Synthesis of Pyrryl Aryl Sulfones Targeted at the HIV-1 Reverse Transcriptase

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Various aryl 1-pyrryl sulfones were synthesized and tested as inhibitors of HIV-1. 2-Nitrophenyl-2-ethoxycarbonyl-1-pyrryl sulfone, the most active among test derivatives, was selected as lead compound of the aryl pyrryl sulfone series. The *in vitro* anti-HIV-1 activity and cytotoxicity of 41 compounds is reported. Some structure-activity relationships are discussed also in comparison with the known NPPS (2-nitrophenyl phenyl sulfone).

Synthese von Pyrryl-aryl-sulfonen als Hemmstoffe der Reversen Transkriptase des HIV-1

Verschiedene 1-Pyrryl-sulfone werden synthetisiert und auf Hemmwirkung gegen HIV-1 geprüft. 2-Nitrophenyl-2-ethoxycarbonyl-1-pyrryl-sulfon, die wirksamste der Test-Verbindungen, wurde zur Leitsubstanz in der Aryl-pyrryl-sulfon-Reihe. *in vitro*-anti-HIV-Aktivität und Cytotoxizität von 41 Verbindungen werden beschrieben. Einige Struktur-Wirkung-Beziehungen werden auch unter Bezug auf das bekannte NPPS (2-Nitrophenyl-phenyl-sulfon) diskutiert.

The search for new chemotherapeutic agents capable to inhibit retrovirus replication became urgent after the discovery that human immunodeficiency viruses (HIV-1 and HIV-2) were the etiological agents of AIDS[1,2]. Nucleoside analogues such as AZT, ddI and ddC[3], have been among the first anti-HIV compounds described, followed by non-nucleoside compounds, also targeted at the reverse transcriptase (RT).

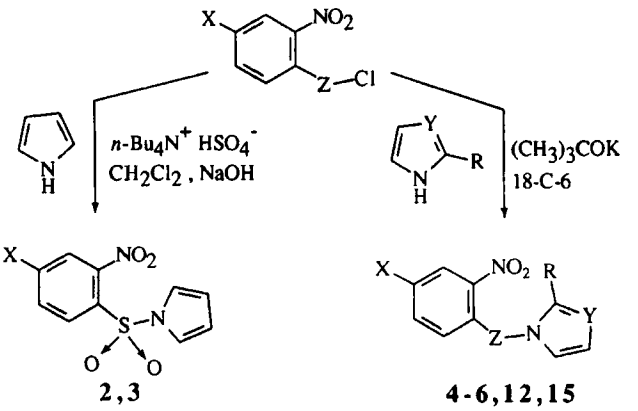
Recently, diarylsulfones have emerged as a new chemical class of non-nucleoside reverse transcriptase inhibitors and some structural features responsible for their antiviral activity have been identified: a nitro group *ortho* to the position of the sulfur attachment and the oxidation state of sulfur atom. 2-Nitrophenyl phenyl sulfone (**1**, NPPS) was selected as lead compound after a detailed investigation of anti-HIV-1 activity of various diarylsulfones[4].

Our interest in derivatives bearing a pyrrole ring as potential inhibitors of HIV-1 replication prompted us to synthesize and test *in vitro* against HIV-1 various pyrryl nitrophenyl sulfones (**2-5**, **7**, **8**) and some related derivatives (**6**, **9-41**) (Table 1).

Chemistry

Compounds **4**[5], **12**[6], **13**[7], **14**[7], **16**[8], **17**[5], **18**[9], **19**[10], **20**[10], **21**[8], **22**[10], **23-25**[11], and **26**[12], have been described by us.

Nitroderivatives **2**[13] and **3** were prepared by phase-transfer reaction of the 2-nitrobenzenesulfonyl chloride or its 4-chloroderivative[14] with pyrrole in the presence of *n*-tetrabutylammonium hydrogen sulfate.



Scheme 1; for R, X, and Z see Table 1

Compounds **5** and **6** were obtained by reaction of 4-chloro-2-nitrobenzenesulfonyl chloride or 2-nitrobenzenesulfonyl chloride with 2-ethoxycarbonyl-1*H*-pyrrole[15] or 1*H*-imidazole, respectively, in the presence of potassium tert-butoxide and 18-crown-6. **15** was also prepared starting from 2-nitrobenzenesulfenyl chloride and 2-ethoxycarbonyl-1*H*-pyrrole (Scheme 1).

Alkaline hydrolysis of **4** afforded the acid **8**. This compound was transformed into **7** by reaction with ethyl chloroformate in the presence of 4-methylmorpholine followed by treatment of the intermediate mixed anhydride with glycine ethyl ester hydrochloride (Scheme 2).

Ester **9** was prepared as reported for the corresponding methyl ester[16] by treating the known acid **10**[17] firstly with oxalyl chloride and then with anhydrous ethanol. The synthesis of the acid **11** was achieved starting from 2-nitroben-

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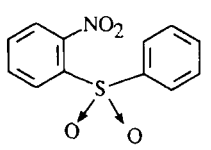
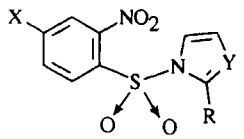
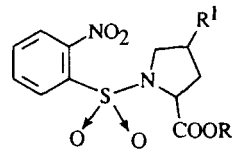
Table 1: Chemical Structure of Derivatives **1-41**



