, **m′**,**v′**,**z′**,**b″** were synthesized by reaction of respective benzenesulfonyl chlorides[40−44] with alkyl pyrrole-2-carboxylates[45,46] and 2-acetylpyrrole[47] in the presence of potassium *tert*-butoxide and 18-crown-6. Nitroaryl indolyl sulfones **9a**,**c**,**e**,**g**,**i** were obtained by phase-transfer reaction of respective benzenesulfonyl chlorides with indole or ethyl indole-2-carboxylate in the presence of *n*-tetrabutylammonium hydrogen sulfate in benzene−aqueous 50% potassium hydroxide medium (Scheme 1, B).

Iron powder reduction of nitro derivatives in glacial acetic acid by heating at 60 °C for 2 h furnished the related anilines **8e**,**r**,**t**,**v**,**x**,**z**,**b′**,**d′**,**f′**,**h′**,**j′**,**l′**,**n′**,**w′**,**y′**,**a″**,**c″** and **9b**,**d**,**f**,**h**,**j**. Alkaline hydrolysis of ethyl 1-[(2-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**8h**) led to the corresponding carboxylic acid **8i**. Treatment of 1-[(2-fluorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylic acid (**8k**) with cyclohexylamine or formylhydrazine in the presence of *N*-[3-(dimethylamino)propyl]-*N′*-ethylcarbodiimide hydrochloride (EDC) and 4-(dimethylamino)-pyridine (DMAP) gave the respective amides **8l**,**o**.

Reaction of **8b** with formaldehyde in the presence of sodium cyanoborohydride in methanol−hydrochloric acid afforded the required *N*-methyl derivative **8c** with the concomitant formation of 10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide (**10**)[36] (Scheme 1, C). In a similar way were prepared the *N*-alkyl derivatives **8o′**,**p′**,**q′** by reacting ethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**8d′**) with formaldehyde, acetaldehyde, and butyraldehyde, respectively.

Amides **8s′**,**t′** were obtained by refluxing **8d′** with acetyl and propionyl chloride in pyridine. Formamido **8r′** was achieved by reacting **8d′** with acetoformic anhydride. Ethyl 1-[[5-chloro-2-[(ethoxycarbonyl)acetamido]phenyl]sulfonyl]-1*H*-pyrrole-2-carboxylate (**8u′**) was synthesized by refluxing **8d′** with diethyl malonate in xylene in the presence of 2-hydroxypyridine with azeotropic removal of ethanol.

Results and Discussion

Aryl pyrrolyl sulfones **8** and aryl indolyl sulfones **9** were assayed for cytotoxicity and anti-HIV activity. The antiviral activities were determined by measuring the extent of protection against the HIV-induced cytopathogenicity and were compared with those of AZT and nevirapine, used as reference drugs. Compounds that resulted active in cell culture were then tested in enzyme assays against recombinant HIV-1 RTs from both wild type and clinically relevant mutant viruses.

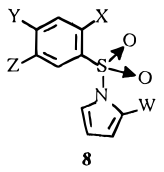
As shown in Table 1, the majority of compounds was found noncytotoxic for MT-4 cells at doses higher than 100 μM. Notable exceptions were compounds **8w**,**y**, **a′**,**c′**,**e′**,**i′**,**x′**,**z′**,**b″** and **9c**,**e**,**f**,**i** that were cytotoxic at doses of 10 μM or lower.

Among the 65 synthesized sulfones, 16 (**8d**,**g**,**j**,**p**, **x**,**b′**,**n′**,**r′-w′** and **9a**,**b**,**h**) were selectively active against the HIV-1 multiplication in acutely infected MT-4 cells at concentrations ranging between 10 and 1 μM. Five additional compounds (**8b′**,**d′**,**f′**,**h′**,**j′**) were highly potent, showing EC_{50}s in the submicromolar range. SAR studies allow to identify the NH_2 group and the Cl atom at positions 2 and 5, respectively, of the phenyl ring and the alkoxycarbonyl substituent at position 2 of the pyrrole moiety as the structural features that seem essential for the anti-HIV activity of title compounds.

Maximum potency and selectivity of [(2-amino-5-chlorophenyl)sulfonyl]pyrrole derivatives correlate with the presence in the pyrrole ring of methoxy- (**8b′**), ethoxy- (**8d′**), or isopropoxy-(**8h′**)-carbonyl substituents; in fact, as the alkoxy group becomes bulkier (**8f′**,**l′**,**n′**) or a double bond is introduced in the alkyl chain (**8j′**), the selectivity diminishes because of either a decrease in potency or an increase in cytotoxicity.

When acyl groups such as CHO (**8r′**), $COCH_3$ (**8s′**), or COC_2H_5 (**8t′**) are introduced at the NH_2 group, the antiviral potency is partly retained, whereas when more lipophilic alkyl substituents are attached to the NH_2 group (**8o′**−**q′**), or when the latter is replaced with NO_2

Table 1. Cyclotoxicities and Anti-HIV-1 Activities of Derivatives **8a**−**c″** and **9a**−**j**[a]



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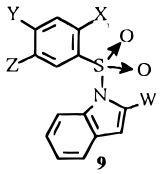

