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5*H*-Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTDs): A Novel Class of Non-Nucleoside Reverse Transcriptase Inhibitors

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Abstract—With the aim of developing novel inhibitors of human immunodeficiency virus, various derivatives (**10–17**) related to 5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine (PBTD) were prepared and tested in vitro. The title tricyclic derivatives were obtained by intramolecular cyclization of the open-chain intermediate arylpyrrylsulfones, followed by *N*-alkylation at position 10. Among test derivatives some 10-alkyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxides were found to exert potent and specific activity against HIV-1. In particular, 7-chloro derivatives **11i** and **j** showed a potency comparable to that of nevirapine. However, when the chloro atom was shifted to the 8 position, the related products were scarcely active or totally inactive. Replacement of the pyrrole with pyrrolidine led to inactive products and the reduction of SO_2 to S strongly diminished the antiviral potency. PBTD derivatives active in cell cultures were also inhibitory to the recombinant HIV-1 RT in enzyme assays, thus allowing the conclusion that PBTDs are a new class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Introduction

The discovery of human immunodeficiency virus (HIV) as the etiological agent of AIDS (acquired immune deficiency syndrome) has prompted efforts aimed at the development of drugs useful for the prevention and treatment of this lethal disease.[1–5] Studies on nucleoside analogues have led to the discovery of 3′-azido-2′,3′-dideoxythymidine, **1** (AZT, azidothymidine or zidovudine, Chart 1),[6–8] which has been the first drug to be licensed for the treatment of AIDS and AIDS-related complex (ARC). Despite its clinical efficacy in relieving symptoms and prolonging survival, AZT produces serious side-effects, such as bone marrow suppression and causes the emergence of drug-resistant variants. DDI (2′,3′-dideoxyinosine, didanosine, **2**),[9] a purine dideoxynucleoside approved as an alternative drug for patients who do not tolerate AZT, also shows unfavorable side effects and leads to the selection of drug-resistant mutants.

The search for novel agents endowed with low toxicity has led to the identification of non-nucleoside inhibitors, which are also targeted at the reverse transcriptase (RT), but interact with this enzyme at a site different from that of nucleoside analogues. The first lead compounds have been HEPT [1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine] **3**[10] and TIBO derivatives, such as the tetrahydroimidazobenzodiazepinone **4**,[11–15] which turned out to be highly specific inhibitors of HIV-1. Then, new compounds such as nevirapine **5**,[16,17] its analogues (**6** and **7**)[18] and other tricyclic systems (**8** and **9**)[19,20] have been reported and included in the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).[21]

Continuing in the search for new NNRTIs, after the synthesis of tricyclic benzodiazepines incorporating a pyrrole ring[22–36] we present here novel derivatives

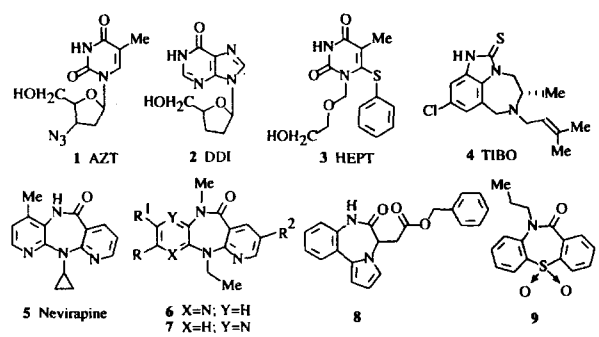


Chart 1.

Key words: Pyrrolobenzothiadiazepines/NNRTIs agents/anti-HIV-1 agents/anti-AIDS/reverse trancriptase inhibitors.

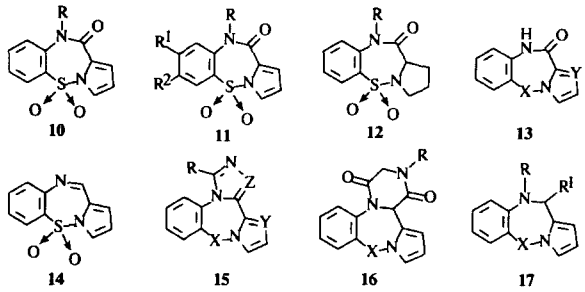


Chart 2.

of 5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine (PBTD) (Tables 1 and 2) represented by formulas **10–17** (Chart 2).

Results and Discussion

Chemistry

10-Alkyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxides (**10b–q** and **10s**) were obtained by alkylation of **10a**[26] with alkyl halides, in the presence of potassium carbonate (Scheme 1). Similarly, chloro derivatives **11b–h** and **11j–p** were obtained starting from **11a** and **11i**, which were synthesized as reported in Scheme 1 by intramolecular cyclization of the related aminosulfones **19a**,[26] **b** and **c** in the presence of 2-hydroxypyridine as a bifunctional catalyst. The latter compounds were prepared by reduction of nitrosulfones **18a**,[26] **b**,[36] and **c**, which were obtained by reacting nitrobenzenesulfonyl chlorides[37,38] with 2-ethoxycarbonyl-1*H*-pyrrole.[39]

The cyclopropyl derivative **10r** was obtained by intramolecular cyclization of 1-(2-fluorobenzenesulfonyl)-1*H*-pyrrole-2-(*N*-cyclopropyl)carboxyamide (**22b**) in the presence of sodium hydride and cuprous iodide. Compound **22b** was synthesized by treating the acid **21** with cyclopropylamine in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP). Preparation of **21** was performed by alkaline hydrolysis of ester **20**, which was prepared by reacting 2-fluorobenzenesulfonyl chloride[40] with 2-ethoxycarbonyl-1*H*-pyrrole as reported above for derivatives **18a–c**. The benzyl derivative **10q** was synthesized using the same method (Scheme 2).

Pyrrolidino derivatives **12** were prepared starting from 2-ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)pyrrolidine (**23**),[36] which was reduced to the corresponding amino ester **24** with iron powder in glacial acetic acid. Intramolecular cyclization of **24** by heating in the presence of 2-hydroxypyridine as a bifunctional catalyst afforded 1,2,3,11a-tetrahydro-5*H*-pyrrolo[1,2-*b*][1,2,5]-benzothiadiazepin-11 (10*H*)-one-5,5-dioxide (**12a**). Treatment of the latter compound with alkyl halides in the presence of potassium carbonate furnished the required 10-alkyl derivatives **12b–h** (Scheme 3). 5*H*-Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one (**13a**) was obtained by reaction of 1-(2-aminobenzenesulfenyl)-1*H*-pyrrole (**25**)[29] with bis(trichloromethyl)carbonate (triphosgene) in the presence of triethylamine. Compound **25** was also used as the starting material in the reaction with ethyl glyoxylate hemiacetal to afford, via a Pictet–Spengler type condensation,[41] 10,11-dihydro-11-ethoxycarbonyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine (**17a**). The latter was transformed into **17b** by treatment with chloroacetyl chloride in the presence of sodium hydrogen carbonate (Scheme 4).

Reaction of **17g**[31] with acetic anhydride and 4-methylbenzoyl chloride afforded amides **17c** and **17j**, respectively (Scheme 5). Lithium aluminum hydride reduction of **17g** afforded 10,11-dihydro-11-hydroxymethyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-5,5-dioxide (**17e**), which was transformed into its mesylate **17i** by reaction with methanesulfonyl chloride in

Table 1. Chemical structure of derivatives **10–12**

Compound	R	R^1	R^2
10a	H	—	—
10b	Me	—	—
10c	Et	—	—
10d	Propyl	—	—
10e	Isopropyl	—	—
10f	*n*-Butyl	—	—
10g	Isobutyl	—	—
10h	Allyl	—	—
10i	2-Butenyl	—	—
10j	3-Me-2-butenyl	—	—
10k	CH_2COOMe	—	—
10l	CH_2COOEt	—	—
10m	CH_2COOCH_2Ph	—	—
10n	CH_2OMe	—	—
10o	CH_2CH_2OMe	—	—
10p	CH_2cyclopropyl	—	—
10q	CH_2Ph	—	—
10r	Cyclopropyl	—	—
10s	$CH_2CH_2N(Me)_2$	—	—
11a	H	Cl	H
11b	Me	Cl	H
11c	Et	Cl	H
11d	Propyl	Cl	H
11e	Isopropyl	Cl	H
11f	Allyl	Cl	H
11g	2-Butenyl	Cl	H
11h	3-Me-2-butenyl	Cl	H
11i	H	H	Cl
11j	Me	H	Cl
11k	Et	H	Cl
11l	Propyl	H	Cl
11m	Isopropyl	H	Cl
11n	Allyl	H	Cl
11o	2-Butenyl	H	Cl
11p	3-Me-2-butenyl	H	Cl
12a	H	—	—
12b	Me	—	—
12c	Et	—	—
12d	Propyl	—	—
12e	Isopropyl	—	—
12f	*n*-Butyl	—	—
12g	Isobutyl	—	—
12h	CH_2 cyclopropyl	—	—

pyridine or into the esters **17k** and **l** by reaction with 4-chlorobenzoyl chloride and 4-chlorophenylacetyl chloride, respectively.

Compounds **10a**,[26] **13b**,[27] **13c**,[28] **14**,[30] **15a**,[26] **b**,[27] **c**,[28] **d**,[30] **16a**,[31] **b–e**,[25] **17d**,[31] **f**,[30] **g**,[31] **h**,[30] **m**,[28] **n–p**[24] and **q**[22] have been described in previous works.

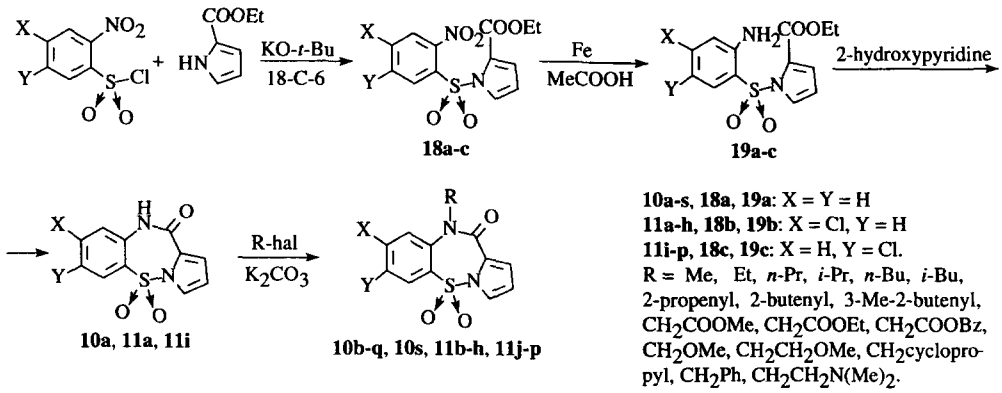
Antiviral activity

The cytotoxicity and capability of compounds **10–17** to inhibit HIV-1-induced cytopathicity was tested in MT-4 cells (Tables 3 and 4). In these in vitro assays AZT and nevirapine were used as reference compounds and confirmed both potent and selective HIV-1 inhibitors.