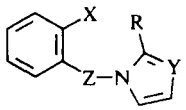
1 NPPS



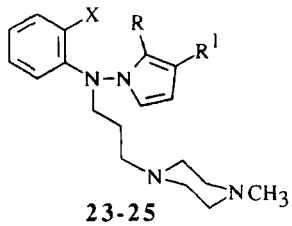
2-8



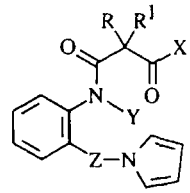
9-11



12-22



23-25



26-41

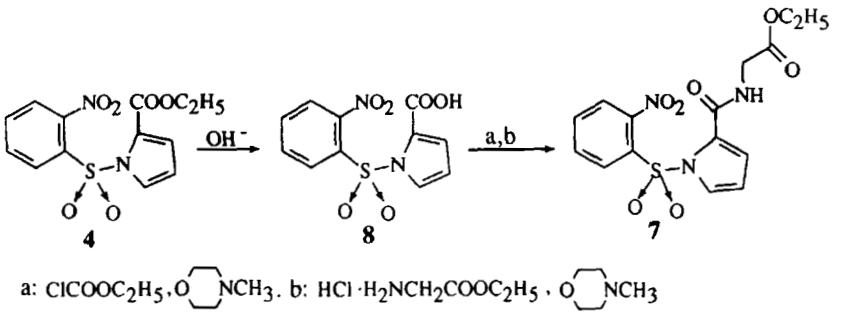
Compd	X	Y	Z	R	R^1
2	H	CH	-	H	-
3	Cl	CH	-	H	-
4	H	CH	-	$COOC_2H_5$	-
5	Cl	CH	-	$COOC_2H_5$	-
6	H	N	-	H	-
7	H	CH	-	$CONHCH_2COOC_2H_5$	-
8	H	CH	-	COOH	-
9	-	-	-	C_2H_5	H
10	-	-	-	H	H
11	-	-	-	H	OH
12	NO_2	CH	S	H	-
13	NO_2	CH	NH	H	-
14	NO_2	CH	NCH_3	H	-
15	NO_2	CH	S	$COOC_2H_5$	-
16	NO_2	CH	CH_2	$COOC_2H_5$	-
17	NH_2	CH	SO_2	$COOC_2H_5$	-
18	NHCHO	CH	SO_2	H	-
19	NO_2	N	CH_2	$COOC_2H_5$	-
20	NH_2	N	CH_2	$COOC_2H_5$	-
21	NH_2	CH	CH_2	$COOC_2H_5$	-
22	NO_2	N	CH_2	$COCCl_3$	-
23	NO_2	-	-	H	CHO
24	NO_2	-	-	CHO	-
25	NHCHO	-	-	H	H
26	OCH_3	H	NCH_3	H	H
27	OCH_3	H	SO_2	H	H
28	OH	H	SO_2	H	H
29	NH_2	H	SO_2	H	H
30	NH-C_6H_4-*p*Cl	H	SO_2	H	H
31	OCH_3	H	SO_2	CH_3	H
32	OH	H	SO_2	CH_3	H
33	NH_2	H	SO_2	CH_3	H
34	NH-C_6H_4-*p*Cl	H	SO_2	CH_3	H
35	OCH_3	H	SO_2	CH_3	CH_3
36	OH	H	SO_2	CH_3	CH_3
37	NH_2	H	SO_2	CH_3	CH_3
38	NH-C_6H_4-*p*Cl	H	SO_2	CH_3	CH_3
39	OCH_3	CH_3	SO_2	CH_3	CH_3
40	OH	CH_3	SO_2	CH_3	CH_3
41	OCH_3	H	S	H	H

zenesulfonyl chloride and 4-hydroxyproline in alkaline medium as reported for **10** (Scheme 3).

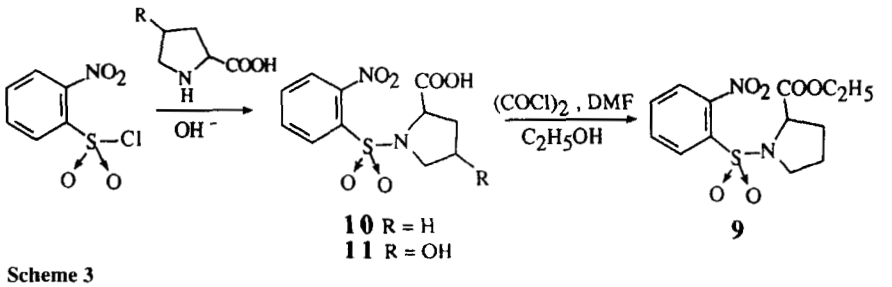
Reaction of methyl malonyl chloride with 1-(2-aminobenzenesulfonyl)-1*H*-pyrrole[13] or with 1-(2-aminobenzenesulfenyl)-1*H*-pyrrole[6] in the presence of triethylamine led to the amides **27** and **41**, respectively.

Compound **27** was methylated to **31**, which reacted with iodomethane/K_2CO_3 to afford **35**. A direct synthesis of **35** starting from **27** was also performed. *N*-Methylation of **35** to afford **39** was carried out with iodomethane/potassium *tert*-butoxide and 18-crown-6 (Scheme 4).