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compd	X	Y	Z	W	CC_{50}[b]	EC_{50}[c]	SI[d]
8a	NO_2	H	H	H	36	>36	
8b	NH_2	H	H	H	228	>228	
8c	$NHCH_3$	H	H	H	>300	>300	
8d	NO_2	H	H	$COOCH_3$	>300	5	>60
8e	NH_2	H	H	$COOCH_3$	>300	22	>14
8f	NO_2	H	H	$COOC_2H_5$	>300	15	>20
8g	NH_2	H	H	$COOC_2H_5$	≥300	10	>30
8h	Cl	H	H	$COOC_2H_5$	141	27	5
8i	Cl	H	H	COOH	>300	247	
8j	F	H	H	$COOC_2H_5$	132	13	10
8k	F	H	H	COOH	>300	>300	
8l	F	H	H	CONH-cyclohexyl	300	>300	
8m	F	H	H	$CONHCH_2$-phenyl	>300	40	7
8n	F	H	H	CONH-cyclopropyl	300	>300	
8o	F	H	H	CONHNHCHO	300	>300	
8p	NO_2	H	H	$COCH_3$	100	2	50
8q	NO_2	Cl	H	H	15	>15	
8r	NH_2	Cl	H	H	75	>75	
8s	NO_2	Cl	H	$COOCH_3$	>300	>300	
8t	NH_2	Cl	H	$COOCH_3$	248	>248	
8u	NO_2	Cl	H	$COOC_2H_5$	>300	15	>20
8v	NH_2	Cl	H	$COOC_2H_5$	238	>238	
8w	NO_2	Cl	Cl	$COOC_2H_5$	5	>5	
8x	NH_2	Cl	Cl	$COOC_2H_5$	>300	12	>25
8y	NO_2	H	Cl	H	2	>2	
8z	NH_2	H	Cl	H	165	95	2.0
8a′	NO_2	H	Cl	$COOCH_3$	12	10	1.2
8b′	NH_2	H	Cl	$COOCH_3$	>300	0.18	>1666
8c′	NO_2	H	Cl	$COOC_2H_5$	12	>12	
8d′	NH_2	H	Cl	$COOC_2H_5$	>300	0.14	>2140
8e′	NO_2	H	Cl	COO-*n*-C_3H_7	10	>10	
8f′	NH_2	H	Cl	COO-*n*-C_3H_7	110	0.22	500
8g′	NO_2	H	Cl	COO-*i*-C_3H_7	>300	30	>10
8h′	NH_2	H	Cl	COO-*i*-C_3H_7	>300	0.14	>2140
8i′	NO_2	H	Cl	$COOCH_2CH{=}CH_2$	4.3	>4.3	
8j′	NH_2	H	Cl	$COOCH_2CH{=}CH_2$	100	0.40	250
8k′	NO_2	H	Cl	$COOCH_2$-phenyl	300	>300	
8l′	NH_2	H	Cl	$COOCH_2$-phenyl	>300	150	>2
8m′	NO_2	H	Cl	$COO(CH_2)_2N(C_2H_5)_2$	30	>30	
8n′	NH_2	H	Cl	$COO(CH_2)_2N(C_2H_5)_2$	162	12	13.5
8o′	$NHCH_3$	H	Cl	$COOC_2H_5$	300	≥300	
8p′	$NIIC_2H_5$	H	Cl	$COOC_2H_5$	300	>300	
8q′	NH-*n*-C_4H_9	H	Cl	$COOC_2H_5$	>300	>300	
8r′	NHCHO	H	Cl	$COOC_2H_5$	>300	1.0	>300
8s′	$NHCOCH_3$	H	Cl	$COOC_2H_5$	≥300	1.0	≥300
8t′	$NHCOC_2H_5$	H	Cl	$COOC_2H_5$	>300	1.0	>300
8u′	$NHCOCH_2COOC_2H_5$	H	Cl	$COOC_2H_5$	290	2.6	111
8v′	NO_2	H	CH_3	$COOC_2H_5$	>300	9.8	>30.6
8w′	NH_2	H	CH_3	$COOC_2H_5$	>300	1.7	>176
8x′	Cl	H	NO_2	H	2	>2	
8y′	Cl	H	NH_2	H	91	>91	
8z′	Cl	H	NO_2	$COOCH_3$	12	≥12	
8a″	Cl	H	NH_2	$COOCH_3$	150	75	2.0
8b″	Cl	H	NO_2	$COOC_2H_5$	6	≥6	
8c″	Cl	H	NH_2	$COOC_2H_5$	72	≥72	
9a	NO_2	H	H	H	24	5	5
9b	NH_2	H	H	H	58	11	5
9c	NO_2	Cl	H	H	8	>8	
9d	NH_2	Cl	H	H	37	>37	
9e	NO_2	H	Cl	H	2	>2	
9f	NH_2	H	Cl	H	1	1	
9g	NO_2	H	Cl	$COOC_2H_5$	>100	>100	
9h	NH_2	H	Cl	$COOC_2H_5$	50	1.8	28
9i	Cl	H	NO_2	H	3	>3	
9j	Cl	H	NH_2	H	>300	150	>2.0
AZT					>20	0.01	>2000
Nevirapine					<300	0.30	>1000

[a] Data represent mean values for three separate experiments. Variation among triplicate samples was <15%. [b] Compound dose (μM) required to reduce the viability of mock-infected cells by 50%, as determined by the MTT method. [c] Compound dose (μM) required to achieve 50% protection of MT-4 cells from HIV-1-induced cytopathogenicity, as determined by the MTT method. [d] Selectivity index: CC_{50}/EC_{50} ratio.

(*i.e.*, **8a′**,**c′**,**e′**,**g**), the antiviral activity is strongly reduced, if not completely lost. Strong reduction or loss of activity is also observed in the following cases: when the Cl atom at 5-position of the phenyl ring is shifted to position 4 (**8t**,**v**), when 4,5-dichloro-substituted compounds (**8x**) are considered, when the positions of the 5-Cl atom and the NH_2/NO_2 groups are reversed (**8x′**−**c″**), and when the Cl atom is removed from the phenyl ring. Only in two cases (**9a**,**b**) the replacement of the pyrrole ring with an indole moiety led to compounds endowed with some anti-HIV activity.

As already observed,[34] a number of very active anti-HIV compounds, mostly NNRTIs, incorporate a *p*-chloroaniline moiety or the related 5-chloro-2-pyridylamine as a structural element. These inhibitors include 8-Cl-TIBO (R86183),[6] 7-Cl-PBTD (**2**),[31] 3,3-dialkyl-3,4-dihydroquinoxaline-2(1*H*)-thione (S-2720),[5] quinazolinone (L-738,372),[5] PETT (MSC-127),[10] indole derivative **6**,[34] anti-Tat Ro 5-3335 and Ro 24-7429 derivatives,[5] oxathiin carboxanilide (NSC 615985; Uniroyal),[17] and all the active pyrrolyl aryl sulfones reported here. In the latter case, however, the *p*-chloroaniline moiety acts as a pharmacophore only when the sulfonyl substituent is proximal to the amino group (compare **8z′**−**c″** with **8a′**−**d′**). Furthermore, in our compounds the nature of the pharmacophore cannot be altered without affecting the anti-HIV activity. In fact, alkylation of **8d′** abates the activity (**8o′**−**q′**), whereas acylation leads to active, although not very potent, amides (**8r′**−**u′**).

As stated above, the best anti-HIV-1 activity of [(2-amino-5-chlorophenyl)sulfonyl]pyrroles is associated with the presence of an alkoxycarbonyl group bound at position 2 of the pyrrole ring. This peculiar requisite well correlates with the presence of the bioisosteric aminocarbonyl group at the position 2 of the indole nucleus of derivative **6**, which has been found to exhibit potent activity against the HIV-1 RT.

None of the compounds was found active against HIV-2 in *de novo* infected C8166 cells (data not shown).

