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Anti-HIV-1 activity of pyrryl aryl sulfone (PAS) derivatives: synthesis and SAR studies of novel esters and amides at the position 2 of the pyrrole nucleus

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Abstract

A SAR study has been performed in order to evaluate how much the ester function could be a determinant for the anti-human immunodeficiency virus type-1 activity of pyrryl aryl sulfones (PASs), a potent family of non-nucleoside reverse transcriptase (RT) inhibitors discovered in the last years. Twenty-three new esters were prepared with the aim to enhance the inhibitory potency of **4a** and **4c**, two PAS agents endowed with good activity (EC_{50} = 0.14 μM) and deprived of cytotoxicity up to >200 μM. None of test derivatives was as potent as **4a** and **4c** and lacked of selectivity due to their higher cytotoxicity (compounds **22–25**). Antiviral activity correlate with an ester ramified chain.

Keywords: AIDS; HIV-1; NNRTI; Pyrryl aryl sulfones

1. Introduction

Anti-acquired immunodeficiency syndrome (AIDS) drugs fall into three families, the nucleoside reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the protease inhibitors (PIs) [1–3]. Highly active antiretroviral therapy (HAART) regimens, which are based on triple or quadruple combinations of NRTIs, NNRTIs and PIs, reduce the human immunodeficiency virus (HIV) to very low levels, but are unable to extirpate the infection. Long period therapies lead to the emergence of drug resistant mutant strains [4]. Thus, the need of novel anti-AIDS agents active on mutant strains is continuous.

NNRTIs received great attention because are HIV-1 selective, low toxic, and show favorable pharmacokinetic properties. To date three NNRTIs are on the market, namely nevirapine (**1**, Viramune®), delavirdine (**2**, Rescriptor®), and efavirenz (**3**, Sustiva®) (Chart 1), but a wide number of structurally unrelated NNRTIs were identified [5].

Pyrryl aryl sulfones (PASs, **4**) [6–8] are a NNRTI class discovered in our laboratories during studies on novel antiretroviral RT inhibitors related to nitrophenyl phenyl sulfone (NPPS) (**5**) [9] and PBTDs (**6**) [10,11] (Chart 1). SAR studies on PAS derivatives led to go into the structural requirements for high antiviral potency, namely the presence of a *p*-chloroaniline moiety and an ethoxycarbonyl group at position 2 of the pyrrole nucleus [7]. Further SAR studies devoted to design new substituents on the amino group at position 2 of the aryl moiety led to identify acylamino pyrryl aryl sulfones (APASs, **8**), a NNRTI class which resulted as active as pyrrolo[1,2-b)[1,2,5]benzothiadiazepines 5,5-dioxide PBTDs [12]. A previous work [7] showed that replacement of the ethoxycarbonyl function of PAS 980 (**4**) with some alkoxy congeners, such as methoxy, *n-, iso*-propoxy or allyloxy groups, furnished compounds as potent as the parent compound. Furthermore, we observed that in the APAS series the highest antiviral activity was related to the presence of a four member acyl chain (methoxyacetyl or methylthioacetyl) linked to the amino group of **4** [12]. These findings suggested us to explore more deeply how substitution of the ethoxycarbonyl group with different alkoxycarbonyls would influence the antiviral activity in the PAS series. Some

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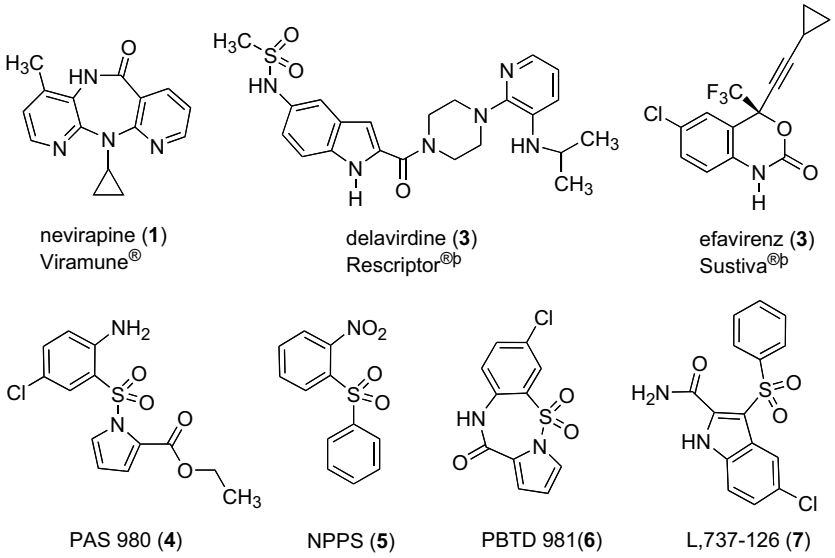