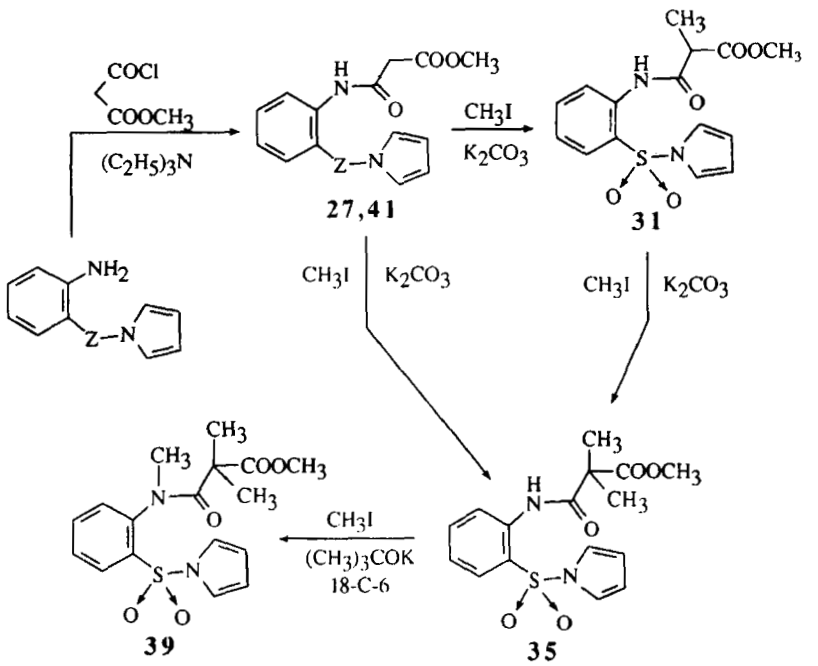
Alkaline hydrolysis of esters **27**, **31**, **35**, and **39** furnished the corresponding acids **28**, **32**, **36**, and **40**. Treatment of **27**, **31**, and **35** with an excess of conc. NH_4OH yielded the related amides **29**, **33**, and **37**. Reaction of **28**, **32**, and **36** with 4-chloroaniline in the presence of *N*-(3-dimethylami-



Scheme 2



Scheme 3



Scheme 4

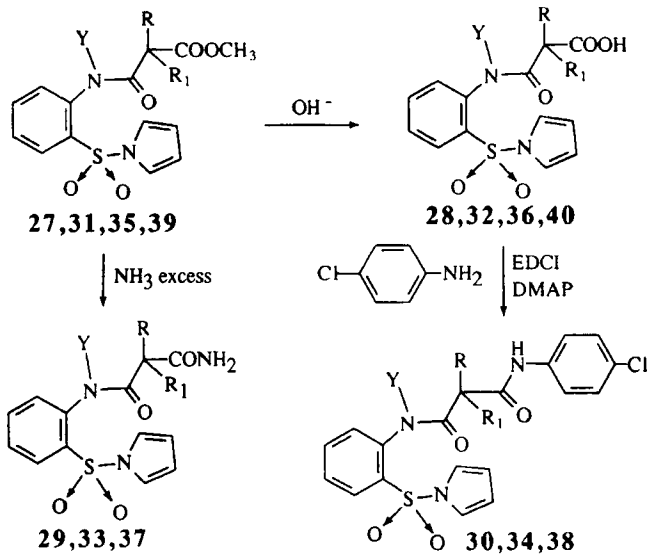
nopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP) furnished the corresponding anilides **30**, **34**, and **38** (Scheme 5).

Antiviral Assays

Materials and Experimental Procedures

Anti-HIV-1 Assays

The activity of the compounds against HIV-1 (HTLV-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 cells. Briefly, 50 µl of culture medium containing 1 x 10^4 MT-4 cells were added to each well of flat-bottomed microtiter trays containing 50 µl of culture medium with or without various concentrations of the test compounds. 20 µl of an HIV-1 or HIV-2 suspension containing 100 $CCID_{50}$ (50% cell culture infective dose) were then added. After a 4-day incubation at 37°C, the number of viable MT-4 cells was determined by the 3-(4,5-dimethylthiazol-1-yl)-2,5-diphenyl tetrazolium bromide (MTT) method. 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[18].



Scheme 5

Reverse Transcriptase Assays

Assays were performed as described[19]. Briefly, highly purified recombinant reverse transcriptase (rRT) was assayed for its RNA 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^{-1} BSA, 0.5 OD260 units ml^{-1} poly(rC)-oligo$(dG)_{12-18}$, 10 µM [^{3}H]-dGTP (1 Ci $mmol^{-1}$). After incubation for 20 min at 37°C, samples were spotted on glass fibre filters (Whatman GF/A) and the acid-insoluble radioactivity was determined.

Results and Discussion

As reported in Table 2, eight compounds (**4**, **13**, **16**, **17**, **23**, **25**, **26**, and **27**) were found selectively active as anti-HIV-1 agents. The best activity was shown by compound **4**, a 2-nitrophenyl 1-pyrryl sulfone bearing a carbethoxy group at the position 2 of pyrrole.

Hydrolysis of the ester function to give **8** and reduction of the nitro group to afford **17**, led to compounds endowed with moderate activity.

Substitution of the pyrrole with a pyrrolidine ring yielded inactive derivatives (compare **4** with **9** and the related acids **10** and **11**).

Among derivatives deprived of substituents in the heterocyclic ring only compound **13** showed a moderate activity, whereas the other derivatives were totally inactive.

Substitution of SO_2 with S (compound **15**) or CH_2 (compound **16**) abated the activity of **4**.

Derivatives with aryl and pyrryl moieties linked by an N-atom showed some activity (**13**, **23**, **25**, and **26**).

Replacement of phenyl, the substituent of NPPS, with pyrrole (compound **2**) or imidazole (compound **6**) led to inactive products. Introduction of chlorine at the 4-position of the 2-nitrophenyl moiety afforded the inactive products **3** and **5**.

Replacement of SO_2 of **4** with CH_2 yielded compound **16** which retained some of the initial anti-HIV-1 activity of the sulfone. However, the activity of **4** and **16** was abated when an imidazole replaced the pyrrole (compare **19** with **16** and **4**).