In order to establish whether the RT was the target of pyrrolyl aryl sulfones, the more active compounds in cell culture-based assays were tested against recombinant reverse transcriptase (rRT) from wild type (wt) and two clinically relevant mutant viruses carrying mutations at positions 181 (nevirapine-resistance) and 100 (TIBO-resistance). The HIV-2 rRT was also included in the assays since it can be viewed as an enzyme which is highly resistant to NNRTIs; in fact, the replacement of the amino acid residues at positions 176 and 190 with those presept in the HIV-1 enzyme has been reported to result in a chimeric RT which is fully susceptible to inhibition by nevirapine. The ability of the compounds to inhibit the recombinant enzymes is shown in Table 2. Compounds **8b′**,**d′**,**f′**,**h′**,**j′** were active against the wt rRT of HIV-1 at concentrations comparable to those active in cell culture-based assays. On the contrary, compounds **8r′**−**u′** were inactive on the wt enzyme at a concentration more than 10 times higher than the EC_{50} in cell culture. Since the latter compounds were also inactive when tested for the ability to inhibit the DNA-dependent DNA polymerase and RNase-H functions of the wt rRT (data not shown), it may be suggested that substitutions at the NH_2 group lead to compounds targeting a different step of the HIV multiplication.

When tested against the rRT from HIV-1 mutants resistant to nevirapine (Y181C) and TIBO (L100I), the compounds were inhibitory at concentrations at least 10 times higher, suggesting that pyrrolyl aryl sulfones fall within the same subgroup of NNRTIs with nevirapine, pyridinone, and diaryl sulfones. As expected, none of the compounds was active against the HIV-2 rRT.

Table 2. Activities of Derivatives **8b′**,**d′**,**f′**,**h′**,**j′**,**r′**−**w′** against Recombinant Reverse Transcriptase

	$IC_{50} \pm SD$[a]			
compd	wt IIIB	Y181C	L100I	HIV-2
8b′	0.45 ± 0.09	6.9 ± 2.3	7.4 ± 1.2	>20
8d′	0.40 ± 0.05	7.5 ± 1.4	8.5 ± 1.0	>20
8f′	0.40 ± 0.14	5 ± 1.5	10 ± 3.1	>20
8h′	0.27 ± 0.10	8 ± 2.0	14 ± 1.2	>20
8j′	0.90 ± 0.12	14 ± 2.5	>20	>20
8r′	>20	>20	>20	>20
8s′	>20	>20	>20	>20
8t′	>20	>20	>20	>20
8u′	>20	>20	>20	>20
8v′	5 ± 0.4	>20	>20	>20
8w′	4 ± 1.2	>20	>20	>20
nevirapine	0.60 ± 0.1	>20	3.5 ± 0.18	>20
TIBO	0.90 ± 0.05	9 ± 1.1	>20	>20

[a] Compound dose (μM) required to inhibit the HIV rRT activities by 50%. SD = standard deviation.

Further biological assays for derivatives **8b′**,**d′**,**f′**,**h′**,**j′** are in progress to isolate and characterize resistant mutants and to study the combined inhibitory effect of these derivatives with nucleoside analogues (AZT, ddC, or ddI) on the replication of HIV-1.

Experimental Section

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Infrared spectra (IR) (Nujol mulls) were run on a Perkin-Elmer 1310 spectrophotometer. ^{1}H-NMR spectra were recorded on Varian Gemini (200 MHz) and Bruker AM-200 (200 MHz) FT spectrometers in the indicated solvent. Chemical shifts are expressed in δ units from tetramethylsilane (TMS) as an internal standard. NMR spectral data are reported as a list. Column chromatographies were packed with alumina (Merck, 70−230 mesh) and silica gel (Merck, 70−230 mesh). Aluminum oxide/TLC-cards (Fluka, aluminum oxide-precoated aluminum cards with fluorescent indicator 254 nm) and silica gel/TLC-cards (Fluka, silica gel-precoated aluminum cards with fluorescent indicator 254 nm) were used for thin layer chromatography (TLC). Developed plates were visualized by UV light. Organic solutions were dried over anhydrous sodium sulfate. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator (Büchi) operating at reduced pressure. Elemental analyses were performed by Laboratories of Professor A. Pietrogrande, University of Padova, Italy. Analytical results which are indicated only by symbols were found within ±0.4% of the theoretical values. Benzenesulfonyl chlorides: 2-nitrobenzenesulfonyl chloride (Fluka), 2-chlorobenzenesulfonyl chloride,[40] 2-fluorobenzenesulfonyl chloride,[41] 4-chloro-2-nitrobenzenesulfonyl chloride,[40] 2-chloro-5-nitrobenzenesulfonyl chloride,[38] 5-chloro-2-nitrobenzenesulfonyl chloride,[42] 5-methyl-2-nitrobenzenesulfonyl chloride (yield 64%, mp 62−63 °C, from benzene/ligroin), and 4,5-dichloro-2-nitrobenzenesulfonyl chloride (yield 47%, mp 100−101 °C, from ligroin) prepared as reported by Meerwein[40] and Hoffman.[43] Pyrrole-2-carboxylic acid esters: methyl pyrrole-2-carboxylate,[44] ethyl pyrrole-2-carboxylate,[45] *n*-propyl pyrrole-2-carboxylate prepared as reported by Hardbuck[44] [yield 97%, bp 120−122 °C/0.16 mmHg (lit.[46] bp 164−167 °C/5 cmHg)]; isopropyl pyrrole-2-carboxylate,[44] allyl pyrrole-2-carboxylate,[44] benzyl pyrrole-2-carboxylate,[44] 2-(diethylamino)ethyl pyrrole-2-carboxylate[44] prepared as reported by Hardbuck[44] [yield 95%, mp hydrochloride 126−127 °C, from absolute ethanol/dry diethyl ether (lit.[47] hydrochloride mp 129 °C)]; and 2-acetylpyrrole.[48]

1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole (8y). A solution of 5-chloro-2-nitrobenzenesulfonamide[37] (5.72 g, 0.024 mol) and 2,5-dimethoxytetrahydrofuran (3.83 g, 0.029 mol) in glacial acetic acid (30 mL) was refluxed for 4 h. After evaporation, the residue was treated with crushed ice and extracted with ethyl acetate. Organic layer was separated, washed with brine, and dried. Removal of the solvent gave a residue, which was purified on a silica gel column (chloroform): yield 64%; mp 99−100 °C (cyclohexane). ^{1}H-NMR ($CDCl_3$): δ 6.41 (t, 2H), 7.23 (t, 2H), 7.53 (d, 1H), 7.65−7.78 (m, 2H). Anal. ($C_{10}H_7ClN_2O_4S$, 286.69) C, H, N, Cl, S.

1-[(2-Chloro-5-nitrophenyl)sulfonyl]-1*H*-pyrrole (8x′): prepared as **8y** starting from 2-chloro-5-nitrobenzenesulfonamide;[38] yield 40%; mp 90−91 °C (cyclohexane). ^{1}H-NMR ($CDCl_3$): δ 6.38 (t, 2H), 7.22 (t, 2H), 7.71 (d, 1H), 8.35 (dd, 1H), 8.59 (d, 1H). Anal. ($C_{10}H_7ClN_2O_4S$, 286.69) C, H, N, Cl, S.