Chart 1. Clinically used and sulfone NNRTIs.

amides related to the potent indole derivative L-737,126 (**7**) were also synthesized [13] (Chart 2).

2. Chemistry

1-(Phenylsulfonyl)-1*H*-pyrroles **9–19, 32, 36** and **37** were prepared by phase transfer reaction of appropriates phenylsulfonyl chlorides and pyrroles in the presence of 18-crown-6 and potassium *tert*-butoxide, according to the procedure of by Guida and Mathre [14]. For compounds **33–35** and **38** [15] a different procedure was adopted. The phenylsulfonyl chloride or its 5-chloroderivative [16] was reacted with 2-trichloroacetyl-1*H*-pyrrole [17] in the presence of 18-crown-6 and potassium *tert*-butoxide, to give the related 1-(phenylsulfonyl)-2-trichloroacetyl-1*H*-pyrroles **45** and **46**, which were then treated with amine or hydrazine according to Bailey [18,19]. Reduction of nitro group was performed by heating at 60 °C with iron powder in glacial acetic acid with formation of amino sulfones **20–27, 29–31, 39–43** (Scheme 1). 1-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carbohydrazide (**44**) was obtained starting from **4a**, as previously reported [15].

2-Hydroxyethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**28**) was obtained by chlorotrimethylsilane/sodium iodide dealkylation of 2-methoxyethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (**27**) in acetonitrile according to Olah [20] (Scheme 2).

The novel *sec*-butyl, cyclopropylmethyl, propargyl, cyclopentyl, cyclohexyl and 2-methoxyethyl 1*H*-pyrrole-2-carboxylic esters were prepared by heating trichloroacetyl-1*H*-pyrrole [17] with an equimolar amount of an appropriate alcohol in the presence of potassium carbonate. A similar procedure was used in the preparation of *N*-benzyl, *N*-methyl 1*H*-pyrrole-2-carboxyamide in the presence of triethylamine.

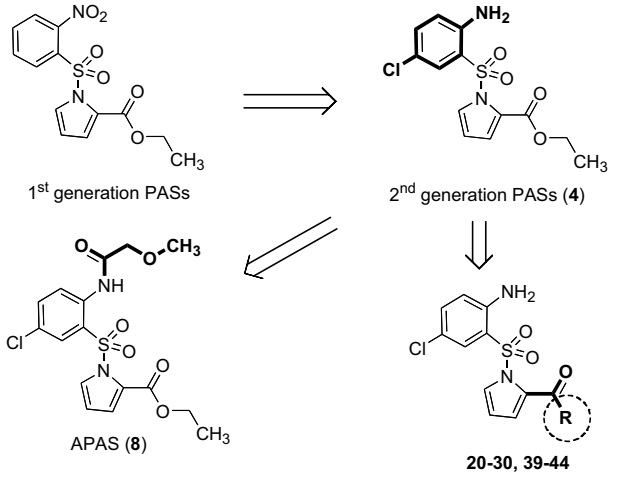
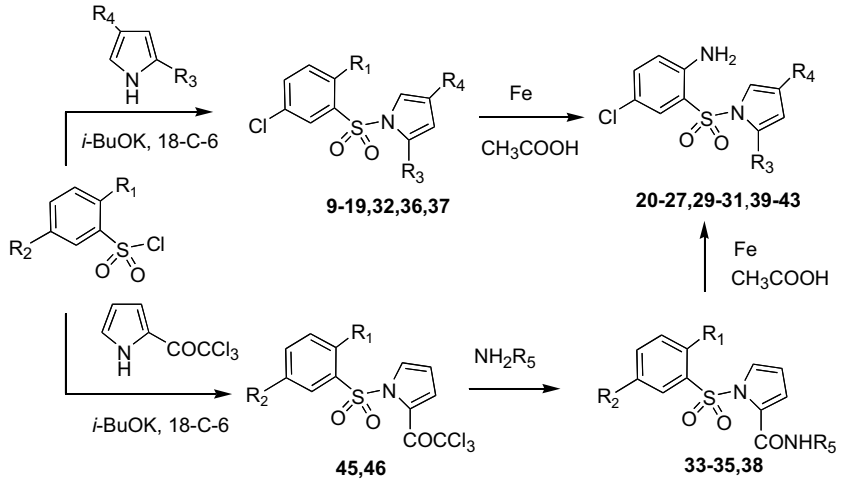