Only derivatives bearing a carbethoxy group in the pyrrole ring exhibited anti-HIV-1 activity (**4** > **16** > **17**).

In conclusion, we confirm that the anti-HIV-1 activity is associated with the aromatic sulfone structure; however, unlike NPPS the aryl pyrryl sulfones are active only when a carbethoxy group is present at the 2-position of the pyrrole ring.

The most active derivative **4** can be considered a new lead compound and its activity needs to be improved by chemi-

Table 2: Anti-HIV Activities of Derivatives **2-41**

compd	CC_{50}[a]	EC_{50}[b]	S.I.[c]
2	36.35	>36.35	-
3	15.38	>15.38	-
4	>308	15.08	>20
5	>278.7	>278.7	-
6	14.45	>14.45	-
7	>262.2	>262.2	-
8	>337.5	>337.5	-
9	255	>255	-
10	>333	>333	-
11	>316.2	>316.2	-
12	95.57	>95.57	-
13	>492	354	>1.4
14	>460	>460	-
15	13.41	>13.41	-
16	>364.6	55.61	>6.3
17	≥339	310	≥1.1
18	>399.56	>399.56	-
19	>363.3	>363.3	-
20	>407	>407	-
21	>409.36	>409	-
22	163.8	>163.8	-
23	134	89.35	1.5
24	>178	>178	-
25	>197.4	175	>1.1
26	>348	40	>8.7
27	>370	63	>5.8
28	>325	>325	-
29	>325	>325	-
30	48	>48	-
31	>279	>279	-
32	>310	>310	-
33	>311	>311	-
34	23	>23	-
35	>285	>285	-
36	>297	>297	-
37	>298	>298	-
38	>224	>224	-
39	>274	>274	-
40	>285	>285	-
41	>344	>344	-
NPPS[d]	-	3.4	-

[a] 'Cytotoxic concentration (µM) of compound required to reduce the viability of mock-infected MT-4 cells by 50%.

[b] 'Effective concentration (µM) of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1.

[c] 'Selectivity index: ratio CC_{50}/EC_{50}.

[d] 'Data taken from lit.[4].

cal modifications. Our first attempts in this direction failed to yield products with higher potency (compare derivatives **5**, **15**, **16**, **20**, and **21**).

Unlike the NPPS diarylsulfone structure, the 2-nitrophenyl 1-pyrryl sulfone skeleton needs, in order to be active as an anti-HIV agent, the presence of a carbethoxy function. However, NO_2 and SO_2 groups are also of capital importance for inhibition of the HIV-1 multiplication; in fact their modification (*i.e.* NO_2 to NH_2 and SO_2 to S) abolished the antiviral activity.

The lack of activity showed by the acid **8** indicated that inhibition of HIV-1 is strictly associated with the ester function.

None of the compounds was effective in reducing the HIV-1 yield in chronically infected H9/III_B cells, nor the HIV-2 multiplication in acutely infected C 8166 cells.

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Experimental Part

M.p.: Büchi 510 (uncorr.).- IR-spectra (nujol mulls): Perkin Elmer 1310.- ^{1}H-NMR-spectra: Varian EM-390 (90 MHz), Varian Gemini (200 MHz), TMS. The recorded data were consistent with the assigned structure. δ in ppm.- Column chromatography: silica gel Merck (70-230 Mesh) and alumina Merck (70-230 Mesh).- TLC: 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).- Microanalyses: Laboratories of Prof. A. Pietrogrande, University of Padova (Italy). Elemental analyses were found within ± 0.3% of the theoretical values.- Organic extracts were dried over anhydrous Na_2SO_4.- Evaporation of solvents under reduced pressure.

1-(2-Nitrobenzenesulfonyl)-1H-pyrrole (**2**)

A solution of 2-nitrobenzenesulfonyl chloride (88.65 g, 0.40 mol) in CH_2Cl_2 (100 ml) was dropped onto an ice-cooled well-stirred mixture of pyrrole (17.44 g, 0.26 mol), *n*-tetrabutylammonium hydrogen sulfate (8.82 g, 0.026 mol), CH_2Cl_2 (110 ml) and 50% NaOH (210 ml). The reaction was kept at room temp. overnight, then filtered and diluted with H_2O (100 ml) and CH_2Cl_2 (100 ml). After shaking, the org. layer was separated, washed with brine and dried. After removal of the solvent the residue was purified on a silica gel column ($CHCl_3$). Yield 33%; m.p. 69-71°C (toluene/ligroin); lit.[13]: m.p. 67-68°C.

1-(4-Chloro-2-nitrobenzenesulfonyl)-1H-pyrrole (**3**)

Prepared as above starting from 4-chloro-2-nitrobenzenesulfonyl chloride. Yield 25%; m.p. 79-80°C (ligroin).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 6.38 (t, J = 2.2 Hz, 2H pyrrole), 7.23 (t, J = 2.2 Hz, 2H, pyrrole), 7.63-7.80 (m, 3H, benzene).- $C_{10}H_7ClN_2O_4S$ (286.70) (C, H, N, Cl, S).