General Procedure for the Condensation of Arylsulfonyl Chlorides with 1*H*-Pyrrole-2-carboxylic Acid Esters and 2-Acetylpyrrole: Example−Methyl 1-[(2-Nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8d). A solution of 2-(methoxycarbonyl)-1*H*-pyrrole[44] (12.50 g, 0.10 mol) in dry THF (210 mL) was added dropwise to a well-stirred mixture of potassium *tert*-butoxide (13.46 g, 0.10 mol) and 18-crown-6 (2.83 g, 0.01 mol) in the same solvent (210 mL). After 15 min the suspension was cooled on an ice bath and then treated by dropping with a solution of 2-nitrobenzenesulfonyl chloride (22.16, 0.10 mol) in dry THF (210 mL). Stirring was continued at room temperature for 3.5 h; then the mixture was concentrated to a small volume, and the residue was shaken between ethyl acetate and water. The organic layer was separated, washed with brine, and dried. Removal of the solvent furnished a residue which was purified by chromatography on alumina (chloroform): yield 58%; mp 143 °C (toluene/cyclohexane). IR: ν 1720 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ 3.61 (s, 3H), 6.56 (t, 1H), 7.26 (m, 1H), 7.75−8.05 (m, 4H), 8.16 (dd, 1H). Anal. ($C_{12}H_{10}N_2O_6S$, 310.28) C, H, N, S.

By this procedure were prepared the following sulfones.

Ethyl 1-[(2-Chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8h): yield 84%; mp 78−80 °C (ligroin). IR: ν 1710 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H), 4.12 (q, 2H), 6.30 (t, 1H), 7.08 (m, 1H), 7.38−7.60 (m, 3H), 7.82 (m, 1H), 8.35 (dd, 1H). Anal. ($C_{13}H_{12}ClNO_4S$, 313.75) C, H, N, Cl, S.

2-Acetyl-1-[(2-nitrophenyl)sulfonyl]-1*H*-pyrrole (8p): yield 45%; mp 148−149 °C (toluene/cyclohexane). IR: ν 1670 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ 2.33 (s, 3H), 6.59 (t, 1H), 7.54 (m, 1H), 7.78−8.00 (m, 4H), 8.12 (m, 1H). Anal. ($C_{12}H_{10}N_2O_5S$, 294.28) C, H, N, S.

Methyl 1-[(4-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8s): yield 60%; mp 149−150 °C (toluene/cyclohexane). IR: ν 1720 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ 3.64 (s, 3H), 6.57 (t, 1H), 7.26 (m, 1H), 7.77 (m, 1H), 7.92 (d, 1H), 8.03 (dd, 1H), 8.42 (d, 1H). Anal. ($C_{12}H_9ClN_2O_6S$, 344.72) C, H, N, Cl, S.

Ethyl 1-[(4,5-Dichloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8w): yield 82%; mp 115 °C (cyclohexane). IR: ν 1700 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.28 (t, 3H), 4.20 (q, 2H), 6.36 (t, 1H), 7.12 (m, 1H), 7.63 (m, 1H), 7.94 (s, 1H), 8.49 (s, 1H). Anal. ($C_{13}H_{10}Cl_2N_2O_6S$, 393.20) C, H, N, Cl, S.

Methyl 1-[(5-chloro-2nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8a′): yield 68%; mp 128−129 °C (toluene/cyclohexane). IR: ν 1710 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ 3.66 (s, 3H), 6.57 (t, 1H), 7.26 (m, 1H), 7.77 (m, 1H), 7.97 (d, 1H), 8.17 (dd, 1H), 8.23 (d, 1H). Anal. ($C_{12}H_9ClN_2O_6S$, 344.72) C, H, N, Cl, S.

***n*-Propyl 1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8e′):** yield 71%; mp 98−99 °C (cyclohexane). IR: ν 1710 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 0.92 (t, 3H), 1.65 (m, 2H), 4.08 (t, 2H), 6.36 (t, 1H), 7.11 (m, 1H), 7.61−7.83 (m, 3H), 8.27 (d, 1H). Anal. ($C_{14}H_{13}ClN_2O_6S$, 372.78) C, H, N, Cl, S.

Isopropyl 1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8g′): yield 71%; mp 132−133 °C (cyclohexane). IR: ν 1690 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.23 (d, 6H), 5.04 (m, 1H), 6.35 (t, 1H), 7.09 (m, 1H), 7.60−7.85 (m, 3H), 8.25 (d, 1H). Anal. ($C_{14}H_{13}ClN_2O_6S$, 372.78) C, H, N, Cl, S.

Allyl 1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8i′): yield 60%; mp 123−124 °C (cyclohexane). IR: ν 1700 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 4.63 (m, 2H), 5.26 (m, 2H), 5.87 (m, 1H), 6.37 (t, 1H), 7.16 (dd, 1H), 7.64−7.83 (m, 3H), 8.31 (d, 1H). Anal. ($C_{14}H_{11}ClN_2O_6S$, 370.76) C, H, N, Cl, S.

Benzyl 1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8k′): yield 65%; mp 146−147 °C (toluene/cyclohexane). IR: ν 1720 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 5.18 (s, 2H), 6.38 (t, 1H), 7.18 (m, 1H), 7.33 (m, 5H), 7.65−7.81 (m, 3H), 8.30 (d, 1H). Anal. ($C_{18}H_{13}ClN_2O_6S$, 420.82) C, H, N, Cl, S.

2-(Diethylamino)ethyl 1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8m′): yield 66%; mp 65−66 °C (ligroin). IR: ν 1710 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.00 (t, 6H), 2.55 (q, 4H), 2.70 (t, 2H), 4.18 (t, 2H), 6.35 (t, 1H), 7.10 (m, 1H), 7.60−7.72 (m, 3H), 8.30 (d, 1H). Anal. ($C_{17}H_{20}ClN_3O_6S$, 429.87) C, H, N, Cl, S.

Ethyl 1-[(5-Methyl-2-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8v′): yield 43%; mp 99 °C (toluene/cyclohexane). IR: ν 1710 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, 3H), 2.52 (s, 3H), 4.15 (q, 2H), 6.34 (t, 1H), 7.10 (m, 1H), 7.53 (d, 1H), 7.60−7.78 (m, 2H), 8.04 (s, 1H). Anal. ($C_{14}H_{14}N_2O_6S$, 338.33) C, H, N, S.