Chart 2. SAR studies in the PAS series.

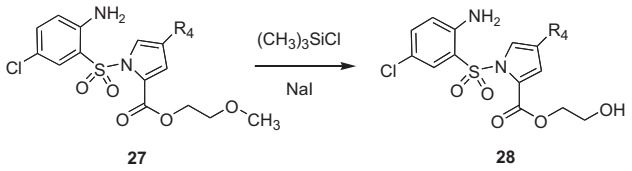
3. Results and discussion

The anti-HIV-1 activities (EC_{50}s) of PAS derivatives **9–44** together with their cytotoxicities (CC_{50}s) and the corresponding selectivity indexes (SIs) are reported in Tables 1 and 2. The anti-HIV-1 activities were established by determining their ability to prevent the virus-induced cytopathogenicity in MT-4 cells, as described elsewhere [21]. Compounds **4a–d** [7] and **5** [10] were used as reference compounds.

Thirty-six compounds were tested, and fifteen of them showed significant antiviral activity. Four compounds (**10, 31, 34** and **40**) had EC_{50} values in the 10–100 μM range. Eight compounds (**21, 23–25, 27–29** and **32**) showed EC_{50} values between 1–10 μM, ranging from 1.6 (**21**) to 9 μM (**28**) with CC_{50} values from >200 (**21, 27, 28** and **32**) to 13 μM



Scheme 1[a]. [a]R_1: H, Cl, NO_2; R_2: H, Cl; R_3: carboxylic ester (see Table 1),CN; R_4: COOEt, 4-methylpiperazin-1-ylmethyl; R_5: H, NH_2, NHMe, NHEt.



Scheme 2

(**29**). Derivative **22** displayed the highest antiviral activity within the series showing EC_{50} = 0.9 μM, CC_{50} = 71.3 μM, and selectivity index = 79.2.

SAR analysis led to highlight the following points: (i) independently from the presence of an alkoxycarbonyl group or a carboxyamide function at position 2 of the pyrrole ring, the nitro derivatives **9–19** and **33–38** were quite inactive; (ii) among the amino derivatives, only ester (**20–28, 30** and **31**) or cyano (**29**) compounds showed high antiviral activity, whereas the corresponding amides were scarcely active (**40**) or inactive (**39, 41–44**); (iii) the highest antiviral activity within the series was found in 2-methylpropyl (*sec*-butyl) ester of 1-[(2-amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylic acid (**22**) which showed EC_{50} = 0.9 μM, CC_{50} = 71.3 μM, and selectivity index = 79.2; (iv) the inhibitory activity of **22** was partially retained when the *sec*-butyl chain of the ester function was replaced with the *iso*-butyl or the cyclopropylmethyl chain, but it was lost with the *n*-butyl chain (compare **22** with **21, 23** and **20**, respectively); (v) substitution the *sec*-butyl chain of **22** with a methoxyethyl chain reduced by 3.5-fold the inhibitory activity of the parent compound; a further about 3-fold reduction of activity was observed when this chain was replaced with a hydroxyethyl one (compare **22** with **27** and **28**); nevertheless, compounds **27** and **28** were no cytotoxic; (vi) replacement of the *sec*-butyl chain of **22** with a propargyl abated twofold the antiviral activity, and increased of the same magnitude the cytotoxicity (compare **22** with **24**); (vii) insertion of cyclic groups furnished less active (**25**), inactive (**26**), or more cytotoxic (**30**) compounds; (viii) replacement of the *sec*-butoxycarbonyl function of **22** with a cyano group reduced (3.9-fold) the anti-HIV-1 activity, but this compound resulted somewhat cytotoxic (compare **22** with **29**); (ix) transposition of the ethoxycarbonyl group of **4a** from position 2 of the pyrrole ring to position 3 dramatically reduced antiviral activity and increased cytotoxicity (compare **31** with **4a**); (xi) when the 2-amino group of **4a** was replaced with a chlorine atom, the resulting dichloro derivative **32** was 54-fold less active than the parent compound, but it resulted no cytotoxic (compare **32** with **4a**).