2-Ethoxycarbonyl-1-(4-chloro-2-nitrobenzenesulfonyl)-1H-pyrrole (**5**)

A solution of 2-ethoxycarbonyl-1*H*-pyrrole[15] (20.87 g, 0.15 mol) in anhydrous THF (320 ml) was added dropwise to a stirred mixture of 18-crown-6 (4.23 g, 0.016 mol) and potassium *tert*-butoxide (20.20 g, 0.15 mol) in the same solvent (320 ml). After 15 min a solution of 4-chloro-2-nitrobenzenesulfonyl chloride (38.41 g, 0.15 mol) in anhydrous THF (320 ml) was slowly dropped while cooling on an ice-bath. Stirring was continued at room temp. for 3.5 h. After concentration to a small volume, H_2O and CH_2Cl_2 were added by shaking. The org. layer was separated, washed with brine and dried. Removal of the solvent gave a residue which was purified by passing through an alumina column ($CHCl_3$). Yield 71%; m.p. 124-125°C (toluene/cyclohexane).- IR: $\tilde{\nu}$ = 1710 cm^{-1} (CO).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.23 (t, J = 7 Hz, 3H, $COOCH_2C\underline{H}_3$), 4.26 (q, J = 7 Hz, 2H, $COOC\underline{H}_2CH_3$), 6.30 (t, J = 3 Hz, 1H, pyrrole), 7.10 (q, J = 1.8 Hz, 1H, pyrrole), 7.60-7.73 (m, 3H, pyrrole and benzene), 8.36 (d, J = 8 Hz, 1H, benzene).- $C_{13}H_{11}ClN_2O_6S$ (358.75) (C, H, Cl, N, S).

1-(2-Nitrobenzenesulfonyl)-1H-imidazole (**6**)

Prepared from 2-nitrobenzenesulfonyl chloride and 1*H*-imidazole as reported for **5**. The reaction was kept at room temp. overnight. The crude product was purified on a silica gel column (ethyl acetate). Yield 70%; m.p. 110-111°C (toluene/cyclohexane).- ^{1}H-NMR (90 MHz) (CD_3OD): δ 7.18 (m, 1H), 7.65 (m, 1H), 7.71-8.11 (m, 3H), 8.25-8.48 ppm (m, 2H).- $C_9H_7N_3O_4S$ (253.23) (C, H, N, S).

2-Ethoxycarbonylmethyleneaminocarbonyl-1-(2-nitrobenzenesulfonyl)-1H-pyrrole (**7**)

A solution of ethyl chloroformate (0.80 g, 0.0074 mol) in anhydrous THF (7 ml) was dropped onto a solution of **8** (2.19 g, 0.0074 mol) and 4-methylmorpholine (0.75 g, 0.0074 mol) in the same solvent (45 ml) while cooling to -15°C. After 15 min a mixture of glycine ethyl ester hydrochloride (1.03 g, 0.0074 mol) and 4-methylmorpholine (0.75 g, 0.0074 mol) in anhydrous THF (15 ml) was added in one portion, then the reaction was stirred at room temp. for 1 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The org. layer was separated, washed with brine and dried. Removal of the solvent gave a residue, which was purified by chromatography on a silica gel column (CH_2Cl_2). Yield 14%; m.p. 126-127°C (benzene/petroleum ether).- IR: $\tilde{\nu}$ = 1650 and 1750 (CO), 3340 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.25 (t, J = 7 Hz, 3H, $COOCH_2C\underline{H}_3$), 3.98-4.38 (m, 4H, $COOC\underline{H}_2CH_3$ and CH_2), 6.28 (t, J = 3 Hz, 1H, pyrrole), 6.55 (broad, 1H, NH, exch. by D_2O), 6.75 (q, J = 1.5 Hz, 1H, pyrrole), 7.28 (q, J = 1.5 Hz, 1H, pyrrole), 7.71-7.88 (m, 3H, benzene), 8.28 (m, 1H, benzene).- $C_{15}H_{15}N_3O_7S$ (381.36) (C, H, N, S).

1-(2-Nitrobenzenesulfonyl)-1H-pyrrole-2-carboxylic acid (**8**)

A mixture of **4**[5] (1.00 g, 0.003 mol), N KOH (4.0 ml), ethanol (12 ml) and THF (12 ml) was stirred at room temp. for 5 h, then poured on crushed ice and treated with N HCl until pH 2. After extraction with ethyl acetate, the org. layer was washed with brine and dried. Evaporation of the solvent gave the crude acid which was purified by crystallization from toluene. Yield 60%; m.p. 213-214°C.- IR: $\tilde{\nu}$ = 1680 cm^{-1} (CO).- ^{1}H-NMR (90 MHz) ([D_6]DMSO): δ 6.51 (t, J = 3 Hz, 1H, pyrrole), 7.15 (q, J = 1.5 Hz, 1H, pyrrole), 7.65-8.25 (m, 5H, pyrrole and benzene), 12.91 (broad, 1H, COOH, exch. by D_2O).- $C_{11}H_8N_2O_6S$ (296.25) (C, H, N, S).

2-Ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)pyrrolidine (**9**)

Oxalyl chloride (15.86 g, 0.125 mol) and anhydrous *N,N*-dimethylformamide (0.6 ml) were sequentially added into a suspension of **10**[17] in anhydrous toluene (250 ml). The resulting solution was stirred at room temp. under N_2 for 3 h. Absol. ethanol (250 ml) was then added and stirring was maintained for 1 h. After concentration ethyl acetate and $NaHCO_3$ solution were added by shaking. The org. layer was separated, washed with brine and dried. Evaporation of solvents gave satisfactorily pure **9**. Yield 83%; m.p. 107-108°C (toluene/cyclohexane).- IR: $\tilde{\nu}$ = 1740 cm^{-1} (CO).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.16 (t, J = 7 Hz, 3H, $COOCH_2C\underline{H}_3$), 1.80-2.33 (m, 4H, 3-H and 4-H pyrrolidine), 3.60 (m, 2H,

5-H pyrrolidine), 4.10 (q, J = 7 Hz, 2H, $COOCH_2CH_3$), 4.56 (m, 1H, 2-H pyrrolidine), 7.66 (m, 3H, benzene), 8.13 (m, 1H, benzene).- $C_{13}H_{16}N_2O_6S$ (328.34) (C, H, N, S).