Methyl 1-[(2-Chloro-5-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8z′): yield 60%; mp 159−161 °C (toluene/cyclohexane). IR: ν 1720 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ 3.64 (t, 3H), 6.55 (t, 1H), 7.25 (m, 1H), 7.95−8.05 (m, 2H), 8.59 (dd, 1H), 8.89 (d, 1H). Anal. ($C_{12}H_9ClN_2O_6S$, 344.72) C, H, N, Cl, S.

Ethyl 1-[(2-Chloro-5-nitrophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8b″): yield 80%; mp 120−121 °C (cyclohexane). IR: ν 1730 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H), 4.13 (q, 2H), 6.35 (t, 1H), 7.01 (m, 1H), 7.65 (d, 1H), 7.79 (m, 1H), 8.39 (dd, 1H), 9.18 (d, 1H). Anal. ($C_{13}H_{11}ClN_2O_6S$, 358.75) C, H, N, Cl, S.

General Procedure for the Condensation of Benzenesulfonyl Chlorides with Indole and Ethyl 2-Indolecarboxylate: Example−1-[(2-Nitrophenyl)sulfonyl]-1*H*-indole (9a). KOH (50%, 20 mL) was dropped while stirring into a solution of indole (2.34 g, 0.02 mol) and *n*-tetrabutylammonium hydrogen sulfate (0.68 g, 0.002 mol) in benzene (40 mL). After 5 min a solution of 2-nitrobenzenesulfonyl chloride (4.43 g, 0.02 mol) in benzene (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. During this time a solution of 2-nitrobenzenesulfonyl chloride (2.21 g, 0.01 mol) in the same solvent (10 mL) was added every 20 min. The mixture was diluted with water and the organic layer separated, washed with brine, and dried. Removal of the solvent gave a residue, which was purified by passing through an alumina column (chloroform): yield 93%; mp 98−100 °C (toluene/cyclohexane). ^{1}H-NMR ($CDCl_3$): δ 6.74 (d, 1H), 7.22−7.38 (m, 2H), 7.54−7.78 (m, 6H), 7.85 (m, 1H). Anal. ($C_{14}H_{10}N_2O_4S$, 302.30) C, H, N, S.

By this procedure were prepared the following sulfones.

1-[(4-Chloro-2-nitrophenyl)sulfonyl]-1*H*-indole (9c): yield 80%; mp 134 °C (toluene/cyclohexane). ^{1}H-NMR ($CDCl_3$): δ 6.74 (d, 1H), 7.23−7.43 (m, 2H), 7.52−7.63 (m, 3H), 7.68−7.78 (m, 2H), 7.83 (m, 1H). Anal. ($C_{14}H_9ClN_2O_4S$, 336.74) C, H, N, Cl, S.

1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-indole (9e): yield 95%; mp 110−111 °C (toluene/cyclohexane). ^{1}H-NMR ($CDCl_3$): δ 6.76 (d, 1H), 7.25−7.49 (m, 2H), 7.57−7.71 (m, 4H), 7.78−7.93 (m, 2H). Anal. ($C_{14}H_9ClN_2O_4S$, 336.75) C, H, N, Cl, S.

Ethyl 1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1*H*-indole-2-carboxylate (9g): yield 16%; mp 157−158 °C (toluene/cyclohexane). IR: ν 1710 cm^{-1} (CO). ^{1}H-HMR ($CDCl_3$): δ 1.22−1.33 (m, 3H), 4.18−4.36 (m, 2H), 7.35−7.62 (m, 3H), 7.62−7.82 (m, 2H), 7.82−8.05 (m, 2H), 8.10 (d, 1H). Anal. ($C_{17}H_{13}ClN_2O_6S$, 408.81) C, H, N, Cl, S.

1-[(2-Chloro-5-nitrophenyl)sulfonyl]-1*H*-indole (9i): yield 73%; mp 133−134 °C (toluene/cyclohexane). ^{1}H-NMR ($CDCl_3$): δ 6.71 (d, 1H), 7.20−7.34 (m, 2H), 7.52−7.74 (m, 4H), 8.30 (dd, 1H), 9.00 (d, 1H). Anal. ($C_{14}H_9ClN_2O_4S$, 336.74) C, H, N, Cl, S.

General Procedure for Reduction of Nitro Group to Amino: Example−1-[(2-Amino-4-chlorophenyl)sulfonyl]-1*H*-pyrrole (8r). Iron powder (5.2 g) was added over a period of 15 min to a stirred solution of **8q**[32] (5.00 g, 0.017 mol) in glacial acetic acid (50 mL) while heating at 60 °C; then the mixture was maintained at 60 °C for 2 h. After evaporation of the solvent, the residue was shaken between ethyl acetate and water. Organic extracts were separated, washed with brine, and dried. The residue was purified on an alumina column (chloroform): yield 83%; mp 167−168 °C (toluene/ligroin). IR: ν 3380, 3480 cm^{-1} (NH_2). ^{1}H-NMR (DMSO-d_6): δ 6.31 (t, 2H), 6.58−6.65 (m, 3H), 6.88 (d, 1H), 7.38 (t, 2H), 7.65 (d, 1H). Anal. ($C_{10}H_9ClN_2O_2S$, 256.71) C, H, N, Cl, S.

By this procedure were prepared the following sulfones.

1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole (8z): from **8y**; yield 81%; mp 128−129 °C (ligroin). IR: ν 3360, 3470 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 5.16 (br s, 2H), 6.29 (t, 2H), 6.61 (d, 1H), 7.14−7.25 (m, 3H), 7.65 (d, 1H). Anal. ($C_{10}H_9ClN_2O_2S$, 256.71) C, H, N, Cl, S.

1-[(5-Amino-2-chlorophenyl)sulfonyl]-1*H*-pyrrole (8y′): from **8x′**; yield 80%; mp 133−135 °C (toluene/ligroin). IR: ν 3380, 3480 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 3.97 (br s, 2H), 6.30 (t, 2H), 6.74 (dd, 1H), 7.14−7.25 (m, 4H). Anal. ($C_{10}H_9ClN_2O_2S$, 256.71) C, H, N, Cl, S.

Methyl 1-[(2-Aminophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8e): from **8d**; yield 63%; mp 119−120 °C (toluene/cyclohexane). IR: ν 1720 (CO), 3360, 3480 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 3.73 (s, 3H), 5.17 (br s, 2H), 6.29 (t, 1H), 6.71 (m, 2H), 7.08 (m, 1H), 7.25 (m, 1H), 7.64 (dd, 1H), 7.71 (m, 1H). Anal. ($C_{12}H_{12}N_2O_4S$, 280.29) C, H, N, S.

Methyl 1-[(2-Amino-4-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8t): from **8h**; yield 90%; mp 113−114 °C (toluene/cyclohexane). IR: ν 1700 (CO), 3350, 3480 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 3.74 (s, 3H), 5.29 (br s, 2H), 6.29 (t, 1H), 6.62−6.74 (m, 2H), 7.09 (m, 1H), 7.57 (d, 1H), 7.68 (m, 1H). Anal. ($C_{12}H_{11}ClN_2O_4S$, 314.74) C, H, N, Cl, S.