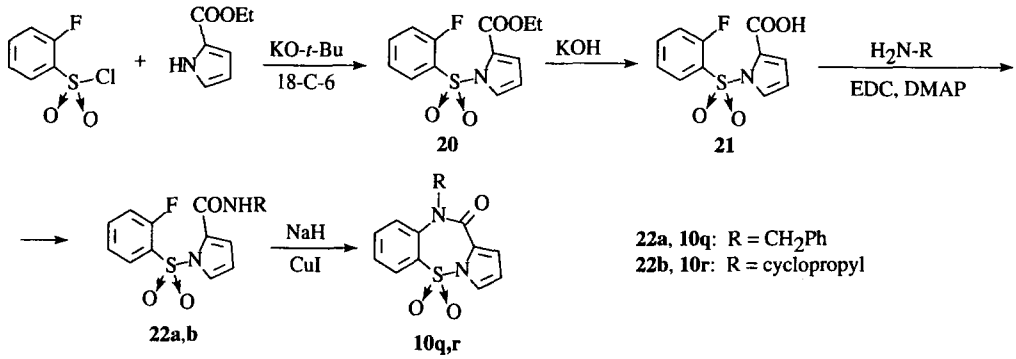
The majority of compounds were noncytotoxic for MT-4 cells at doses higher than 300 μM; notable exceptions were compounds **17a,d,h,m**, which resulted in cytotoxicity with values as low as 6 μM. Maximum activity was obtained with the compounds of series **10** and the related chloro derivatives **11i–p**, among which compounds **11i** and **j** were endowed with the highest potency (EC_{50} = 1.0 and 0.5 μM, respectively) and

Table 2. Chemical structure of derivatives **13–17**

Compound	X	Y	Z	R	R'
13a	S	CH	—	—	—
13b	CH_2	CH	—	—	—
13c	CH_2	N	—	—	—
14	—	—	—	—	—
15a	SO_2	CH	N	H	—
15b	CH_2	CH	N	H	—
15c	CH_2	N	N	4-Pyridyl	—
15d	SO_2	CH	CH	H	—
16a	SO_2	—	—	CH_2Ph	—
16b	NMe	—	—	$(CH_2)_2N(Me)_2$	—
16c	NMe	—	—	$(CH_2)_3N(Me)_2$	—
16d	NMe	—	—	$(CH_2)_2$-1-piperidinyl	—
16e	NMe	—	—	$(CH_2)_2$-morpholinyl	—
17a	S	—	—	H	COOEt
17b	S	—	—	$COCH_2Cl$	COOEt
17c	SO_2	—	—	COMe	COOEt
17d	SO_2	—	—	$COCH_2Br$	COOEt
17e	SO_2	—	—	H	CH_2OH
17f	SO_2	—	—	H	COOH
17g	SO_2	—	—	H	COOEt
17h	SO_2	—	—	H	CH_2NO_2
17i	SO_2	—	—	H	CH_2OSO_2Me
17j	SO_2	—	—	*p*-Tolyl	COOEt
17k	SO_2	—	—	H	CH_2O-*p*-Cl-benzoyl
17l	SO_2	—	—	H	CH_2O-*p*-Cl-phenacyl
17m	NMe	—	—	$COCH_2Cl$	COOEt
17n	$N(CH_2)_3$-1-(4-Me-piperazinyl)	—	—	H	H
17o	$N(CH_2)_3$-1-(4-Me-piperazinyl)	—	—	H	Me
17p	$N(CH_2)_3$-1-(4-Me-piperazinyl)	—	—	H	Ph
17q	SO_2	—	—	H	H



Scheme 1.

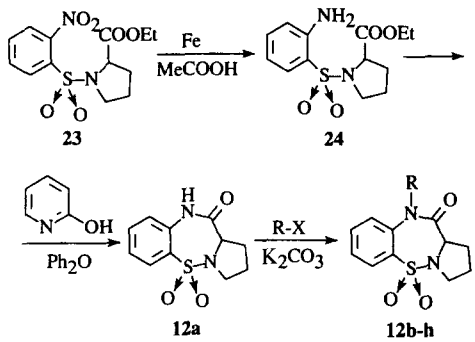


Scheme 2.

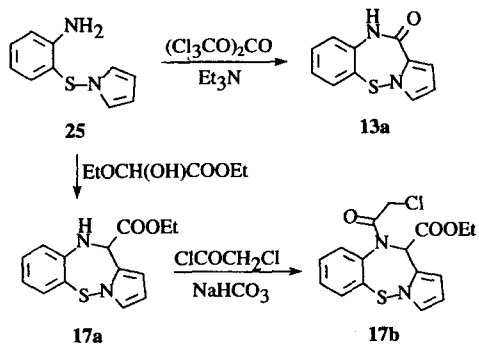
selectivity (S.I. = >300 and >600, respectively). Compounds belonging to the other series were considerably less potent and selective (**13a**, **15a**, **16b–e** and **17b,k,l**) or totally inactive (**12a–h**, **13b,c**, **14**, **15b–d**, **16a** and **17a,c–j,m–q**).

SAR studies identified several structural features of the title pyrrolobenzothiadiazepines that are essential for the anti-HIV activity. The first one relates to the effect of the alkyl and alkylidene substituents at the position 10 of the pyrrolobenzothiadiazepine ring. Among the compounds of series **10**, derivatives bearing a hydrogen atom at position 10 (**10a**), a small alkyl group (**10b,c** and **e**) or a linear alkenyl (**10h** and **i**) substituent were fairly potent, being inhibitory to HIV-1 at doses below 11 μM. Maximum potency and selectivity were exhibited by the ethyl (**10c**) and isopropyl (**10e**) derivatives. On the contrary, when the N-substituent was a propyl (**10d**), a linear (**10f**) or ramified butyl (**10g**) and a ramified alkenyl (**10j**) group, the activity significantly decreased or vanished.

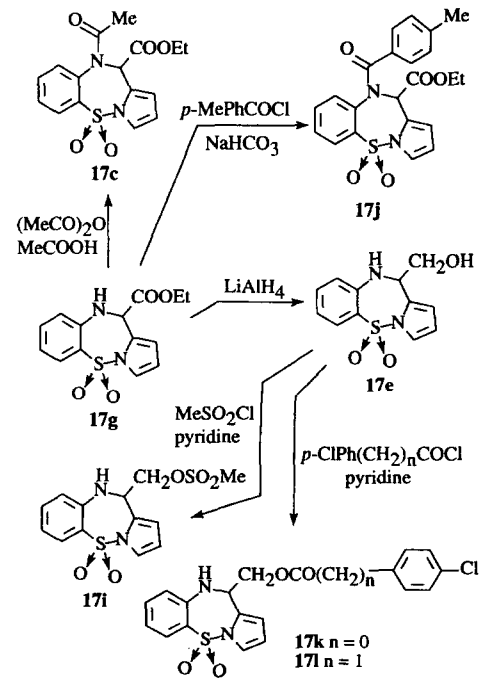
When a chlorine atom was introduced at position 8 of the benzene ring, a consistent reduction and then loss of activity were observed as the bulkiness of the substituent at position 10 increased (compare **10a–e** and **10h–j** with **11a–h**). On the contrary, the introduction of a chlorine atom at position 7 resulted in compounds endowed with higher potency and selectivity than counterparts of series **10** when the N-substituent was a hydrogen atom or a methyl group (compare **11i,j** with **10a,b**). The results reported in Table 3 for 7-chloro, 8-chloro and the related unsubstituted derivatives suggest that the *p*-chloroanilino



Scheme 3.



Scheme 4.



Scheme 5.

moiety of the benzothiadiazepine ring is crucial for the anti-HIV-1 activity. It is noteworthy that this feature is also peculiar to other potent anti-HIV agents such as TIBO derivatives R82913 and R86183,[11-15] Ro 5-3335,[42,43] the PETT derivative MSC-127,[44] some dihydroquinazolinones[45] and chloro derivatives of nevirapine.[46-49]

In order to investigate whether the presence of the pyrrole ring was determinant for the anti-HIV-1 activity, we prepared the pyrrolidinobenzothiadiazepine derivatives of series **12**. Independent of the type of N10 substituent, the activity vanishes when the aromatic pyrrole is replaced by the saturated pyrrolidine ring (data not shown), thus suggesting that the pyrrole aromatic structure is crucial for the anti-HIV-1 activity and indicating that PBTDs share structural similarities with nevirapine.[48] Likewise, the need for the SO_2 group is evident when compounds **10a** and **13a** and **b** are compared. As a matter of fact, the substitution of the above group with either S (**13a**) or CH_2 (**13b**) leads to loss of activity. Also determinant for the antiviral activity is the presence of the NHCO group at position 11. Reduction of carbonyl to CH_2 or introduction of an azometine linkage at positions 10,11 lead to inactive compounds (**17q** and **14**, respectively).

Unlike a new series of tetracyclic imidazodipyridodiazepines that have recently been described[49] as RT inhibitors superior to nevirapine, the imidazo derivatives **13c** and **15d**, and the related tetracyclic triazoles **15a–c**, were devoid of anti-HIV-1 activity. Inactive or poorly active compounds were also obtained when a wide range of substituents were introduced at positions 10 and/or 11 of the pyrrolobenzothiadiazepine nucleus

Table 3. Anti-HIV-1 activity and cytotoxicity of derivatives **10–12** in MT-4 cells[a]

Compound	CC_{50}[b]	EC_{50}[c]	IC_{50}[d]	SI[e]
10a	>300	11	4.0	>27
10b	300	10	11	30
10c	168	4.0	10	42
10d	136	26	24	5
10e	100	3.5	6.3	28
10f	≥300	>300	ND	—
10g	184	>184	ND	—
10h	150	5	9.5	30
10i	52	7.5	21	7
10j	41	>41	ND	—
10k	>300	92	ND	>3.3
10l	>300	23	31	13
10m	>300	>300	ND	—
10n	>300	19	ND	15
10o	>300	51	ND	6
10p	>300	32	ND	10
10q	>300	>300	ND	—
10r	>300	60	ND	>5
10s	>300	>300	ND	—
11a	>300	35	ND	>8
11b	110	20	ND	5.5
11c	>300	13	ND	>23
11d	>300	>300	ND	—
11e	>300	>300	ND	—
11f	32	>32	ND	—
11g	300	>300	ND	—
11h	>300	>300	ND	—
11i	>300	1.0	0.7	>300
11j	>300	0.5	0.5	>600
11k	283	2.4	2.7	118
11l	126	14	ND	9
11m	>300	>300	ND	—
11n	>300	3.7	2.9	>81
11o	>300	4.1	3.1	>73
11p	>300	129	ND	>2
AZT	>20	0.01	—	>2000
Nevirapine	>300	0.25	0.7	>1200

[a]Data represent mean values for three separate experiments. Variation among triplicate samples was less than 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 cytopathicity as determined by MTT method.
[d]Compound dose (μM) required to inhibit the HIV-1 rRT activity by 50%.
[e]Selectivity index, CC_{50}/EC_{50} ratio.