4-Hydroxy-1-(2-nitrobenzenesulfonyl)pyrrolidine-2-carboxylic acid (**11**)

2-Nitrobenzenesulfonyl chloride (22.16 g, 0.10 mol) was added portionwise over a period of 5 min to a well-stirred and water-cooled solution of 4-hydroxypyrrolidine-2-carboxylic acid (13.11 g, 0.10 mol) in 3N NaOH (70 ml). After 30 min the mixture was filtered and the solution was made acidic with 37% HCl. After extraction with ethyl acetate, the org. layer was washed with brine and dried. Evaporation of the solvent gave an oily residue which solidified by trituration with CCl_4. The crude acid was purified by crystallization from ethyl acetate/n-hexane. Yield 76%; m.p. 159-161°C.- IR: $\tilde{\nu}$ = 1710 and 1740 (CO), 3420 cm^{-1} (OH).- ^{1}H-NMR (200 MHz) ([D_6]DMSO): δ 1.95-2.25 (m, 2H, 3-H-pyrrolidine), 3.30-3.60 (m, 2H, 5H-pyrrolidine), 4.30 (m, 1H, 4-H-pyrrolidine), 4.45 (t, 1H, 2-H-pyrrolidine), 5.12 (s, 1H, OH, exch. by D_2O), 7.78-8.14 (m, 4H, benzene).- $C_{11}H_{12}N_2O_7S$ (316.28) (C, H, N, S).

2-Ethoxycarbonyl-1-(2-nitrobenzenesulfenyl)-1H-pyrrole (**15**)

15 was prepared as reported for **5** starting from 2-nitrobenzenesulfenyl chloride and 2-ethoxycarbonyl-1*H*-pyrrole. Yield 71%; m.p. 83-84°C (cyclohexane).- IR: $\tilde{\nu}$ = 1700 cm^{-1} (CO).- $C_{13}H_{12}N_2O_4S$ (292.31) (C, H, N, S).

1-[2-(2-Methoxycarbonylacetamido)benzenesulfonyl]-1H-pyrrole (**27**)

A solution of methyl malonyl chloride (6.82 g, 0.05 mol) in anhydrous THF (20 ml) was dropped into an ice-cooled solution of 1-(2-aminobenzenesulfonyl)-1*H*-pyrrole (11.11 g, 0.05 mol) and triethylamine (5.60 g, 0.05 mol) in the same solvent (100 ml). The reaction was stirred at room temp. overnight, then filtered and the solvent evaporated. The residue was purified by chromatography (SiO_2/$CHCl_3$). Yield 52%; m.p. 124°C (ethanol).- IR: $\tilde{\nu}$ = 1690 and 1740 (CO), 3340 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 3.56 (s, 2H, CH_2), 3.85 (s, 3H, CH_3), 6.31 (t, J = 2.2 Hz, 2H, pyrrole), 7.11-7.35 (m, 3H, pyrrole and benzene), 7.61 (m, 1H, benzene), 7.88 (m, 1H, benzene), 8.45 (d, J = 8 Hz, 1H, benzene), 10.08 (s, 1H, NH, exch. by D_2O).- $C_{14}H_{14}N_2O_5S$ (322.23) (C, H, N, S).

1-[2-(Acetamido-2-carboxy)benzenesulfonyl]-1H-pyrrole (**28**)

A mixture of **27** (2.50 g, 0.0077 mol), N KOH (10 ml), ethanol (28 ml) and THF (34 ml) was stirred at room temp. for 3 h, then poured on crushed ice and acidified with N HCl until pH 2. After extraction with ethyl acetate the org. layer was separated, washed with brine and dried. Removal of the solvent gave the crude acid, which was purified by crystallization from toluene. Yield 87%; m.p. 134-135°C.- IR: $\tilde{\nu}$ = 1670 and 1720 (CO), 3360 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 3.50 (s, 2H, CH_2), 6.30 (t, J = 2.2 Hz, 2H, pyrrole), 7.26-7.50 (m, 3H, pyrrole and benzene), 7.70 (m, 1H, benzene), 7.96 (m, 2H, benzene), 10.03 (broad, 2H, NH and OH, exch. by D_2O).- $C_{13}H_{12}N_2O_5S$ (308.30) (C, H, N, S).

1-[2-(Acetamido-2-carboxyamide)benzenesulfonyl]-1H-pyrrole (**29**)

A solution of **27** (0.50 g, 0.0015 mol) in ethanol (15 ml) was treated with 30% NH_4OH (5 ml) while heating at 60°C. Every 2 h the same amount of 30% NH_4OH was added. After 6 h the solution was cooled and extracted with ethyl acetate. The org. layer was washed with N acetic acid, then with brine and dried. Removal of the solvent gave a residue which was purified on a silica gel column (ethyl acetate). Yield 63%; m.p. 143-144°C (toluene).- IR: $\tilde{\nu}$ = 1650 and 1680 (CO), 3380 and 3420 cm^{-1} (NH and NH_2).- ^{1}H-NMR (90 MHz) ([D_7]DMF): δ 3.53 (s, 2H, CH_2), 6.53 (t, J = 2.2 Hz, 2H, pyrrole), 7.30-7.83 (m, 4H, pyrrole and benzene), 7.93-8.43 ppm (m, 3H, benzene and NH, 1H exch. by D_2O).- $C_{13}H_{13}N_3O_4S$ (307.32) (C, H, N, S).