Ethyl 1-[(2-Amino-4,5-dichlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8x): from **8p**; yield 84%; mp 132−133 °C (toluene/cyclohexane). IR: ν 1695 (CO), 3360, 3450 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 1.28 (t, 3H), 4.22 (q, 2H), 5.28 (br s, 2H), 6.31 (t, 1H), 6.81 (s, 1H), 7.09 (m, 1H), 7.63−7.68 (m, 2H). Anal. ($C_{13}H_{12}Cl_2N_2O_4S$, 363.21) C, H, N, Cl, S.

Methyl 1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8b′): from **8s**; yield 88%; mp 156−159 °C (toluene/ligroin). IR: ν 1700 (CO), 3360, 3480 cm^{-1} (NH_2). ^{1}H-NMR (DMSO-d_6): δ 3.36 (s, 3H), 6.35−6.50 (m, 3H), 6.88 (d, 1H), 7.12 (m, 1H), 7.40 (dd, 1H), 7.72 (d, 1H), 8.06 (m, 1H). Anal. ($C_{12}H_{11}ClN_2O_4S$, 314.74) C, H, N, Cl, S.

***n*-Propyl 1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8f′):** from **8w**; yield 90%; mp 65−66 °C (cyclohexane). IR: ν 1710 (CO), 3360, 3460 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 0.92 (t, 3H), 1.66 (m, 2H), 4.10 (t, 2H), 5.25 (br s, 2H), 6.30 (t, 1H), 6.63 (d, 1H), 7.08 (m, 1H), 7.20 (dd, 1H), 7.52 (d, 1H), 7.67 (m, 1H). Anal. ($C_{14}H_{15}ClN_2O_4S$, 342.80) C, H, N, Cl, S.

Isopropyl 1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8h′): from **8a′**; yield 91%; mp 127 °C (toluene/cyclohexane). IR: ν 1695 (CO), 3345, 3440 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 1.24 (d, 6H), 5.06 (m, 1H), 5.24 (br s, 2H), 6.29 (t, 1H), 6.62 (d, 1H), 7.04 (m, 1H), 7.20 (dd, 1H), 7.53 (d, 1H), 7.63 (m, 1H). Anal. ($C_{14}H_{15}ClN_2O_4S$, 342.80) C, H, N, Cl, S.

Allyl 1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8j′): from **8e′**; yield 94%; mp 77 °C (cyclohexane). IR: ν 1700 (CO), 3360, 3460 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 4.65 (m, 2H), 5.26 (m, 4H), 5.90 (m, 1H), 6.30 (t, 1H), 6.64 (d, 1H), 7.11 (m, 1H), 7.23 (dd, 1H), 7.55 (d, 1H), 7.68 (m, 1H). Anal. ($C_{14}H_{13}ClN_2O_4S$, 340.78) C, H, N, Cl, S.

Benzyl 1-[(2-Amino-5-chlorophenyl]sulfonyl]-1*H*-pyrrole-2-carboxylate (81′): from **8g′**; yield 96%; mp 92−93 °C (toluene/cyclohexane). IR: ν 1720 (CO), 3360, 3460 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 5.20 (br s, 4H), 6.32 (m, 1H), 6.63 (m, 1H), 7.10−7.80 (m, 9H). Anal. ($C_{18}H_{15}ClN_2O_4S$, 390.84) C, H, N, Cl, S.

2-(Diethylamino)ethyl 1-[(2-Amino-5-chlorophenyl)-sulfonyl]-1*H*-pyrrole-2-carboxylate (8n′): from **8i′**; yield 87%; mp 80−81 °C (ligroin). IR: ν 1710 (CO), 3360, 3450 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 0.99 (t, 6H), 2.53 (q, 4H0, 2.70 (t, 2H), 4.19 (t, 2H), 5.23 (br s, 2H), 6.29 (t, 1H), 6.61 (d, 1H), 7.06 (m, 1H), 7.19 (dd, 1H), 7.53 (d, 1H), 7.66 (m, 1H). Anal. ($C_{17}H_{22}ClN_3O_4S$, 399.89) C, H, N, Cl, S.

Ethyl 1-[(2-Amino-5-methylphenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8w′): from **8k′**; yield 73%; mp 117 °C (toluene/cyclohexane). IR: ν 1690 (CO), 3360, 3460 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H), 2.19 (s, 3H), 4.19 (q, 2H), 5.04 (br s, 2H), 6.27 (t, 1H), 6.60 (d, 1H), 7.00-7.15 (m, 2H), 7.36 (m, 1H), 7.66 (m, 1H). Anal. ($C_{14}H_{16}N_2O_4S$, 308.35) C, H, N, S.

Methyl 1-[(5-Amino-2-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8a″): from **8m′**; yield 84%; mp 157 °C (toluene/cyclohexane). IR: ν 1720 (CO), 3360, 3460 cm^{-1} (NH_2). ^{1}H-NMR (DMSO-d_6): δ 3.63 (s, 3H), 5.92 (br s, 2H), 6.44 (d, 1H), 6.83 (d, 1H), 7.20 (m, 2H), 7.43 (m, 1H), 7.84 (m, 1H). Anal. ($C_{12}H_{11}ClN_2O_4S$, 314.74) C, H, N, Cl, S.

Ethyl 1-[(5-Amino-2-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8c″): from **8v′**; yield 86%; mp 110−111 °C (toluene/ligroin). IR: ν 1720 (CO), 3360, 3450 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H), 4.00−4.20 (m, 4H), 6.28 (t, 1H), 6.77 (dd, 1H), 7.08−7.20 (m, 2H), 7.62 (d, 1H), 7.81 (m, 1H). Anal. ($C_{13}H_{13}ClN_2O_4S$, 328.77) C, H, N, Cl, S.

1-[(2-Aminophenyl)sulfonyl]-1*H*-indole (9b): yield 54%; mp 115−116 °C (toluene/cyclohexane). IR: ν 3370, 3450 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 5.13 (br s, 2H), 6.55−6.73 (m, 3H), 7.15−7.35 (m, 3H), 7.53−7.64 (m, 2H), 7.75 (dd, 1H), 7.93 (d, 1H). Anal. ($C_{14}H_{12}N_2O_2S$, 272.32) C, H, N, S.

1-[(2-Amino-4-chlorophenyl)sulfonyl]-1*H*-indole (9d): yield 75%; mp 143−145 °C (toluene/cyclohexane). IR: ν 3370, 3480 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 5.20 (br s, 2H), 6.58−6.67 (m, 3H), 7.19−7.42 (m, 2H), 7.52−7.68 (m, 3H), 7.88 (d, 1H). Anal. ($C_{14}H_{11}ClN_2O_2S$, 306.76) C, H, N, Cl, S.