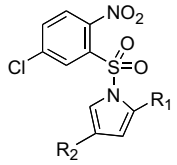
In conclusion, we explored substitutions of the ester function at the position 2 of the pyrrole ring of PAS derivatives. Although the new esters were less potent and sometimes more cytotoxic than the previously reported derivatives **4a–d**, this study demonstrated that a ramified ester chain and the presence of the *p*-chloroanilino moiety were both crucial determinants for the anti-HIV-1 activity of PAS derivatives.

4. Experimental

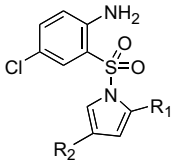
4.1. Chemistry

Melting points (m.p.) were determined on a Büchi 510 apparatus and are uncorrected. Boiling points (b.p.) were determined by distillation under diminished pressure on a pear-shaped Claisen-Vigreux flask by using Edwards Speedivac 2SC50B high vacuum pump equipped with Edwards Pirani vacuum gauge. Infrared spectra (IR) were run on Perkin-Elmer 1310 and SpectrumOne spectrophotometers. Band position and absorption ranges are given in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker AM-200 (200 MHz) and Bruker Avance 400 MHz FT spectrometers in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Column chromatographies were packed with alumina Merck (70–230 mesh) and silica gel Merck (70–230 mesh). Aluminum oxide thin layer chromatography (TLC) cards

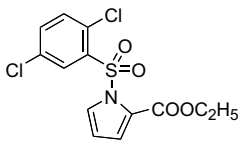
Table 1
Structures and anti-HIV-1 activities of PAS derivatives **9–32**[a]



9-19



4a-d, 20-31

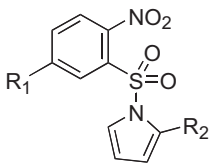


32

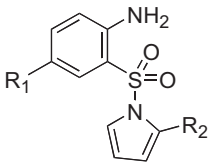
Compound	R_1	R_2	CC_{50}[b]	EC_{50}[c]	SI[d]
9	$COO(CH_2)_3CH_3$	H	22	>22	–
10	$COOCH_2CH(CH_3)_2$	H	24	14	1.7
11	$COOCH(CH_3)C_2H_5$	H	32.5	≥32.5	–
12	$COOCH_2$-*cyclo*-C_3H_5	H	96	>96	–
13	$COOCH_2C{\equiv}CH$	H	4.9	>4.9	–
14	COO-*cyclo*-C_5H_9	H	11	>11	–
15	COO-*cyclo*-C_6H_{11}	H	160	>160	–
16	$COOCH_2CH_2OCH_3$	H	12	>12	–
17	$C{\equiv}N$	H	1.4	>1.4	–
18	$COOC_6H_5$	H	15.5	>15.5	–
19	H	$COOC_2H_5$	0.7	>0.7	–
20	$COO(CH_2)_3CH_3$	H	>200	>200	–
21	$COOCH_2CH(CH_3)_2$	H	>200	1.6	>125.0
22	$COOCH(CH_3)C_2H_5$	H	71.3	0.9	79.2
23	$COOCH_2$-*cyclo*-C_3H_5	H	39	2.3	17.0
24	$COOCH_2C{\equiv}CH$	H	118	1.86	63.4
25	COO-*cyclo*-C_5H_9	H	53.6	2	26.8
26	COO-*cyclo*-C_6H_{11}	H	>200	>200	–
27	$COOCH_2CH_2OCH_3$	H	>200	3.2	62.5
28	$COOCH_2CH_2OH$	H	>200	9	>22.2
29	$C{\equiv}N$	H	13	3.5	3.7
30	$COOC_6H_5$	H	24	>24	–
31	H	$COOC_2H_5$	44	15	2.9
32	–	–	>200	7.6	>26.3
4a[e]	$COOCH_2CH_3$	H	>200	0.14	>1428.6
4b[e]	$COOCH_2CH_2CH_3$	H	110	0.2	550.0
4c[e]	COO $CH(CH_3)_2$	H	>200	0.14	>1428.6
4d[e]	$COOCH_2CH{=}CH_2$	H	100	0.4	250.0
5[f]	–	–	>100	0.5	>200.0