1-{2-[Acetamido-2-(4-chlorophenyl)carboxyamide]benzenesulfonyl}-1H-pyrrole (**30**)

A mixture of **28** (1.00 g, 0.0032 mol), 4-choroaniline (0.41 g, 0.032 mol), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (0.62 g, 0.0032 mol), 4-dimethylaminopyridine (0.39 g, 0.0032 mol) and anhydrous THF (10 ml) was stirred at room temp. for 48 h. The solvent was evaporated and the residue extracted with ethyl acetate. The org. layer was separated, washed with 10% HCl, then with brine and dried. Removal of the solvent gave a product which was purified by chromatography (SiO_2/$CHCl_3$). Yield 48%; m.p. 156°C (benzene/cyclohexane).- IR: $\tilde{\nu}$ = 1680 (CO), 3270 and 3320 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ([D_6]DMSO): δ 3.70 (s, 2H, CH_2), 6.33 (t, J = 2.2 Hz, 2H, pyrrole), 7.33-7.56 (m, 5H, pyrrole and benzene), 7.66-7.90 (m, 3H, benzene), 7.93-8.33 (m, 2H, benzene), 12.13 and 12.50 (2s, 2H, NH, exch. by D_2O).- $C_{19}H_{16}ClN_3O_4S$ (417.86) (C, H, N, Cl, S).

1-[2-(2-Methoxycarbonylpropionamido)benzenesulfonyl]-1H-pyrrole (**31**)

A mixture of **27** (4.83 g, 0.015 mol), ICH_3 (2.13 g, 0.015 mol), K_2CO_3 (3.04 g, 0.022 mol) and acetone (130 ml) was stirred at room temp. overnight. After concentration to a small volume, the residue was extracted with ethyl acetate. The org. layer was separated, washed with brine and dried. Removal of the solvent gave a product which was purified by chromatography (SiO_2/CH_2Cl_2). The first fractions were discarded and further elution afforded compound **31**. Yield 70%; m.p. 89-90°C (cyclohexane).- IR: $\tilde{\nu}$ = 1700 and 1740 (CO), 3360 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.36 (d, J = 7 Hz, 3H, CH_3), 3.56 (q, J = 7 Hz, 1H, CH), 3.83 (s, 3H, CH_3), 6.39 (t, J = 2.2 Hz, 2H pyrrole), 7.10-7.36 (m, 3H, pyrrole and benzene), 7.60 (m, 1H, benzene), 7.86 (m, 1H, benzene), 8.56 (d, J = 8 Hz, 1H, benzene), 9.93 ppm (s, 1H, NH, exch. by D_2O).- $C_{15}H_{16}N_2O_5S$ (336.36) (C, H, N, S).

1-[2-(Propionamido-2-carboxy)benzenesulfonyl]-1H-pyrrole (**32**)

Prepared as reported for **28** starting from **31**. Yield 59%; m.p. 118-119°C (toluene/cyclohexane).- IR: $\tilde{\nu}$ = 1650 and 1710 (CO), 3390 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ([D_6]DMSO): δ 1.33 (d, J = 7 Hz, 3H, CH_3), 3.75 (q, J = 7 Hz, 1H, CH), 6.35 (t, J = 2.2 Hz, 2H, pyrrole), 7.28-7.55 (m, 3H, pyrrole and benzene), 7.75-8.15 (m, 3H, benzene), 9.91 (s, 1H, NH, exch. by D_2O).- $C_{14}H_{14}N_2O_5S$ (322.33) (C, H, N, S).

1-[2-(Propionamido-2-carboxyamide)benzenesulfonyl]-1H-pyrrole (**33**)

Prepared as reported for **29** starting from **31**. Yield 93%; m.p. 161-162°C (toluene).- IR: $\tilde{\nu}$ = 1650 and 1670 (CO), 3310 and 3380 cm^{-1} (NH and NH_2).- ^{1}H-NMR (90 MHz) ([D_6]DMSO): δ 1.38 (d, J = 7 Hz, 3H, CH_3), 3.48 (q, J = 7 Hz, 1H, CH), 6.35 (t, J = 2.2 Hz, 2H, pyrrole), 7.48 (m, 3H, pyrrole and benzene), 7.80 (m, 1H, benzene), 8.01 (m, 1H, benzene), 8.23 (m, 1H, benzene), 10.15 (s, 1H, NH, exch. by D_2O).- $C_{14}H_{15}N_3O_4S$ (321.35) (C, H, N, S).

1-{2-[Propionamido-2-(4-chlorophenyl)carboxyamide]benzenesulfonyl}-1H-pyrrole (**34**)

Prepared as reported for **30** starting from **32**. Yield 52%; m.p. 173-174°C (benzene/cyclohexane).- IR: 1670 (CO), 3240 and 3280 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ([D_6]DMSO/$CDCl_3$ 1:1): δ 1.55 (d, J = 7 Hz, 3H, CH_3), 3.75 (q, J = 7 Hz, 1H, CH), 6.25 (t, J = 2.2 Hz, 2H, pyrrole), 7.33 (m, 5H, pyrrole and benzene), 7.55-8.08 (m, 4H, benzene), 8.35 (d, J

= 8 Hz, 1H, benzene), 10.98 and 11.41 (2s, 2H, NH, exch. by D_2O).- $C_{20}H_{18}ClN_3O_4S$ (431.89) (C, H, N, Cl, S).