Table 4. Anti-HIV-1 activity and cytotoxicity of derivatives **13–17** in MT-4 cells[a]

Compound	CC_{50}[b]	EC_{50}[c]	IC_{50}[d]	SI[e]
13a	>300	200	>100	>1.5
13b	>300	>300	ND	—
13c	>300	>300	ND	—
14	46	>46	ND	—
15a	>300	46	ND	>6.5
15b	>300	>300	ND	—
15c	>300	>300	ND	—
15d	85	>85	ND	—
16a	>300	>300	ND	—
16b	>300	193	ND	>1.5
16c	>300	186	24	>1.5
16d	>300	189	>100	>1.5
16e	>300	198	6.3	>1.5
17a	10	>10	ND	—
17b	>300	176	ND	>1.5
17c	>300	>300	ND	—
17d	10	>10	ND	—
17e	200	>200	ND	—
17f	>300	>300	ND	—
17g	>300	>300	ND	—
17h	7	>7	ND	—
17i	130	>130	ND	—
17j	>300	>300	ND	—
17k	186	99	ND	1.8
17l	240	72	ND	3.3
17m	6	>6	ND	—
17n	62	>62	ND	—
17o	173	>173	ND	—
17p	47	>47	ND	—
17q	129	≥129	ND	—
AZT	>20	0.01	—	>2000
Nevirapine	>300	0.25	0.7	>1200

[a]Data represent mean values for three separate experiments. Variation among triplicate samples was less than 15%.
[b]Compound dose (μM) required to reduce the viability of mock-infected cells by 50%, as determined by the MTT method.
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[d]Compound dose (μM) required to inhibit the HIV-1 rRT activity by 50%.
[e]Selectivity index, CC_{50}/EC_{50} ratio.

to obtain **10k–s** and **17a–m**. Some tricyclic (**17m–p**) and tetracyclic pyrrolobenzotriazepine derivatives (**16b–e**) related to the pyrrolobenzothiadiazepine structure were also prepared and tested against HIV-1, but none of them showed appreciable activity.

Several compounds that were active against HIV-1, namely derivatives **10a,c,e,h** and **11i,j**, were tested for their capability to also prevent the HIV-2-induced cytopathicity in acutely infected MT-4 cells. None of them was found active at doses as high as 100 μM (data not shown), thus suggesting that pyrrolobenzothiadiazepines are specific HIV-1 inhibitors. Some of the compounds that resulted active in cell cultures were tested in enzyme assays against highly purified recombinant HIV-1 RT using homopolymeric template-primers. As shown in Tables 3 and 4, IC_{50} values obtained with the recombinant homodimeric enzyme were very close to EC_{50} values, allowing to conclude that pyrrolobenzothiadiazepines are a new class of non-nucleoside reverse transcriptase inhibitors.

Experimental

Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra (Nujol mulls) were run on a Perkin–Elmer 1310 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) CW spectrometer or a Varian Gemini (200 MHz) FT spectrometer in the indicated solvent. Chemical shifts are expressed in ppm with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR-APT and ^{1}H–^{13}C NMR two dimensional correlation were acquired on a Varian Gemini (200 MHz) in the same solvents. The HPLC apparatus consisted of a Perkin–Elmer Sigma 3B pump (0.5 mL/min) equipped with a (Multi)wavelength detector Perkin–Elmer LC-75 measuring at 214 nm and a Perkin–Elmer 024 recorder (1 cm/min) using a Merck LiChrospher® 100 RP-18 (5 mm) in LichroCART® column [125 mm × 4 mm, methanol/buffer $(NH_4)_3PO_4$ 0.05 M (pH 7.4) 80:20 as eluent]. Chromatography columns 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 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 Dipartimento di Scienze Farmaceutiche, University of Padova, Italy. Analytical results which are indicated only by symbols were found within ±0.4% of the theoretical values.

8-Chloro-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxide (11a). A mixture of **19b** (17.50 g, 0.053 mol) and 2-hydroxypyridine (5.06 g, 0.053 mol) was heated at 170 °C while stirring under vacuum for 63 h. After cooling the residue was purified on an alumina column (chloroform:ethanol, 95:5). Yield 54%; mp 269 °C (toluene/cyclohexane); IR: ν 1630 cm^{-1} (CO); ^{1}H NMR (90 MHz, DMSO-d_6): δ 6.56 (m, 1H, pyrrole), 7.21 (m, 1H, pyrrole), 7.43–7.71 (m, 3H, pyrrole and benzene), 8.08 (d, 1H, J = 9.0 Hz, benzene), 11.21 ppm (broad s, 1H, NH, disappeared on treatment with D_2O); anal. $C_{11}H_7ClN_2O_3S$ (282.70) C, H, N, Cl, S.

7-Chloro-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxide (11i). Prepared as **11a** starting from **19c**. Yield 42%; mp 276–278 °C (toluene/cyclohexane); IR: ν 1650 cm^{-1} (CO); ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.56 (t, 1H, J=3.1 Hz, pyrrole), 7.18 (dd, 1H, J=1.6 and 3.1 Hz, pyrrole), 7.48 (d, 1H, J=8.7 Hz, benzene C9-H), 7.60 (dd, 1H, J=1.6 and 3.1 Hz, pyrrole), 7.88 (dd, 1H, J=2.2 and 8.7 Hz, benzene C8-H), 7.97 (d, 1H, J=2.2 Hz, benzene C6-H), 11.26 ppm (s, 1H, disappeared on treatment with D_2O); anal. $C_{11}H_7ClN_2O_3S$ (282.70) C, H, N, Cl, S.

1,2,3,11a-Tetrahydro-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxide (12a). A solution of **24** (9.00 g, 0.030 mol) and 2-hydroxypyridine (1.95 g, 0.030 mol) in diphenylether (30 mL) was heated at 180 °C under stirring for 18 h and then poured onto *n*-hexane (100 mL). The clear solution was discarded and the gummy residue was washed with *n*-hexane, then dissolved in chloroform and purified by chromatography on an alumina column (chloroform). Yield 64%; mp 234–236 °C (aqueous DMF); IR: ν 1650 cm^{-1} (CO); ^{1}H NMR (200 MHz, DMSO-*d*6): δ 1.72–1.93 (m, 3H, H_2C4- and HHC3-pyrrolidine), 2.31 (m, 1H, HHC3-pyrrolidine), 2.81 (m, 1H, HHC5-pyrrolidine), 3.32 (m, 1H, HHC5-pyrrolidine), 4.34 (t, 1H, HC2-pyrrolidine), 7.24 (m, 2H, benzene), 7.65 (m, 2H, benzene), 10.45 ppm (s, 1H, NH, disappeared on treatment with D_2O); anal. $C_{11}H_{12}N_2O_3S$ (252.28) C, H, N, S.

Alkylation of 10, 11 and 12. Example, 10-methyl-5*H*-pyrrolo1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxide (10b). A mixture of **10a** (1.00 g, 0.004 mol), methyl iodide (0.85 g, 0.006 mol), potassium carbonate (1.28 g, 0.009 mol) and acetone (50 mL) was stirred at room temperature for 26 h. After concentration to a small volume the residue was shaken between ethyl acetate and water. The organic layer was isolated, washed with brine and dried. Removal of the solvent gave the crude product, which was purified by passing through an alumina column (chloroform). Yield 86%; mp 121–122 °C (toluene/cyclohexane); IR: ν 1620 cm^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.60 (s, 3H, CH_3), 6.28 (t, 1H, pyrrole), 7.05 (dd, 1H, pyrrole), 7.26–7.56 (m, 3H, pyrrole and benzene), 7.70 (m, 1H, benzene), 8.05 ppm (dd, 1H, benzene); anal. $C_{12}H_{10}N_2O_3S$ (262.28) C, H, N, S.

Alkylating agent, reaction time (h), yield (%), mp (°C), crystallization solvent, IR, ^{1}H NMR, formula, M_r and analyzed elements for derivatives **10c–q**, **10s** (from **10a**), **11b–h** (from **11a**), **11j–p** (from **11i**) and **12b–h** (from **12a**) obtained by the above procedure are reported below:

10c. Ethyl iodide, 48 h, 98%, 93–94 °C, ligroin; IR: ν 1620 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3H, J=7.2 Hz, $CH_2C\underline{H}_3$), 3.77 (m, 1H, J=7.2 Hz, $C\underline{H}HCH_3$), 4.66 (m, 1H, J=7.2 Hz, $CH\underline{H}CH_3$), 6.26 (t, 1H, J=3.4 Hz, pyrrole), 6.98 (dd, 1H, J=1.7 and 3.4 Hz, pyrrole), 7.25 (m, 1H, pyrrole), 7.35–7.50 (m, 2H, benzene), 7.63 (dt, 1H, J=1.5 and 8.0 Hz, benzene), 8.01 ppm (dd, 1H, J=1.5 and 8.0 Hz, benzene); anal. $C_{13}H_{12}N_2O_3S$ (276.31) C, H, N, S.

10d. Propyl iodide, 48 h, 86%, 79–81 °C, ligroin; IR: ν 1620 cm^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.90 (t, 3H, J=7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.41–1.96 (m, 2H, $CH_2C\underline{H}_2CH_3$), 3.43–3.80 (m, 1H, $C\underline{H}HCH_2CH_3$), 4.43–4.63 (m, 1H, $CH\underline{H}CH_2CH_3$), 6.25 (t, 1H, pyrrole), 7.00 (dd, 1H, pyrrole), 7.23–7.80 (m, 4H, pyrrole and benzene), 8.03 ppm (dd, 1H, benzene); anal. $C_{14}H_{14}N_2O_3S$ (290.33) C, H, N, S.

10e. Isopropyl iodide, 160 h (alkyl halide and potassium carbonate were added every 48 h), 49%, 112–113 °C, cyclohexane; IR: ν 1630^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.28 [d, 3H, J=7.5 Hz, $CH(C\underline{H}_3)CH_3$], 1.65 [d, 3H, J=7.5 Hz, $CH(CH_3)C\underline{H}_3$], 4.68 [m, 1H, J=7.5 Hz, $C\underline{H}(CH_3)CH_3$], 6.23 (t, 1H, pyrrole), 6.95 (dd, 1H, pyrrole), 7.25 (m, 1H, pyrrole), 7.31–7.80 (m, 3H, benzene), 8.06 ppm (dd, 1H, benzene); anal. $C_{14}H_{14}N_2O_3S$ (290.33), C, H, N, S.

10f. Butyl iodide, 60 h, 60%, 99–100 °C, cyclohexane; IR: ν 1620 cm^{-1} (CO). ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.90 (m, 3H, $CH_2CH_2CH_2C\underline{H}_3$), 1.15–1.90 (m, 4H, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 3.50–3.86 (m, 1H, $C\underline{H}HCH_2CH_2CH_3$), 4.50–4.86 (m, 1H, $CH\underline{H}CH_2CH_2CH_3$), 6.26 (t, 1H, pyrrole), 7.00 (dd, 1H, pyrrole), 7.25–7.83 (m, 4H, pyrrole and benzene), 8.06 ppm (dd, 1H, benzene); anal. $C_{15}H_{16}N_2O_3S$ (304.36) C, H, N, S.

10g. Isobutyl bromide, 160 h (alkyl halide and potassium carbonate were added every 48 h), 55%, 129–130 °C, cyclohexane; IR: ν 1620 cm^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.93 [t, 6H, J=7.5 Hz, $CH_2CH(C\underline{H}_3)_2$], 2.03 [m, 1H, J=7.5 Hz, $CH_2C\underline{H}(CH_3)_2$], 3.43 [dd, 1H, J=7.5 and 15 Hz, $C\underline{H}HCH(CH_3)_2$], 4.70 [dd, 1H, J=7.5 and 15 Hz, $CH\underline{H}CH(CH_3)_2$], 6.26 (t, 1H, pyrrole), 7.03 (dd, 1H, pyrrole), 7.26–7.86 (m, 4H, pyrrole and benzene), 8.10 ppm (dd, 1H, benzene); anal. $C_{15}H_{16}N_2O_3S$ (304.36) C, H, N, S.