1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-indole (9f): yield 87%; mp 106−107 °C (toluene/cyclohexane). IR: ν 3340, 3440 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 5.13 (br s, 2H), 6.47−6.56 (m, 1H), 6.65 (d, 1H), 7.12 (dd, 1H), 7.17−7.42 (m, 2H), 7.54−7.60 (m, 2H), 7.71 (d, 1H), 7.90 (d, 1H). Anal. ($C_{14}H_{11}ClN_2O_2S$, 306.77) C, H, N, Cl, S.

Ethyl 1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-indole-2-carboxylate (9h): yield 50%; mp 77−78 °C (cyclohexane). IR: ν 1710 (CO), 3360, 3470 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 1.43 (t, 3H), 4.43 (m, 2H), 5.46 (br s, 2H), 6.65 (d, 1H), 7.15−7.54 (m, 4H), 7.54−7.62 (m, 1H), 7.62−7.95 (m, 2H). Anal. ($C_{17}H_{15}ClN_2O_4S$, 378.83) C, H, N, Cl, S.

1-[(5-Amino-2-chlorophenyl)sulfonyl]-1*H*-indole (9j): yield 60%; mp 117−118 °C (toluene/cyclohexane). IR: ν 3360, 3460 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$): δ 3.96 (br s, 2H), 6.61−6.74 (m, 2H), 7.11 (d, 1H), 7.16−7.28 (m, 2H), 7.48 (d, 1H), 7.51−7.62 (m, 1H), 7.62−7.76 (m, 2H). Anal. ($C_{14}H_{11}ClN_2O_2S$, 306.76) C, H, N, Cl, S.

1-[(2-Chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylic Acid (8i). KOH (1 N, 14.4 mL) was dropped into an ice-cooled solution of **8h** (3.00 g, 0.0096 mol) in ethanol (45 mL) and THF (45 mL), and the mixture was stirred at room temperature for 5 h. The mixture was poured on crushed ice, filtered, and treated with 12 N HCl until pH 2 was reached. The precipitate was separated by suction, washed with water, dried, and purified by crystallization from ethanol: yield 50%; mp 204−205 °C (ethanol). ^{1}H-NMR (DMSO-d_6): δ 6.47 (t, 1H), 7.13 (m, 1H), 7.58−7.80 (m, 3H), 7.88 (m, 1H), 8.21 (m, 1H). Anal. ($C_{11}H_8ClNO_4S$, 285.70) C, H, N, Cl, S.

1-[(2-Fluorophenyl)sulfonyl]-1*H*-pyrrole-2-(*N*-cyclohexylcarboxamide) (8l). A mixture of **8k** (3.00 g, 0.011 mol), cyclohexylamine (0.91 g, 0.016 mol), EDC (2.10 g, 0.011 mol), DMAP (1.34 g, 0.011 mol), dichloromethane (50 mL), and anhydrous THF (50 mL) was stirred at room temperature for 96 h. After concentration, the residue was extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried. Removal of the solvent gave crude **81**, which was

purified by chromatography on silica gel (chloroform): yield 90%; mp 135−136 °C (toluene/cyclohexane). IR: ν 1640 (CO), 3370 cm^{-1} (NH).[1] ^{1}H-NMR ($CDCl_3$): δ 1.03−1.48 (m, 5H), 1.48−1.80 (m, 3H), 1.80−1.95 (m, 2H), 3.77 (m, 1H), 6.04 (d, 1H), 6.19 (t, 1H), 6.56 (m, 1H), 7.11 (m, 1H), 7.31 (m, 1H), 7.48−7.66 (m, 2H), 8.05 (m, 1H). Anal. ($C_{17}H_{19}FN_2O_3S$, 350.40) C, H, N, F, S.

1-[(2-Fluorophenyl)sulfonyl]-1*H*-pyrrole-2-[*N*-(formylamino)carboxamide] (8o): prepared as **8l** by using formylhydrazine; crude product purified by chromatography on silica gel (ethyl acetate/ethanol, 9:1); yield 40%; mp 198−199 °C (ethanol). IR: ν 1620, 1670 (CO), 3140, 3230 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6): δ 6.43 (t, 1H), 7.02 (m, 1H), 7.35−7.50 (m, 2H), 7.68−7.88 (m, 2H), 7.88−8.04 (m, 2H), 10.05 (br s, 1H), 10.35 (br s, 1H). Anal. ($C_{12}H_{10}FN_3O_4S$, 311.28) C, H, N, F, S.

1-[[2-(Methylamino)phenyl]sulfonyl]-1*H*-pyrrole (8c). $NaBH_3CN$ (0.32 g, 0.005 mol) was carefully added into a mixture of **8b**[36] (1.00 g, 0.0045 mol), 37% aqueous formaldehyde (0.4 mL), 6 N HCl/CH_3OH, 1:1 (0.74 mL), and methanol (18 mL); then reaction mixture was stirred at room temperature for 36 h. After concentration the mixture was extracted with chloroform, washed with 5% $NaHCO_3$ and then with brine, and dried. Removal of the solvent furnished a residue, which was purified on an alumina column (dichloromethane/petroleum ether, 1:1). First fractions gave **8c**: yield 45%; mp 134 °C (ligroin). IR: ν 3440 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): δ 2.87 (d, 3H), 6.15−6.35 (m, 3H), 6.67 (m, 2H), 7.15 (t, 2H), 7.40 (m, 1H), 7.72 (dd, 1H). Anal. ($C_{11}H_{12}N_2O_2S$, 236.28) C, H, N, S.

Further elution with the same solvent afforded **8b** (34%) and then 10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide: yield 20%; mp 167−168 °C (benzene) (lit.[36] mp 167−168 °C).

Ethyl 1-[[5-Chloro-2-(methylamino)phenyl]sulfonyl]-1*H*-pyrrole-2-carboxylate (8o′): prepared as **8c** starting from **8d′**; crude product purified on an alumina column (chloroform); yield 62%; mp 119−120 °C (cyclohexane). IR: ν 1720 (CO), 3420 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): δ 1.27 (t, 3H), 2.88 (d, 2H), 4.21 (q, 2H), 6.29 (m, 2H), 6.64 (d, 1H), 7.07 (m, 1H), 7.33 (dd, 1H), 7.61 (m, 2H). Anal. ($C_{14}H_{15}ClN_2O_4S$, 342.79) C, H, N, Cl, S.