[a] Data represent mean values for three separate experiments. Variation among triplicate samples was <15%.
[b] Compound concentration (μM) required to reduce the viability of mock-infected MT-four cells by 50% (MTT-method).
[c] Compound concentration (μM) required to achieve 50% protection of infected MT-4 cells from the HIV-1_{IIIB}-induced cytopathogenicity (MTT-method).
[d] Selectivity index: CC_{50}/EC_{50} ratio.
[e] Ref. [7].
[f] Ref. [10].

Table 2
Structures and anti-HIV-1 activities of PAS derivatives **33–44**[a]



33-38



39-44

Compound	R_1	R_2	CC_{50}[b]	EC_{50}[c]	SI[d]
33	H	$CONH_2$	>200	>200	–
34	Cl	$CONH_2$	52	27	1.9
35	Cl	$CONHC_2H_5$	16.6	>16.6	–
36	Cl	$CON(C_2H_5)_2$	13	>13	–
37	Cl	$CON(CH_3)C_6H_5$	17	>17	–
38	Cl	$CONHNH_2$	>200	>200	–
39	H	$CONH_2$	>200	>200	–
40	Cl	$CONH_2$	200	15	13.9
41	Cl	$CONHC_2H_5$	>200	>200	–
42	Cl	$CON(C_2H_5)_2$	146	>146	–
43	Cl	$CON(CH_3)C_6H_5$	87	>87	–
44	Cl	$CONHNH_2$	>200	>200	–

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

Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nm) and silica gel TLC cards Fluka (silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for TLC. Developed plates were visualized by Spectroline ENF 260C/F UV apparatus. Organic solutions were dried over anhydrous sodium sulfate. Concentration and evaporation of the solvent after reaction or extraction was carried out on a rotary evaporator Büchi Rotavapor operating at reduced pressure. Elemental analyses were found within ±0.4% of the theoretical values (Appendices A and B). Materials: 5-chloro-2-nitrobenzenesulfonyl chloride [15]; *n*-butyl 1*H*-pyrrole-2-carboxylate was prepared as reported by Harbuck and Rapoport [19], yield 92%, m.p. 36–39 °C, Ref. [21] m.p. 36–38 °C; *iso*-butyl 1*H*-pyrrole-2-carboxylate was prepared as reported by Harbuck and Rapoport [19], yield 85%, m.p. 66–67 °C (petroleum ether), Ref. [22] m.p. 68–69 °C; 2-cyano-1*H*-pyrrole [23]; phenyl 1*H*-pyrrole-2-carboxylate [22]; ethyl 1*H*-pyrrole-3-carboxylate was prepared according to van Leusen et al. [24], m.p. 35–38 °C (ligroin), Ref. [25] m.p. 40 °C (ligroin); 2-trichloroacetyl-1*H*-pyrrole [16]; ethyl 1*H*-pyrrole-2-carboxylate [16]; *N,N*-diethyl 1*H*-pyrrole-2-carboxyamide was prepared as reported by Bailey and Johnson [17], yield 48%, m.p. 93–94 °C (cyclohexane), Ref. [26] m.p. 99.5 °C (ligroin).

*4.1.1. General procedure for condensation of benzenesulfonyl chlorides with esters of 1*H*-pyrrole-2-carboxylic acid,* N,N*-dialkyl 1*H*-pyrrole-2-carboxyamides and 2-trichloroacetyl-1*H*-pyrrole example*

n-Butyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**9**). To a stirred mixture of potassium *tert*-butoxide (1.34 g, 0.012 mol) and 18-crown-6 (0.28 g, 0.0011 mol) in anhydrous THF (21 ml) was added dropwise a solution of *n*-butyl 1*H*-pyrrole-2-carboxylate (1.67 g, 0.010 mol) in the same solvent (21 ml). Stirring was maintained for 15 min, then the suspension was cooled to 0 °C, while a solution of 5-chloro-2-nitrobenzenesulfonyl chloride [15]