10h. 2-Propenyl bromide, 21 h, 95%, 105–107 °C, ligroin; IR: ν 1620 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.56 (dd, 1H, J=5.5 and 15.5 Hz, $C\underline{H}HCH{=}CH_2$), 4.79 (dd, 1H, J=5.5 and 15.5 Hz, $CH\underline{H}CH{=}CH_2$), 5.23 (m, 2H, $CH_2CH{=}C\underline{H}_2$), 6.00 (m, 1H, $CH_2C\underline{H}{=}CH_2$), 6.28 (t, 1H, J=3.2 Hz, pyrrole), 7.00 (m, 1H, pyrrole), 7.25 (m, 1H, pyrrole), 7.36 (m, 1H, benzene), 7.50–7.68 (m, 2H, benzene), 7.98 ppm (dd, 1H, benzene); anal. $C_{14}H_{12}N_2O_3S$ (288.32) C, H, N, S.

10i. 2-Butenyl bromide, 24 h, 95%, 120–122 °C, cyclohexane; IR: ν 1620 cm^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.65 (m, 3H, $CH_2CH{=}CHC\underline{H}_3$), 4.35–4.95 (m, 2H, $C\underline{H}_2CH{=}CHCH_3$), 5.58–5.82 (m, 2H, $CH_2C\underline{H}{=}C\underline{H}CH_3$), 6.27 (t, 1H, pyrrole), 7.02 (dd, 1H, pyrrole), 7.25–7.42 (m, 4H, pyrrole and benzene), 8.03 ppm (dd, 1H, benzene); anal. $C_{15}H_{14}N_2O_3S$ (302.34) C, H, N, S.

10j. 3-Methyl-2-butenyl bromide, 24 h, 99%, 98–101 °C, cyclohexane; IR: ν 1620 cm^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.67 [s, 6H, $CH_2CH{=}C(C\underline{H}_3)_2$], 4.35–5.02 [m, 2H, $C\underline{H}_2CH{=}C(CH_3)_2$], 5.42 [m, 1H, $CH_2C\underline{H}{=}C(CH_3)_2$], 6.25 (t, 1H, pyrrole), 7.02 (dd, 1H, pyrrole), 7.25–7.80 (m, 4H, pyrrole and benzene), 8.03 ppm (dd, 1H, benzene); anal. $C_{16}H_{16}N_2O_3S$ (316.37) C, H, N, S.

10k. Methyl bromoacetate, 24 h, 87%, 198 °C, toluene; IR: ν 1630 and 1740 cm^{-1} (CO); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.75 (s, 3H, $COOCH_3$), 4.75 (s, 2H, CH_2), 6.45 (t, 1H, J=3.3 Hz, pyrrole), 7.08 (dd, 1H, J=1.6 and 3.3 Hz, pyrrole), 7.50–7.62 (m, 2H, pyrrole and benzene), 7.72 (d, 1H, J=7.8 Hz, benzene), 7.90 (m, 1H, benzene), 8.06 ppm (dd, 1H, J=1.4 and 7.8 Hz, benzene); anal. $C_{14}H_{12}N_2O_5S$ (320.32) C, H, N, S.

10l. Ethyl bromoacetate, 17 h, 71%, 141–142 °C, toluene/cyclohexane; IR: ν 1640 and 1740 cm^{-1} (CO); ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.33 (t, 3H, J=7.5 Hz, $COOCH_2C\underline{H}_3$), 4.08–4.50 (q, J=7.5 Hz and d, J=16.5 Hz, part B of ABq, 3H, $C\underline{H}HCOOC\underline{H}_2CH_3$), 4.91 (d, 1H, J=16.5 Hz, part A of ABq, $CH\underline{H}COOEt$), 6.28 (t, 1H, pyrrole), 7.01 (dd, 1H, pyrrole), 7.28–7.61 (m, 2H, pyrrole and benzene), 7.71 (m, 2H, benzene), 8.08 ppm (d, 1H, J=7.5 Hz, benzene); anal. $C_{15}H_{14}N_2O_5S$ (334.34) C, H, N, S.

10m. Benzyl bromoacetate, 24 h, 95%, 121 °C, toluene/cyclohexane; IR: ν 1640 and 1730 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.26 and 4.98 (two d, 2H, J=17.1 Hz, ABq, CH_2), 5.32 (s, 2H, CH_2), 6.30 (t, 1H, J=3.3 Hz, pyrrole), 7.05 (dd, 1H, J=1.6 and 3.5 Hz, pyrrole), 7.26–7.40 (m, 7H, pyrrole and benzene), 7.62 (d, 2H, J=3.7 Hz, benzene), 8.00 ppm (d, 1H, J=7.8 Hz, benzene); anal. $C_{20}H_{16}N_2O_5S$ (396.41) C, H, N, S.

10n. Methyl chloromethyl ether, 5 h, 76%, 100–101 °C, ligroin; IR: ν 1630 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.58 (s, 3H, CH_3), 5.00 and 5.56 (two d, 2H, J=9.9 Hz, ABq, CH_2), 6.29 (t, 1H, J=3.4 Hz, pyrrole), 7.05 (dd, 1H, J=1.7 and 3.5 Hz, pyrrole), 7.27 (m, 1H, pyrrole), 7.37 (t, 1H, J=8.0 Hz, benzene), 7.66 (dt, 1H, J=1.4 and 7.5 Hz, benzene) 7.85 (d, 1H,

J=8.1 Hz, benzene), 8.01 ppm (dd, 1H, J=1.5 and 8.0 Hz, benzene); anal. $C_{13}H_{12}N_2O_4S$ (292.31) C, H, N, S.

10o. 2-Chloroethyl methyl ether, 160 h, 36%, 101–102 °C, ligroin; IR: ν 1620 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.31 (s, 3H, CH_3), 3.59–3.62 (m, 1H, CHH), 3.70–4.10 (m, 2H, CH_2), 4.42–4.58 (m, 1H, CHH), 6.25 (t, 1H, J=3.4 Hz, pyrrole), 6.95 (dd, 1H, J=1.7 and 3.5 Hz, pyrrole), 7.23 (m, 1H, pyrrole), 7.37 (t, 1H, J=8.1 Hz, benzene), 7.60–7.78 (m, 2H, benzene), 7.97 ppm (dd, 1H, J=8.0 Hz, benzene); anal. $C_{14}H_{14}N_2O_4S$ (306.33) C, H, N, S.

10p. (Chloromethyl)cyclopropane and 1:1 KI, 24 h, 90%, 127–128 °C, cyclohexane; IR: ν 1620 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.08–0.55 (m, 4H, CH_2 cyclopropane), 1.10 (m, 1H, CH cyclopropane), 3.61 and 4.44 (two dd, 2H, J=7.4 and 14.2 Hz, AB system, CH_2-*c*-C_3H_5), 6.24 (t, 1H, J=3.2 Hz, pyrrole), 6.96 (m, 1H, pyrrole), 7.24 (m, 1H, pyrrole), 7.38 (dt, 1H, J=1.2 and 7.9 Hz, benzene), 7.50 (m, 1H, benzene), 7.65 (dt, 1H, J=1.5 and 8.3 Hz, benzene), 8.01 ppm (dd, 1H, J=1.5 and 7.9 Hz, benzene); anal. $C_{15}H_{14}N_2O_3S$ (302.34) C, H, N, S.

10q (from 10a). Benzyl bromide, 5 h, 90%, 149–150 °C, cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 5.14 and 5.46 (two d, 2H, J=15.8 Hz, ABq, CH_2), 6.29 (t, 1H, J=3.4 Hz, pyrrole), 7.08 (dd, 1H, J=1.6 and 3.5 Hz, pyrrole), 7.12–7.55 (m, 9H, pyrrole and benzene), 7.95 ppm [dd, 1H, J=1.5 and 7.9 Hz, benzene C6(9)—H]; anal. $C_{18}H_{14}N_2O_3S$ (338.38) C, H, N, S.

10s. 2-(Dimethylamino)ethyl chloride hydrochloride and 1:3 K_2CO_3, 67 h, 86%, 118 °C, toluene/cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 2.22 [s, 6H, $CH_2CH_2N(CH_3)_2$], 2.46–2.78 [m, 2H, $CH_2CH_2N(CH_3)_2$], 3.71–3.87 [m, 1H, $CHHCH_2N(CH_3)_2$], 4.53–4.69 [m, 1H, $CHHCH_2N(CH_3)_2$], 6.23 (t, 1H, J=3.4 Hz, pyrrole), 6.94 (dd, 1H, J=1.7 and 3.5 Hz, pyrrole), 7.21 (dd, 1H, J=1.7 and 3.1 Hz, pyrrole), 7.32–7.40 (m, 1H, benzene), 7.62 (m, 2H, benzene), 7.97 ppm [d, 1H, J=7.4 Hz, benzene C6(9)-H] anal. $C_{15}H_{17}N_3O_3S$ (319.37) C, H, N, S.

11b. Methyl iodide, 18 h, 88%, 150 °C, toluene/cyclohexane; IR: ν 1620 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 3.58 (s, 3H, CH_3), 6.31 (t, 1H, pyrrole), 7.08 (dd, 1H, pyrrole), 7.28–7.51 (m, 3H, pyrrole and benzene), 7.98 ppm [d, 1H, J=8.3 Hz, benzene C6—H]; anal. $C_{12}H_9ClN_2O_3S$ (296.72) C, H, N, Cl, S.

11c. Ethyl iodide, 18 h, 72%, 127 °C, toluene/cyclohexane; IR: ν 1640 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 1.38 (t, 3H, J=7.5 Hz, CH_2CH_3), 3.78 (m, 1H, J=7.5 Hz, $CHHCH_3$), 4.61 (m, 1H, J=7.5 Hz, $CHHCH_3$), 6.28 (t, 1H, pyrrole), 7.01 (dd, 1H, pyrrole), 7.21–7.58 (m, 3H, pyrrole and benzene), 7.98 ppm (d, 1H, J=8.3 Hz, benzene C6-H); anal. $C_{13}H_{11}ClN_2O_3S$ (310.75), C, H, N, Cl, S.

11d. Propyl iodide, 45 h, 53%, 141 °C, cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 0.90 (t, 3H, J=7.5 Hz, $CH_2CH_2CH_3$), 1.45–2.01 (m, 2H, $CH_2CH_2CH_3$), 3.36–3.78 (m, 1H, $CHHCH_2CH_3$), 4.41–4.78 (m, 1H, $CHHCH_2CH_3$), 6.25 (t, 1H, pyrrole), 7.00 (dd, 1H, pyrrole), 7.21–7.55 (m, 3H, pyrrole and benzene), 7.95 ppm (d, 1H, J=8.3 Hz, benzene, C6—H); anal. $C_{14}H_{13}ClN_2O_3S$ (324.79) C, H, N, Cl, S.

11e. Isopropyl iodide, 160 h (alkyl halide and potassium carbonate were added every 48 h), 48%, 102–103 °C, ligroin (−25 °C); IR: ν 1620 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.42 [d, 6H, J=6.2 Hz, $CH(CH_3)_2$], 5.45 [m, 1H, J=6.2 Hz, $CH(CH_3)_2$], 6.38 (t, 1H, J=3.2 Hz, pyrrole), 6.82 (dd, 1H, J=1.5 and 3.5 Hz, pyrrole), 7.18–7.40 (m, 3H, pyrrole and benzene), 7.85 ppm (d, 1H, J=9.2 Hz, benzene C6—H); anal. $C_{14}H_{13}ClN_2O_3S$ (324.79) C, H, N, Cl, S.