1-[2-(2-Methoxycarbonyl-2-methylpropionamido)benzenesulfonyl]-1H-pyrrole (**35**)

From **31**. Compound **35** was prepared by the procedure used for the synthesis of **31** from **27**. Yield 62%; m.p. 70-71°C (ligroin).- IR: $\tilde{\nu}$ = 1680 and 1720 (CO), 3320 and 3360 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.60 (s, 6H, CH_3), 3.83 (s, 3H, CH_3), 6.30 (t, J = 2.2 Hz, 2H, pyrrole), 7.13-7.33 (m, 3H, pyrrole and benzene), 7.46-7.90 (m, 2H, benzene), 8.60 (d, J = 8 Hz, 1H, benzene), 10.11 ppm (s, 1H, NH, exch. by D_2O).- $C_{16}H_{18}N_2O_5S$ (350.39) (C, H, N, S).

From **27**. Compound **35** was readily achieved by reacting **27** with an excess of iodomethane in the presence of K_2CO_3. Yield 50%.

1-[2-(2-Methylpropionamido-2-carboxy)benzenesulfonyl]-1H-pyrrole (**36**)

36 was prepared by alkaline hydrolysis of **35** as reported above. Yield 70%; m.p. 118-120°C (toluene/cyclohexane).- IR: $\tilde{\nu}$ = 1690 (CO), 3340 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.63 (s, 6H, CH_3), 6.26 (t, J = 2.2 Hz, 2H, pyrrole), 7.10-7.33 (m, 3H, pyrrole and benzene), 7.48-7.90 (m, 2H, benzene), 8.55 (d, J = 8 Hz, 1H, benzene), 9.93 and 10.03 (2s, 2H, NH and OH, exch. by D_2O).- $C_{15}H_{16}N_2O_5S$ (336.36) (C, H, N, S).

1-[2-(2-Methylpropionamido-2-carboxyamide)benzenesulfonyl]-1H-pyrrole (**37**)

Prepared as reported for **29** starting from **35**. Yield 35%; m.p. 118-119°C (toluene).- IR: $\tilde{\nu}$ = 1660 (CO), 3320 and 3380 cm^{-1} (NH and NH_2).- ^{1}H-NMR (90 MHz) ([D_6]DMSO): δ 1.46 (s, 6H, CH_3), 6.36 (t, J = 2.2 Hz, 2H, pyrrole), 7.10-8.08 (m, 5H, pyrrole and benzene), 8.36 (d, J = 8 Hz, 1H, benzene), 10.20 (s, 1H, NH, exch. by D_2O).- $C_{15}H_{17}N_3O_4S$ (335.37) (C, H, N, S).

1-{2-[2-Methylpropionamido-2-(4-chlorophenyl)carboxyamide]benzenesulfonyl}-1H-pyrrole (**38**)

Prepared as reported for **30** starting from **36**. Yield 45%; m.p. 172-174°C (benzene/petroleum ether).- IR: $\tilde{\nu}$ = 1670 (CO), 3320 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.71 (s, 6H, CH_3), 6.11 (t, J = 2.2 Hz, 2H, pyrrole), 7.05-7.95 (m, 9H, pyrrole and benzene), 8.48 (d, J = 8 Hz, 1H, benzene), 8.71 and 9.98 ppm (2s, 2H, NH, exch. by D_2O).- $C_{21}H_{20}ClN_3O_4S$ (445.92 (C, H, N, Cl, S).

1-[2-(N-Methyl-2-methoxycarbonyl-2-methylpropionamido)benzenesulfonyl]-1H-pyrrole (**39**)

Prepared by reaction of **35** with a threefold excess of iodomethane in the presence of potassium tert-butoxide and 18-crown-6 as reported above. The crude product was purified by chromatography (SiO_2/CH_2Cl_2). Yield 50%; m.p. 104-105°C (ligroin).- IR: $\tilde{\nu}$ = 1630 and 1730 cm^{-1} (CO).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 1.46 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 6.36 (t, J = 2.2 Hz, 2H, pyrrole), 6.93-7.76 (m, 6H, pyrrole and benzene).- $C_{17}H_{20}N_2O_5S$ (364.11) (C, H, N, S).

1-[2-(N-methyl-2-methylpropionamido-2-carboxy)benzenesulfonyl]-1H-pyrrole (**40**)

Prepared from **39** as reported for **28**. Yield 49%; m.p. 156-158°C (toluene/cyclohexane).- IR: $\tilde{\nu}$ = 1730 cm^{-1} (CO).- ^{1}H-NMR (90 MHz) ([D_6]DMSO/$CDCl_3$ 1:1): δ 1.43 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 6.36 (t, J = 2.2 Hz, 2H, pyrrole), 7.15-7.81 ppm (m, 6H, pyrrole and benzene).- $C_{16}H_{18}N_2O_5S$ (350.39) (C, H, N, S).

1-[2-(2-Methoxycarbonylacetamido)benzenesulfenyl]-1H-pyrrole (**41**)

Prepared as reported for **27** starting from 2-nitrobenzenesulfenyl chloride. Yield 40%; m.p. 91-92°C (cyclohexane).- IR: $\tilde{\nu}$ = 1640 and 1740 (CO), 3300 cm^{-1} (NH).- ^{1}H-NMR (90 MHz) ($CDCl_3$): δ 3.56 (s, 2H, CH_2), 3.83 (s, 3H, CH_3), 6.26 (t, J = 2.2 Hz, 2H, pyrrole), 6.90 (t, J = 2.2 Hz, 2H, pyrrole), 7.06-7.40 (m, 3H, benzene), 8.03 (d, J = 7.5 Hz, 1H, benzene), 9.80 (s, 1H, NH, exch. by D_2O).- $C_{14}H_{14}N_2O_3S$ (290.33) (C, H, N, S).

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