Ethyl 1-[[5-Chloro-2-(ethylamino)phenyl]sulfonyl]-1*H*-pyrrole-2-carboxylate (8p′): prepared as **8o′** by using acetaldehyde; yield 75%; mp 128−129 °C (ligroin). IR: ν 1720 (CO), 3400 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 6H), 3.16 (m, 2H), 4.19 (q, 2H), 6.00 (br s, 1H), 6.29 (t, 1H), 6.62 (d, 1H), 7.06 (m, 1H), 7.29 (dd, 1H), 7.63 (m, 2H). Anal. ($C_{15}H_{17}ClN_2O_4S$, 356.82) C, H, N, Cl, S.

Ethyl 1-[[2-(Butylamino)-5-chlorophenyl]sulfonyl]-1*H*-pyrrole-2-carboxylate (8q′): prepared as **8o′** by using butyraldehyde; yield 22%; mp 98−99 °C (ligroin). IR: ν 1720 (CO), 3390 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): δ 0.94 (t, 3H), 1.26 (t, 3H), 1.46 (m, 2H), 1.62 (m, 2H), 3.12 (q, 2H), 4.20 (q, 2H), 6.05 (br s, 1H), 6.28 (t, 1H), 6.63 (d, 1H), 7.05 (m, 1H), 7.29 (dd, 1H), 7.63 (m, 2H). anal. ($C_{17}H_{21}ClN_2O_4S$, 384.87) C, H, N, Cl, S.

Ethyl 1-[(5-Chloro-2-formamidophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8r′). Formic acid (98−100%, 0.32 g, 0.25 mL, 0.007 mol) was added to acetic anhydride (0.61 g, 0.56 mL, 0.006 mol) at 0 °C. After stirring at room temperature for 2 h, the solution of formic acetic anhydride was added to a solution of **8d′** (1.00 g, 0.003 mol) in dry tetrahydrofuran (5 mL), and the mixture was stirred at room temperature for 24 h. After evaporation, methanol (3.5 mL) was added and the solution was stirred for an additional 30 min. The solvent was removed, and the residue was extracted with ethyl acetate, washed with brine, and dried. Evaporation afforded a crude product which was purified by passing through an alumina column (chloroform): yield 92%; mp 109−111 °C (toluene/cyclohexane). IR: ν 1670, 1720 (CO), 3270, 3300 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6): δ 1.17 (t, 3H), 4.14 (q, 2H), 6.50 (t, 1H), 7.14 (m, 1H), 7.80−8.10 (m, 4H), 8.30 (br s, 1H), 9.80 (br s, 1H). Anal. ($C_{14}H_{13}ClN_2O_5S$, 356.78) C, H, N, Cl, S.

Ethyl 1-[(2-Acetamido-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8s′). Acetyl chloride (1.17 g, 0.0148 mol) was dropped into an ice-cooled solution of **8d′** (1.00 g, 0.003 mol) in dry pyridine (10 mL). The mixture was refluxed overnight, poured on crushed ice, made acidic with 12 N HCl, and shaken with ethyl acetate. The organic layer was separated, washed with brine, and dried. After evaporation of the solvent, the residue was purified on a silica gel column (chloroform): yield 84%; mp 119−121 °C (cyclohexane). IR: ν 1650, 1720 (CO), 3250 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 3H), 2.23 (s, 3H), 4.18 (q, 2H), 6.36 (t, 1H), 7.09 (m, 1H), 7.43−7.55 (m, 2H), 7.71 (m, 1H), 8.42 (d, 1H), 9.47 (br s, 1H). Anal. ($C_{15}H_{15}ClN_2O_5S$, 370.80) C, H, N, Cl, S.

Ethyl 1-[(5-Chloro-2-propionamidophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (8t′): prepared as **8s′** by using propionyl chloride; yield 86%; mp 111−112 °C (cyclohexane). IR: ν 1650, 1720 (CO), 3230 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 6H), 2.48 (q, 2H), 4.18 (q, 2H), 6.36 (t, 1H), 7.09 (m, 1H), 7.43−7.52 (m, 2H), 7.71 (m, 1H), 8.48 (d, 1H), 9.52 (br s, 1H). Anal. ($C_{16}H_{17}ClN_2O_5S$, 384.83) C, H, N, Cl, S.

Ethyl 1-[[5-Chloro-2-[(ethoxycarbonyl)acetamido]-phenyl]sulfonyl]-1*H*-pyrrole-2-carboxylate (8u′). A solution of **8d′** (1.00 g, 0.003 mol), diethyl malonate (1.44 g, 0.009 mol), and 2-hydroxypyridine (0.28g, 0.003 mol) in xylene (30 mL) was refluxed for 48 h with azeotropic removal of ethanol. After evaporation to dryness, the residue was purified by passing through a silica gel column (chloroform): yield 89%; mp 89−90 °C (cyclohexane). IR: ν 1640, 1700, 1730 (CO), 3220 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): δ 1.23−1.42 (m, 6H), 3.51 (s, 2H), 4.13−4.34 (m, 4H), 6.35 (t, 1H), 7.10 (m, 1H), 7.51 (m, 1H), 7.74 (m, 2H), 8.31 (d, 1H), 10.05 (br s, 1H). Anal. ($C_{18}H_{19}ClN_2O_7S$, 442.87) C, H, N, Cl, S.

Antiviral Assay Procedures. Activity of the compounds against HIV-1 (III_B strain) and HIV-2 (CBL·20 strain) multiplication in acutely infected cells was based on the inhibition of virus-induced cytopathogenicity in MT-4 and C8166 cells, respectively. Briefly, 50 μL of culture medium containing 1 × 10^4 cells was added to each well of flat-bottom microtiter trays containing 50 μL of culture medium with or without various concentrations of the test compounds. Then, 20 μL of an HIV suspension containing 100 (HIV-1) or 1000 (HIV-2) $CCID_{50}$ (50% cell culture infective dose) was added. After a 4-day incubation at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-1-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[49] Cytotoxicity of the compounds was evaluated in parallel with their antiviral activity. It was based on the viability of mock-infected cells, as monitored by the MTT method.

RT assays were performed as previously described.[50] Briefly, purified rRT was assayed for its RNA-dependent and DNA-dependent DNA polymerase-associated activities in a 50 μL volume containing: 50 mM Tris-HCl (pH 7.8), 80 mM KCl, 6 mM $MgCl_2$, 1 mM DTT, 0.1 mg mL^{-1} BSA, 0.5 OD_{260} unit mL^{-1} template:primer [poly(rC)-oligo$(dG)_{12-18}$ or poly(dC)-oligo$(dG)_{12-18}$], and 10 μM [^{3}H]dGTP (1 Ci $mmol^{-1}$). After incubation for 30 min at 37 °C, the samples were spotted on glass fiber filters (Whatman GF/A), and the acid-insoluble radioactivity was determined.

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