11f. 2-Propenyl bromide, 21 h, 61%, 129 °C, toluene/cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 4.38–4.95 (m, 2H, $CH_2CH=CH_2$), 5.18–5.45 (m, 2H, $CH_2CH=CH_2$), 5.81–6.35 (m, 2H, $CH_2CH=CH_2$ and pyrrole), 7.01 (dd, 1H, pyrrole), 7.21–7.43 (m, 2H, pyrrole and benzene), 7.55 (d, 1H, J=1.5 Hz, benzene C9—H), 7.95 ppm (d, 1H, J=9.0 Hz, benzene C6—H); anal. $C_{14}H_{11}ClN_2O_3S$ (322.76) C, H, N, Cl, S.

11g. 2-Butenyl bromide, 24 h, 90%, 134–135 °C, cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 1.70 (m, 3H, $CH_2CH=CHCH_3$), 4.33–4.93 (m, 2H, $CH_2CH=CHCH_3$), 5.47–6.03 (m, 2H, $CH_2CH=CHCH_3$), 6.30 (t, 1H, pyrrole), 7.03 (dd, 1H, pyrrole), 7.23–7.47 (m, 2H, pyrrole and benzene), 7.58 (d, 1H, J=1.5 Hz, benzene C9—H), 7.97 ppm (d, 1H, J=9.0 Hz, benzene C6—H); anal. $C_{15}H_{13}ClN_2O_3S$ (336.79) C, H, N, Cl, S.

11h. 3-Methyl-2-butenyl bromide, 24 h, 91%, 145–147 °C, cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 2.08 [s, 6H, $CH_2CH=C(CH_3)_2$], 4.35–4.98 [m, 2H, $CH_2CH=C(CH_3)_2$], 5.28–5.55 [m, 1H, $CH_2CH=C(CH_3)_2$], 6.30 (t, 1H, pyrrole), 7.05 (dd, 1H, pyrrole), 7.22–7.45 (m, 2H, pyrrole and benzene), 7.52 (d, 1H, J=8.5 Hz, benzene C6—H), 7.97 ppm (d, 1H, benzene); anal. $C_{16}H_{15}ClN_2O_3S$ (350.82) C, H, N, Cl, S.

11j. Methyl iodide, 24 h, 99%, 154–155 °C, toluene/cyclohexane; IR: ν 1640 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.58 (s, 3H, CH_3), 6.31 (t, 1H, J=3.3 Hz, pyrrole), 7.02 (dd, 1H, J=1.6 and 3.3 Hz, pyrrole), 7.28 (m, 1H, pyrrole), 7.37 (d, 1H, J=8.4 Hz, benzene C9—H), 7.61 (dd, 1H, J=3.0 and 8.4 Hz, benzene, C8—H), 7.86 ppm (d, 1H, J=3.0 Hz, benzene C6—H); anal. $C_{12}H_9ClN_2O_3S$ (296.72) C, H, N, Cl, S.

11k. Ethyl iodide, 24 h, 96%, 77–78 °C, cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=7.0 Hz, CH_2CH_3), 3.69 (m, 1H, J=7.0 Hz, $CHHCH_3$), 4.63 (m, 1H, J= 7.0, $CHHCH_3$), 6.27

(t, 1H, J=3.4 Hz, pyrrole), 6.98 (dd, 1H, J=1.6 and 3.4 Hz, pyrrole), 7.23 (m, 1H, pyrrole), 7.37 (d, 1H, J=8.7 Hz, benzene C9—H), 7.55 (dd, 1H, J=3.0 and 8.7 Hz, benzene C8—H), 7.95 ppm (d, 1H, J=3.0 Hz, benzene C6—H); anal. $C_{13}H_{11}ClN_2O_3S$ (310.75) C, H, N, Cl, S.

11l. Propyl iodide, 64 h, 88%, 79–80 °C, cyclohexane; IR: ν 1620 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, 3H, J=7.3 Hz, $CH_2CH_2CH_3$), 1.55–1.85 (m, 2H, $CH_2CH_2CH_3$), 3.45–3.65 (m, 1H, $CHHCH_2CH_3$), 4.45–4.68 (m, 1H, $CHHCH_2CH_3$), 6.29 (t, 1H, J=3.3 Hz, pyrrole), 6.97 (m, 1H, pyrrole), 7.22 (m, 1H, pyrrole), 7.38 (d, 1H, J=8.8 Hz, benzene C9—H), 7.60 (dd, 1H, J=2.3 and 8.8 Hz, benzene C8—H), 7.95 ppm (d, 1H, J=2.3 Hz, benzene C6—H); anal. $C_{14}H_{13}ClN_2O_3S$ (324.79) C, H, N, Cl, S.

11m. Isopropyl iodide, 160 h (alkyl halide and potassium carbonate were added every 48 h), 65%, 111 °C, cyclohexane; IR: ν 1620 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 [d, 6H, J=6.4 Hz, $CH(CH_3)_2$], 5.46 [m, 1H, $CH(CH_3)_2$], 6.38 (t, 1H, J=3.6 Hz, pyrrole), 6.82 (dd, 1H, J=1.6 and 3.6 Hz, pyrrole), 7.27 (d, 1H, J=8.7 Hz, benzene C9—H), 7.41 (m, 1H, pyrrole), 7.51 (dd, 1H, J=2.5 and 8.7 Hz, benzene C8—H), 7.94 ppm (d, 1H, J=2.5 Hz, benzene C6—H); anal. $C_{14}H_{13}ClN_2O_3S$ (324.78) C, H, N, Cl, S.

11n. 2-Propenyl bromide, 24 h, 99%, 109–110 °C, cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 4.53 and 4.80 (two dd, 2H, J=5.6 and 15.6 Hz, $CH_2CH=CH_2$), 5.23 (m, 2H, $CH_2CH=CH_2$), 5.97 (m, 1H, $CH_2CH=CH_2$), 6.30 (t, 1H, J=3.5 Hz, pyrrole), 7.01 (dd, 1H, J=1.7 and 3.5 Hz, pyrrole), 7.27 (m, 1H, pyrrole), 7.40–7.59 (m, 2H, benzene), 7.95 ppm (d, 1H, J=3.6 Hz, benzene C6—H); anal. $C_{14}H_{11}ClN_2O_3S$ (322.76) C, H, N, Cl, S.

11o. 2-Butenyl bromide, 24 h, 82%, 148–149 °C, toluene/cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.65 (m, 3H, $CH_2CH=CHCH_3$), 4.34–4.95 (m, 2H, $CH_2CH=CHCH_3$), 5.50–5.82 (m, 2H, $CH_2CH=CHCH_3$), 6.30 (t, 1H, J=3.3 Hz, pyrrole), 7.00 (dd, 1H, J=1.6 and 3.3 Hz, pyrrole), 7.25 (m, 1H, pyrrole), 7.40–7.62 (m, 2H, benzene), 7.96 ppm (d, 1H, J=2.3 Hz, benzene C6—H). $C_{15}H_{13}ClN_2O_3S$ (336.79) C, H, N, Cl, S.

11p. 3-Methyl-2-butenyl bromide, 24 h, 90%, 117–118 °C, toluene/cyclohexane; IR: ν 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.60 [s, 6H, $CH_2CH=C(CH_3)_2$], 4.50 and 4.77 [two dd, 2H, J=6.6 and 15.4 Hz, $CH_2CH=C(CH_3)_2$], 5.32 [m, 1H, $CH_2CH=C(CH_3)_2$], 6.29 (t, 1H, J=3.2 Hz, pyrrole), 7.01 (dd, 1H, J=1.7 and 3.5 Hz, pyrrole), 7.25 (m, 1H, pyrrole), 7.40 (d, 1H, J=8.8 Hz, benzene C9—H), 7.55 (dd, 1H, J=2.4 and 8.7 Hz, benzene C8—H), 7.95 ppm (d, 1H, benzene C6—H); anal. $C_{16}H_{15}ClN_2O_3S$ (350.82) C, H, N, Cl, S.

12b. Methyl iodide, 26 h, 82%, 132–133 °C, toluene/cyclohexane; IR: ν 1670 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.85–2.13 (m, 3H, pyrrolidine), 2.47 (m, 1H, pyrrolidine), 3.31–3.72 (m, 6H, pyrrolidine and CH_3), 7.41 (m, 2H, benzene), 7.66 (m, 1H, benzene), 7.97 ppm (m, 1H, benzene); anal. $C_{12}H_{14}N_2O_3S$ (266.31) C, H, N, S.

12c. Ethyl iodide, 48 h, 98%, 133–134 °C, toluene/cyclohexane; IR: ν 1660 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, 3H, J=7.1 Hz, CH_2CH_3), 1.82–2.13 (m, 3H, pyrrolidine), 2.46 (m, 1H, pyrrolidine), 3.31–3.81 (m, 4H, pyrrolidine and $CHHCH_3$), 4.12 (m, 1H, $CHHCH_3$), 7.40 (m, 2H, benzene), 7.65 (m, 1H, benzene), 7.98 ppm (d, 1H, J=7.8 Hz, benzene); anal. $C_{13}H_{16}N_2O_3S$ (280.34) C, H, N, S.

12d. Propyl iodide, 62 h, 92%, 118–119 °C, toluene/cyclohexane; IR: ν 1670 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H, J=7.3 Hz, $CH_2CH_2CH_3$), 1.54–2.15 (m, 5H, pyrrolidine and $CH_2CH_2CH_3$), 2.47 (m, 1H, pyrrolidine), 3.29–3.71 (m, 4H, pyrrolidine and $CHHCH_2CH_3$), 3.95 (m, 1H, $CHHCH_2CH_3$), 7.40 (m, 2H, benzene), 7.67 (m, 1H, benzene), 7.99 ppm (d, 1H, J=8.1 Hz, benzene); anal. $C_{14}H_{18}N_2O_3S$ (294.37) C, H, N, S.

12e. Isopropyl iodide, 160 h (alkyl halide and potassium carbonate were added every 48 h), 50%, (chromatographical purification: alumina–ethyl acetate) 184–185 °C, toluene/cyclohexane; IR: ν 1660 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.07 and 1.45 [two d, 6H, J=7.0 Hz, $CH(CH_3)_2$], 1.81–2.17 (m, 3H, pyrrolidine), 2.53 (m, 1H, pyrrolidine), 3.26–3.49 (m, 3H, pyrrolidine), 4.65 [m, 1H, $CH(CH_3)_2$], 7.45 (m, 2H, benzene), 7.66 (m, 1H, benzene), 8.00 ppm (m, 1H, benzene); anal. $C_{14}H_{18}N_2O_3S$ (294.37) C, H, N, S.

12f. Butyl iodide, 90 h, 90%, 91–92 °C, cyclohexane; IR: ν 1670 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H, J=7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.18–2.16 (m, 7H, pyrrolidine and $CH_2CH_2CH_2CH_3$), 2.48 (m, 1H, pyrrolidine), 3.30–3.73 (m, 4H, pyrrolidine and $CHHCH_2CH_2CH_3$), 3.97 (m, 1H, $CHHCH_2CH_2CH_3$), 7.40 (m, 2H, benzene), 7.55 (m, 1H, benzene), 8.00 ppm (m, 1H, benzene); anal. $C_{15}H_{20}N_2O_3S$ (308.39) C, H, N, S.

12g. Isobutyl bromide, 160 h, (alkyl halide and potassium carbonate were added every 48 h), 75% (chromatography: alumina–ethyl acetate), 134 °C, cyclohexane; IR: ν 1670 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.81 and 0.95 [two d, 6H, J=6.6 Hz, $CH_2CH(CH_3)_2$], 1.84–2.15 [m, 4H, pyrrolidine and $CH_2CH(CH_3)_2$], 2.47 (m, 1H, pyrrolidine), 3.31–3.85 [m, 5H, pyrrolidine and $CH_2CH(CH_3)_2$], 7.40 (m, 2H, benzene), 7.65 (m, 1H, benzene), 8.02 ppm (m, 1H, benzene); anal. $C_{15}H_{20}N_2O_3S$ (308.39) C, H, N, S.

12h. Chloromethylcyclopropane, 96 h (at 40 °C), 80% (chromatography: alumina–ethyl acetate), 100–101 °C, cyclohexane; IR: ν 1670 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.00–0.46 (m, 4H, cyclopropane), 1.07 (m, 1H, cyclopropane), 1.78–2.13 (m, 3H, pyrrolidine),

2.45 (m, 1H, pyrrolidine), 3.28–3.93 (m, 5H, pyrrolidine and $C\underline{H}_2$-*c*-C_3H_5), 7.43 (m, 2H, benzene), 7.65 (m, 1H, benzene), 7.99 ppm (d, 1H, J=7.7 Hz, benzene); anal. $C_{15}H_{18}N_2O_3S$ (306.38) C, H, N, S.

10-Cyclopropyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxide (10r). A solution of **22b** (1.12 g, 0.0036 mol) in anhydrous DMF (15 mL) was dropped into a water-cooled suspension of sodium hydride (60% in oil, 0.29 g, 0.0072 mol) in anhydrous DMF (7 mL), then cuprous iodide (0.68 g, 0.0036 mol) was added in one portion. The mixture was stirred at room temperature for 40 h, then diluted with water and extracted with ethyl acetate. The organic layer was isolated, washed with brine and dried. Removal of the solvent gave a residue which was purified by chromatography on silica gel (chloroform). Yield 80%; 154–155 °C (toluene/cyclohexane); IR: ν 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.34, 0.82, 0.97, and 1.22 [four m, 4H, $(CH_2)_2$ cyclopropane], 3.44 (m, 1H, CH cyclopropane), 6.25 (t, 1H, J=3.4 Hz, pyrrole), 7.06 (dd, 1H, J=1.8 and 3.5 Hz, pyrrole), 7.26 (m, 1H, pyrrole), 7.34 (dt, 1H, J=1.3 and 7.9 Hz, benzene), 7.57 (d, 1H, benzene), 7.67 (dt, 1H, J=1.5 and 8.2 Hz, benzene), 7.90 ppm (dd, 1H, J=1.3 and 7.9 Hz, benzene); anal. $C_{14}H_{12}N_2O_3S$ (288.32) C, H, N, S.

10-Benzyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one-5,5-dioxide (10q). Prepared as **10r** starting from **22a** (16 h). Yield 94%; mp 149–150 °C (cyclohexane); IR and ^1H NMR spectra were identical with those of the sample prepared from **10a**.

5*H*-Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11(10*H*)-one (13a). A solution of bis(trichloromethyl)carbonate (0.52 g, 0.0017 mol) in dichloromethane (10 mL) was slowly dropped into a solution of 1-(2-aminobenzenesulfenyl)-1*H*-pyrrole (**25**,[29] 1.00 g, 0.0052 mol) and triethylamine (0.53 g, 0.0052 mol) in the same solvent (40 mL). The solution was stirred at room temperature for 5 h, then diluted with water and shaken with ethyl acetate. The organic layer was isolated, washed with brine and dried. The residue was purified on alumina column (ethyl acetate:ethanol 9:1). Yield 35%; mp 189–191 °C (ethyl acetate/*n*-hexane); IR: ν 1620 cm^{-1} (CO); ^1H NMR (90 MHz, DMSO-d_6): δ 6.75 (t, 1H, pyrrole), 7.15 (t, 1H, pyrrole), 7.33–7.81 (m, 5H, pyrrole and benzene), 10.21 ppm (s, 1H, NH, disappeared on treatment with D_2O); anal. $C_{11}H_8N_2OS$ (216.25) C, H, N, S.

10,11-Dihydro-11-ethoxycarbonyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine (17a). A solution of ethyl glyoxylate ethyl hemiacetal (1.00 g, 0.0067 mol) in absolute ethanol (2 mL) was added dropwise into an ice-cooled solution of 1-(2-aminobenzenesulfenyl)-1*H*-pyrrole (**25**,[29] 1.00 g, 0.0052 mol) in the same solvent (7 mL). Reaction mixture was stirred at 0 °C for 3.5 h then at room temperature overnight. After evaporation, the residue was purified by passing through a silica gel column (dichloromethane). Yield 83%; mp 103–104 °C (from cyclohexane); IR: ν 1730 (CO), 3340 cm^{-1} (NH); ^1H NMR (90 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=7.5 Hz, $COOCH_2C\underline{H}_3$), 4.33 (q, 2H, $COOC\underline{H}_2CH_3$), 5.03 (broad d, 1H, J=6.0 Hz, NH, disappeared on treatment with D_2O), 5.93–6.16 (m, 2H, pyrrole), 6.23 (d, 1H, J=6.0 Hz, CH), 6.86 (m, 2H, benzene), 6.76 (dd, 1H, pyrrole), 6.93–7.26 ppm (m, 2H, benzene); anal. $C_{14}H_{14}N_2O_2S$ (274.34) C, H, N, S.

10-Chloroacetyl-10,11-dihydro-11-ethoxycarbonyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine (17b). A solution of chloroacetyl chloride (0.23 g, 0.0020 mol) in dichloromethane (2 mL) was added dropwise into an ice-cooled mixture of **17a** (0.50 g, 0.0018 mol) and $NaHCO_3$ (0.17 g, 0.0021 mol) in the same solvent (5 mL). Reaction was stirred at room temperature for 4 h, then diluted with water. After shaking, the organic layer was isolated, washed with brine and dried. Removal of the solvent gave the crude product, which was purified by chromatography on silica gel (dichloromethane). Yield 74%; mp 128–130 °C (cyclohexane); IR: ν 1670 and 1730 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 1.36 (t, 3H, J=7.5 Hz, $COOCH_2C\underline{H}_3$), 3.36 and 3.79 (two d, 2H, J=12.0 Hz, ABq, $C\underline{H}_2Cl$), 4.36 (q, 2H, J=7.5 Hz, $COOC\underline{H}_2CH_3$), 5.96 (m, 2H, pyrrole), 6.26 (s, 1H, CH), 6.85 (m, 1H, pyrrole), 7.21–7.80 ppm (m, 4H, benzene); anal. $C_{16}H_{15}ClN_2O_3S$ (350.82) C, H, N, Cl, S.

10-Acetyl-10,11-dihydro-11-ethoxycarbonyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-5,5-dioxide (17c). A solution of **17g**[31] (1.00 g, 0.0033 mol) in acetic anhydride (6.5 mL) and acetic acid (6.5 mL) was refluxed for 3 h, then evaporated to dryness. The residue was treated with crushed ice water and solid $NaHCO_3$. After shaking with ethyl acetate, the organic layer was isolated, washed with brine and dried. Removal of the solvent furnished the crude product, which was purified by chromatography on silica gel (chloroform). Yield 75%; mp 143–146 °C (toluene/cyclohexane); IR: ν 1660 and 1740 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, 3H, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 1.94 (s, 3H, $COC\underline{H}_3$), 4.33 (q, 2H, J=7.1 Hz, $COOC\underline{H}_2CH_3$), 6.13 (m, 2H, pyrrole), 6.41 (s, 1H, CH), 7.20 (m, 1H, pyrrole), 7.40–7.75 (m, 3H, benzene), 7.92 ppm (dd, 1H, J=1.3 and 7.6 Hz, benzene); anal. $C_{16}H_{16}N_2O_5S$ (348.37) C, H, N, S.

10,11-Dihydro-11-hydroxymethyl-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-5,5-dioxide (17e). A solution of **17g**[31] (15.00 g, 0.049 mol) in dry THF (150 mL) was slowly dropped into a well-stirred ice-cooled suspension of lithium aluminum hydride (1.85 g, 0.049 mol) in the same solvent (150 mL). The mixture was stirred at 0 °C for 45 min and then carefully treated with crushed ice. After filtration, the solution was concentrated to a small volume and extracted with chloroform. The organic layer was washed with brine and dried. Removal of the solvent gave a residue, which was purified by chromatography on silica gel column (chloroform). Yield 65%; mp 135–136 °C (toluene/ligroin); IR: ν 3360 and 3520 cm^{-1} (OH and NH); ^1H NMR (90 MHz, DMSO-d_6): δ 4.08 (d, 2H,

J=6.0 Hz, CH_2), 5.25 (m, 2H, CH and CH_2OH), 6.28 (m, 2H, pyrrole), 6.68 (m, 1H, benzene), 6.95–7.20 (m, 2H, benzene and NH), 7.30–7.55 (m, 2H, benzene and pyrrole), 7.68 ppm (dd, 1H, J=1.5 and 7.0 Hz, benzene); anal. $C_{12}H_{12}N_2O_3S$ (264.29) C, H, N, S.

10,11-Dihydro-11-methanesulfonyloxymethyl-5*H*-pyrrolo [1,2-*b*] [1,2,5] benzothiadiazepine-5,5-dioxide (17i). Methanesulfonyl chloride (3.55 g, 0.030 mol) was added dropwise over a period of 10 min to an ice-cooled solution of **17e** (7.55 g, 0.028 mol) in dry pyridine (100 mL). The mixture was kept at room temperature for 5 h, then diluted with water and made acidic with 12 N HCl. After extraction with chloroform, the organic solution was washed with brine and dried. Removal of the solvent gave a crude product, which was purified by chromatography on silica gel column (chloroform). Yield 70%; mp 126–127 °C (toluene/ligroin); IR: ν 3360 cm^{-1} (NH); ^1H NMR (90 MHz, $CDCl_3$): δ 3.16 (s, 3H, CH_3), 4.81 (d, 2H, J=6.0 Hz, CH_2), 5.38 (broad s, 1H, NH, disappeared on treatment with D_2O), 5.71 (m, 1H, CH), 6.15–6.35 (m, 2H, pyrrole), 6.68–6.91 (m, 2H, benzene), 7.25–7.48 (m, 2H, pyrrole and benzene), 7.85 ppm (dd, 1H, J=2.0 and 8.0 Hz, benzene); anal. $C_{13}H_{14}N_2O_5S_2$ (342.39) C, H, N, S.

10,11-Dihydro-11-ethoxycarbonyl-10-(4-methylbenzoyl)-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-5,5-dioxide (17j). A mixture of **17g**[31] (1.00 g, 0.0033 mol), 4-methylbenzoyl chloride (0.52 g, 0.0034 mol), $NaHCO_3$ (0.31 g, 0.0037 mol) and 1-bromo-3-chloropropane (50 mL) was refluxed overnight. After cooling, the mixture was filtered and the solvent evaporated. The residue was purified by chromatography on silica gel (chloroform). Yield 43%; mp 186 °C (from toluene/ligroin); IR: ν 1640 and 1740 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 1.38 (t, 3H, J=7.5 Hz, $COOCH_2CH_3$), 2.21 (s, 3H, $PhCH_3$), 4.41 (q, 2H, J=7.5 Hz, $COOCH_2CH_3$), 6.15 (m, 2H, pyrrole), 6.31 (s, 1H, CH), 6.91–7.41 (m, 8H, pyrrole and benzene), 7.91 ppm (m, 1H, benzene); anal. $C_{22}H_{20}N_2O_5S$ (424.47) C, H, N, S.

11-(4-Chlorobenzoyloxymethyl)-10,11-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-5,5-dioxide (17k). 4-Chlorobenzoyl chloride (1.66 g, 1.21 mL, 0.0095 mol) was added dropwise into an ice-cooled solution of **17e** (2.51 g, 0.0095 mol) in dry pyridine (63 mL). The mixture was stirred at room temperature for 3.5 h then diluted with water and made acidic with 12 N HCl. After shaking with chloroform, the organic layer was isolated, washed with brine and dried. Removal of the solvent gave a crude product, which was purified by chromatography on silica gel (chloroform). Yield 50%; mp 192–194 °C (ethanol); IR: ν 1720 (CO), 3360 cm^{-1} (NH); ^1H NMR (90 MHz, $CDCl_3$): δ 4.90 (d, 2H, J=6.0 Hz, CH_2), 5.65 (broad, 1H, CH), 6.36 (m, 2H, pyrrole), 6.73 (m, 1H, benzene), 7.03 (d, 1H, J=9.0 Hz, benzene), 7.28–7.80 (m, 6H, pyrrole, benzene and NH), 8.06 ppm (d, 2H, J=9.0 Hz, benzene); anal. $C_{19}H_{15}ClN_2O_4S$ (402.85) C, H, N, Cl, S.

11-(4-Chlorophenylacetoxymethyl)-10,11-dihydro-5*H*-pyrrolo [1,2-*b*][1,2,5]benzothiadiazepine-5,5-dioxide (17l). This compound was prepared as described for **17k** using 4-chlorophenylacetyl chloride. Yield 81%; mp 124–125 °C (ethanol); IR: ν 1730 (CO), 3360 cm^{-1} (NH); ^1H NMR (90 MHz, $CDCl_3$): δ 3.70 (s, 2H, CH_2Ph), 4.46–4.93 (m, 2H, $CHCH_2$), 5.06 (broad s, 1H, NH, disappeared on treatment with D_2O), 5.50 (m, 1H, $CHCH_2$), 6.10 (m, 1H, pyrrole), 6.23 (t, 1H, pyrrole), 6.46 (d, 1H, J=9.0 Hz, benzene), 6.73 (m, 1H, benzene), 7.11–7.43 (m, 6H, pyrrole and benzene), 7.83 ppm (dd, 1H, J=1.5 and 9.0 Hz, benzene); anal. $C_{20}H_{17}ClN_2O_4S$ (416.87) C, H, N, Cl, S.

2-Ethoxycarbonyl-1-(5-chloro-2-nitrobenzenesulfonyl)-1*H*-pyrrole (18c). A solution of 2-ethoxycarbonyl-1*H*-pyrrole[39] (13.90 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, a solution of 5-chloro-2-nitrobenzenesulfonyl chloride[38] (25.60 g, 0.10 mol) in dry THF (210 mL) was slowly dropped into the ice-cooled suspension. 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 isolated, washed with brine and dried. Removal of the solvent afforded the crude product, which was purified by chromatography on alumina (chloroform). Yield 80%; mp 121–122 °C (toluene/cyclohexane); IR: ν 1710 cm^{-1} (CO); ^1H NMR (90 MHz, $CDCl_3$): δ 1.23 (t, 3H, J=7.5 Hz, $COOCH_2CH_3$), 4.18 (q, 2H, J=7.5 Hz, $COOCH_2CH_3$), 6.33 (t, 1H, J=3.0 Hz, pyrrole), 7.13 (dd, 1H, pyrrole), 7.63–7.93 (m, 3H, pyrrole and benzene), 8.33 ppm (d, 1H, J=1.5 Hz, benzene); anal. $C_{13}H_{11}ClN_2O_6S$ (358.75) C, H, N, Cl, S.

1-(2-Amino-4-chlorobenzenesulfonyl)-2-ethoxycarbonyl-1*H*-pyrrole (19b). Iron powder (12.5 g) was added over a period of 0.5 h to a stirred solution of **18b**[36] (15.00 g, 0.0415 mol) in glacial acetic acid (100 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 combined, washed with brine, and dried. The residue was purified on alumina column (chloroform). Yield 80%; mp 109 °C (ligroin); IR: ν 1690 (CO), 3360 and 3470 cm^{-1} (NH_2); ^1H NMR (90 MHz, $CDCl_3$): δ 1.26 (t, 3H, J=7.5 Hz, $COOCH_2CH_3$), 4.20 (q, 2H, J=7.5 Hz, $COOCH_2CH_3$), 5.26 (broad s, 2H, NH_2, disappeared on treatment with D_2O), 6.26 (t, 1H, pyrrole), 6.66 (m, 2H, benzene), 7.06 (dd, 1H, pyrrole), 7.53–7.76 ppm (m, 2H, pyrrole and benzene); anal. $C_{13}H_{13}ClN_2O_4S$ (328.77) C, H, N, Cl, S.

1-(2-Amino-5-chlorobenzenesulfonyl)-2-ethoxycarbonyl-1*H*-pyrrole (19c). This compound was prepared as described for **19b** starting from **18c**. Yield 80%; 143–145 °C (toluene/cyclohexane) (HPLC: retention time 3′58″); IR: ν 1700 (CO), 3360 and 3480 cm^{-1} (NH_2); ^1H NMR (200 MHz, DMSO-d_6): δ 1.20 (t, 3H,

J=7.0 Hz, $COOCH_2C\underline{H}_3$), 4.17 (q, 2H, J=7.0 Hz, $COOC\underline{H}_2CH_3$), 6.40 (m, 3H, NH_2 and H4 pyrrole), 6.88 (d, 1H, Hm benzene, J_{m-p}=9.0 Hz), 7.10 (m, 1H, H3, pyrrole J_{3-4}=3.5 Hz and J_{3-5}=1.7 Hz), 7.40 (dd, 1H, Hp benzene, J_{m-p}=9.0 Hz, J_{o-p}=2.5 Hz), 7.72 (d, 1H, Ho benzene, J_{o-p}=2.5 Hz), 8.04 ppm (m, 1H, H5 pyrrole); ^{13}C NMR-APT (200 MHz, DMSO-d_6): δ 13.82 (CH_3), 60.40 (CH_2), 109.90, 119.15, 123.16, 129.43, 130.59, and 135.24 (CH), 116.75, 117.60, 124.06, and 146.34 (C), 158.09 ppm (CO); ^{1}H NMR and ^{13}C NMR two dimensional correlation: δ 1.20, 13.82; 4.17, 60.40; 6.40, 109.90; 6.88, 119.15; 7.10, 123.16; 7.40, 135.24; 7.72, 129.43; 8.04, 130.59 ppm; anal. $C_{13}H_{13}ClN_2O_4S$ (328.77) C, H, N, Cl, S.

2-Ethoxycarbonyl-1-(2-fluorobenzenesulfonyl)-1*H*-pyrrole (20). This compound was prepared as described for **18c** by using 2-fluorobenzenesulfonyl chloride. Yield 82%; mp 61–62 °C (from ligroin); IR: ν 1710 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (t, 3H, J=7.1 Hz, $COOCH_2C\underline{H}_3$), 4.15 (q, 2H, J=7.1 Hz, $COOC\underline{H}_2CH_3$), 6.29 (t, 1H, J=3.5 Hz, pyrrole), 7.05 (m, 1H, pyrrole), 7.18 (t, 1H, J=9.8 Hz, benzene), 7.35 (t, 1H, J=7.3 Hz, benzene), 7.58 (m, 1H, benzene), 7.69 (m, 1H, pyrrole), 8.19 ppm (dt, 1H, J=1.7 and 8.0 Hz, benzene); anal. $C_{13}H_{12}FNO_4S$ (297.30) C, H, N, F, S.

1-(2-Fluorobenzenesulfonyl)-1*H*-pyrrole-2-carboxylic acid (21). Aqueous 2 N KOH (7.5 mL) was dropped into an ice-cooled solution of **20** (14.86 g, 0.05 mol) in ethanol (83 mL) and THF (55 mL). The reaction mixture was stirred at room temperature overnight, then poured on crushed ice, filtered and treated with 12 N HCl until pH 2 was reached. The precipitate was isolated by filtration, washed with water, dried and purified by crystallization from ethanol. Yield 36%; mp 188 °C (ethanol); IR: ν 1690 cm^{-1} (CO); ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.46 (t, 1H, J=3.5 Hz, pyrrole), 7.12 (dd, 1H, J=1.8 and 3.5 Hz, pyrrole), 7.41–7.54 (m, 2H, pyrrole and benzene), 7.78–7.85 (m, 2H, benzene), 8.03 ppm (dt, 1H, J=1.8 and 8.1 Hz, benzene); anal. $C_{11}H_8FNO_4S$ (269.24) C, H, N, F, S.

1-(2-Fluorobenzenesulfonyl)-1*H*-pyrrole-2-(*N*-cyclopropyl)carboxyamide (22b). A mixture of **21** (3.00 g, 0.011 mol), cyclopropylamine (0.91 g, 0.016 mol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimidehydrochloride (EDC, 2.10 g, 0.011 mol), 4-dimethylaminopyridine (DMAP, 1.34 g, 0.011 mol), dichloromethane (50 mL) and anhydrous THF (50 mL) was stirred at room temperature for 18 h. After concentration to a small volume, the residue was extraxted with ethyl acetate. The organic layer was isolated, washed with brine and dried. Removal of the solvent gave a crude product, which was purified by chromatography on silica gel (chloroform). Yield 51%; mp 161–162 °C (toluene); IR: ν 1630 (CO), 3280 cm^{-1} (NH); ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.49 and 0.63 [two m, 4H, $(CH_2)_2$ cyclopropane], 2.67 (m, 1H, CH cyclopropane), 6.39 (t, 1H, J=3.4 Hz, pyrrole), 6.80 (m, 1H, pyrrole), 7.40–7.65 (m, 2H, pyrrole and benzene), 7.80 (m, 1H, benzene), 8.00 (m, 1H, benzene), 8.40 ppm (m, 1H, benzene); anal. $C_{14}H_{13}FN_2O_3S$ (308.32) C, H, N, F, S.

1-(2-Fluorobenzenesulfonyl)-1*H*-pyrrole-2-(*N*-benzyl) carboxyamide (22a). This compound was prepared as described for **22b** using benzylamine. Yield 71%, mp 138–140 °C (toluene/cyclohexane); IR: ν 1660 (CO), 3380 cm^{-1} (NH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.45 (d, 2H, J=5.9 Hz, CH_2), 6.21 (t, 1H, J=3.4 Hz, pyrrole), 6.48 (broad t, 1H, NH), 6.60 (dd, 1H, J=1.6 and 3.4 Hz, pyrrole), 7.12 (t, 1H, J=9.9 Hz, benzene), 7.23–7.35 (m, 6H, pyrrole and benzene), 7.58 (m, 2H, benzene), 8.04 ppm (dt, 1H, J=1.5 and 8.1 Hz, benzene); anal. $C_{18}H_{15}FN_2O_3S$ (358.38) C, H, N, F, S.

1-(2-Aminobenzenesulfonyl)-2-ethoxycarbonylpyrrolidine (24). This compound was prepared as reported above for **19b** starting from **23**.[36] The crude product was used without further purification. Yield 89%; mp 73–74 °C (toluene/cyclohexane); IR: ν 1730 (CO), 3360 and 3460 cm^{-1} (NH_2); ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.06 (t, 3H, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 1.68–2.21 (m, 4H, pyrrolidine), 3.35 (m, 2H, pyrrolidine), 4.11 (q, 2H, J=7.0 Hz, $COOC\underline{H}_2CH_3$), 4.48 (m, 1H, pyrrolidine), 5.25 (broad s, 2H, NH_2, disappeared on treatment with D_2O), 6.71 (m, 2H, benzene), 7.31 (dt, 1H, J=1.5 and 9.0 Hz, benzene), 7.73 ppm (dd, 1H, J=1.5 and 9.0 Hz, benzene); anal. $C_{13}H_{18}N_2O_4S$ (298.36) C, H, N, S.

Antiviral assays

Compounds. Compounds were solubilized in DMSO at 100 μg/mL and then diluted in culture medium.

Cells and viruses. MT-4, C8166, H9/III$_B$ and CEM cells were grown at 37 °C in a 5% CO_2 atmosphere in RPMI 1640 medium, supplemented with 10% fetal calf serum (FCS), 100 IU/mL penicillin G and 100 μg/mL streptomycin. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco). Human immunodeficiency viruses type-1 (HIV-1, III$_B$ strain) and type-2 (HIV-2, ROD strain, kindly provided by Dr L. Montagnier, Paris) were obtained from supernatants of persistently infected H9/III$_B$ and CEM cells, respectively. HIV-1 and HIV-2 stock solutions had titres of 4.5×10^6 and 1.4×10^5 50% cell culture infectious dose ($CCID_{50}$)/mL, respectively.

HIV titration. Titration of HIV was performed in C8166 cells by the standard limiting dilution method (dilution 1:2, four replica wells per dilution) in 96-well plates. The infectious virus titre was determined by light microscope scoring of cytopathicity after 4 days of incubation and the virus titres were expressed as $CCID_{50}$/mL.

Anti-HIV assays. Activity of compounds against the HIV-1 and HIV-2 replication in acutely infected cells was based on the inhibition of virus-induced cytopathicity (CPE) in MT-4 cells. Briefly, 50 μL of culture medium containing 1×10^4 MT-4 cells were added to

each well of flat-bottomed microtitre trays containing 50 μL of culture medium with or without various concentrations of the test compounds. Then, 20 μL of an HIV-1 suspension containing 100 $CCID_{50}$ were added (m.o.i. = 0.01). After a 4 day incubation at 37 °C (8 days for HIV-2), the number of viable cells was determined by the 3-(4,5-dimethylthiazol-1-yl)-2.5-diphenyltetrazolium bromide (MTT) method.[50,51] Cytotoxicity of the compounds was evaluated in parallel with their antiviral activity. It was based on the viability of MT-4 cells, as monitored by the MTT method.

RT assays. RT assays were performed as previously described.[52] Briefly, highly purified recombinant reverse transcriptase (rRT) was assayed for its RNA-dependent DNA polymerase associated activity in a 50 μL volume containing: 50 mM Tris–HCl pH 7.8, 50 mM KCl, 6 mM $MgCl_2$, 1 mM DTT, 0.1 mg/mL BSA, 0.5 OD_{260} units/mL poly(rC)–oligo$(dG)_{12-18}$ 10 μM [^{3}H]-dGTP (1 Ci/mmol). After incubation for 20 min at 37 °C, the samples were spotted on glass fibre filters (Whatman GF /A) and the acid-insoluble radioactivity was determined.

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References

1. Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533.

2. De Clercq, E. *J. Acquired Immune Deficiency Syndromes* **1991**, *4*, 207.

3. Baba, M.; Debyser, Z.; Shigeta, S.; De Clercq, E. *Drugs Future* **1992**, *17*, 891.

4. De Clercq, E. In *Advances in Virus Research*; Maramorosch, K.; Murphy, F. A.; Shatkin, A. J., Eds.; Academic: San Diego, 1993; Vol. 42, pp 1–37.

5. Balzarini, J.; Camarasa M.-J.; Karlsson, A. *Drugs Future* **1993**, *18*, 1043.

6. Pattishall, K. H. In *The Search for Antiviral Drugs. Case Histories from Concept to Clinic*; Adams, J.; Merluzzi, V. J., Eds.; Birkhäuser: Boston, 1993; pp 23–43.

7. Lin, T. S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 109.

8. Fischl, M. A.; Richmann, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King, D. *N. Engl. J. Med.* **1987**, *317*, 185.

9. Faulds, D.; Brogden, N. R. *Drugs* **1992**, *44*, 94.

10. Baba, M.; Shigeta, S.; Tanaka, H.; Miyasaka, T.; Ubasawa, M.; Umezu, K.; Walker, R. T.; Pauwels, R.; De Clercq, E. *Antiviral Res.* **1992**, *17*, 245.

11. Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaekers, A.; Van Gelder, J.; Woestenborghs, R.; Heyrants, J.; Schellekens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. *Nature* **1990**, *343*, 470.

12. Kukla, M. J.; Breslin, H. J.; Pauwels, R.; Fedde, C. L.; Miranda, M.; Scott, M. K.; Sherrill, R. G.; Raeymaekers, A.; Van Gelder, J.; Andries, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 746.

13. Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Miranda, M.; Rodgers, J. D.; Sherrill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 3187.

14. Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G.; Gauthier, D. A.; Ho, C. Y.; Scott, M. K.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1995**, *38*, 771.

15. Ho, W.; Kukla, M. J.; Breslin, H. J.; Ludovici, D. W.; Grous, P. P.; Diamond, C. J.; Miranda, M.; Rodgers, J. D.; Ho, C. Y.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1995**, *38*, 794.

16. Hattox, S. E.; Norris, S. H.; Riska, P. S.; Silverstein, H. H.; St. George, R.; Johnstone, J. N.; Hargrave, K. D.; Grob, P. M. *Drugs Future* **1992**, *17*, 887.

17. Adams, J.; Klunder, J. M. In *Perspectives in Medicinal Chemistry*; Testa, B.; Kyburz, E.; Fuhrer, W.; Giger, R., Eds.; Verlag Helvetica Chimica Acta: Basel, 1993; Ch. 26, pp 407–425.

18. Proudfoot, J. R.; Patel, U. R.; Kapadia, S. R.; Hargrave, K. D., Abstracts of XIIIth International Symposium on Medicinal Chemistry, Paris, September 1994; poster 210.

19. De Lucca, G. V.; Otto, M. J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1639.

20. Klunder, J. M.; Hargrave, K. D.; West, M. A.; Cullen, E.; Pal, K.; Behnke, K. M. L.; Kapadia, S. R.; McNeil, D. W.; Wu, J. C.; Chow, G. C.; Adams, J. *J. Med. Chem.* **1992**, *35*, 1887.

21. Debyser, Z.; Pauwels, R.; Andries, K.; De Clercq, E. *J. Enzyme Inhib.* **1992**, *6*, 47.

22. Chimenti, F.; Vomero, S.; Nacci, V.; Scalzo, M.; Giuliano, R.; Artico, M. *Farmaco* **1974**, *8*, 589.

23. Stefancich, G.; Silvestri, R. *J. Heterocycl. Chem.* **1989**, *26*, 745.

24. Stefancich, G.; Artico, M.; Silvestri, R.; Pantaleoni, G. C.; Giorgi, R.; Palumbo, G. *Farmaco* **1990**, *45*, 7.

25. Stefancich, G.; Artico, M.; Silvestri, R.; Pantaleoni, G. C.; Giorgi, R.; Palumbo, G. *Farmaco* **1992**, *47*, 987.

26. Artico, M.; Silvestri, R.; Stefancich, G. *Synth. Commun.* **1992**, *22*, 1433.

27. Stefancich, G.; Artico, M.; Silvestri, R. *J. Heterocycl. Chem.* **1992**, *29*, 1005.

28. Stefancich, G.; Silvestri, R.; Artico, M. *J. Heterocycl. Chem.* **1993**, *30*, 529.

29. Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Artico, M. *Synth. Commun.* **1994**, *24*, 2685.

30. Silvestri, R.; Artico, M.; Pagnozzi, E.; Stefancich, G. *J. Heterocycl. Chem.* **1994**, *31*, 1033.

31. Stefancich, G.; Silvestri, R.; Pagnozzi E.; Artico, M. *J. Heterocycl. Chem.* **1994**, *31*, 867.

32. 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.

33. Massa, S.; Di Santo, R.; Costi, R.; Artico, M.; Loi, A. G.; Doa, M.; Scano, P.; La Colla, P. *Med. Chem. Res.* **1994**, *4*, 554.

34. Artico, M.; Massa, S.; Mai, A.; Marongiu, M. E.; Piras, G.; Tramontano, E.; La Colla, P. *Antiviral Chem. Chemother.* **1993**, *4*, 361.

35. Massa, S.; Mai, A.; Artico, M.; Sbardella, G.; Tramontano, E.; Loi, A. G.; Scano, P.; La Colla, P. *Antiviral Chem. Chemother.* **1995**, *6*, 1.

36. 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.

37. Meerwein, H.; Dittmar, G.; Göllner, R.; Hafner, K.; Mensch, F.; Steinfort, O. *Chem. Ber.* **1957**, *90*, 841.

38. De Cat, A.; Van Poucke, R. *J. Org. Chem.* **1963**, *28*, 3426.

39. Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51*, 100.

40. Prinsen, A. J.; Cerfontain, H. *Trav. Chim.* **1965**, *84*, 24.

41. Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030.

42. Hsu, M.-C.; Shutt, A. D.; Holly, M.; Slice, L. W.; Sherman, M. I.; Richman, D. D.; Potash, M. J.; Volsky, D. J. *Science* **1991**, *254*, 1799.

43. Hsu, M.-C.; Tam, S. In *The Search for Antiviral Drugs. Case Histories from Concept to Clinic*; Adams, J.; Merluzzi, V. J., Eds.; Birkhäuser: Boston, 1993; p 153.

44. Sahlberg, C.; Engelhardt, P.; Johansson, N.-G.; Noréen, R.; Öberg, B.; Vrang, L.; Zhang, H. Abstracts of XIIIth International Symposium on Medicinal Chemistry, Paris, September 1994; poster 209.

45. Tucker, T. J.; Lyle, T. A.; Wiscoiunt, C. M.; Britcher, S. F.; Young, S. D.; Sanders, W. M.; Lumma, W. C.; Goldman, M. E.; O'Brien, J. A.; Ball, R. G.; Homnick, C. F.; Schleif, W. A.; Emini, E. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 2437.

46. Proudfoot, J. R.; Hargrave, K. D.; Grozinger, K.; Cullen, E.; Mauldin, S.; Kapadia, S. R.; Patel, U. R.; Fuchs, V.; McNeil, D.; Raghavan, P.; David, E.; Grob, P.; Rose, J.; Shih, C.-K.; Adams, J. Abstracts of XIIIth International Symposium on Medicinal Chemistry, Paris, September 1994; poster 211.

47. Proudfoot, J. R.; Patel, U. R.; Kapadia, S. R.; Hargrave, K. D. *J. Med. Chem.* **1995**, *38*, 1406.

48. Schäfer, W.; Friebe, W.-G.; Leinert, H.; Mertens, A.; Poll, T.; von der Saal, W.; Zilch, H.; Nuber, B.; Ziegler, M. L. *J. Med. Chem.* **1993**, *36*, 726.

49. Terrett, N. K.; Bojanic, D.; Merson, J. R.; Stephenson, P. T. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1745.

50. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309.

51. Pauwels, R.; De Clercq, E.; Desmyter, J.; Balzarini, J.; Goubau, P.; Herdewijn, P.; Vanderhaeghe, H.; Vandeputte, M. *J. Virol. Methods* **1987**, *16*, 171.

52. Tramontano, E.; Cheng, Y.-C. *Biochem. Pharmacol.* **1992**, *43*, 1371.

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