(2.56 g, 0.010 mol) in anhydrous THF (21 ml) was dropped. Reaction was stirred at room temperature for 3.5 h, then concentrated to a small volume and extracted with ethyl acetate. Organic extracts were washed with brine and dried. Removal of the solvent furnished the crude product which was purified on column chromatography (alumina/chloroform), to yield **9** (88%); m.p. 68–69 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.20–1.50 and 1.50–1.75 (2m, 4H,), 4.11 (t, *J* = 6.6 Hz, 2H,), 6.34 (m, 1H,), 7.10 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.62 (dd, *J* = 1.8 and 3.2 Hz, 1H), 7.58–7.86 (m, 2H,), 8.32 (d, *J* = 8.6 Hz, 1H). IR (nujol): ν 1710 cm^{-1} (CO). Anal. $C_{15}H_{15}ClN_2O_6S$ (386.80): C, H, N, Cl, S.

By this general procedure were prepared sulfones **10–19, 32, 36, 37** *and* **45, 46** *iso-Butyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate* (**10**). Yield 83% (alumina/chloroform); m.p. 98–99 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 0.92 (d, *J* = 6.7 Hz, 6H), 1.94 (m, *J* = 6.7 Hz, 1H) 3.91 (d, *J* = 6.7 Hz, 2H), 6.36 (3 line m, 1H), 7.12 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.64 (dd, *J* = 1.8 and 3.3 Hz, 1H), 7.72 (dd, *J* = 2.1 and 8.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 8.31 ppm (d, *J* = 2.1 Hz, 1H). IR (nujol): ν 1710 cm^{-1} (CO). Anal. $C_{15}H_{15}ClN_2O_6S$ (386.80): C, H, N, Cl, S.

sec-Butyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**11**). Yield 71% (alumina/chloroform); m.p. 119–120 °C (toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 0.86 (t, *J* = 5.9 Hz, 3H), 1.17 (d, *J* = 5.7 Hz, 3H), 1.67 (m, 2H), 4.87 (m, 1H), 6.36 (3 line m, 1H), 7.10 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.60–7.85 (m, 3H), 8.26 ppm (d, *J* = 2.0 Hz, 1H). IR (nujol): ν 1700 cm^{-1} (CO). Anal. $C_{15}H_{15}ClN_2O_6S$ (386.81): C, H, N, Cl, S.

Cyclopropylmethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**12**). Yield 81% (alumina/chloroform); m.p. 104–105 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 0.27 (m, 2H), 0.53 (m, 2H), 1.10 (m, 1H), 3.95 (d, *J* = 7.3 Hz, 2H), 6.37 (3 line m, 1H), 7.16 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.64 (dd, *J* = 1.8 and 3.2 Hz, 1H), 7.71 (dd, *J* = 2.0 and 8.6 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 8.25 ppm (d, *J* = 2.0 Hz, 1H). IR (nujol): ν 1720 cm^{-1} (CO). Anal. $C_{15}H_{13}ClN_2O_6S$ (384.79): C, H, N, Cl, S.

Propargyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**13**). Yield 57% (alumina/chloroform); m.p. 156–157 °C (toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 2.46 (t, *J* = 2.4 Hz, 1H), 4.75 (d, *J* = 2.4 Hz, 2H), 6.39 (3 line m, 1H), 7.22 (dd, *J* = 1.8 and 3.7 Hz, 1H), 7.62–7.87 (m, 3H), 8.33 ppm (d, *J* = 2.0 Hz, 1H). IR (nujol): ν 1720 (CO), 3270 cm^{-1} (≡C–H). Anal. $C_{14}H_9ClN_2O_6S$ (368.74): C, H, N, Cl, S.

Cyclopentyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**14**). Yield 62% (alumina/chloroform); m.p. 98 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.46–2.00 (m, 8H), 5.21 (m, 1H), 6.35 (3 line m, 1H), 7.05 (dd, *J* = 1.8 and 3.5 Hz, 1H), 7.61 (dd, *J* = 1.8 and 3.2 Hz, 1H), 7.71 (dd, *J* = 2.0 and 8.6 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 8.27 ppm (d, *J* = 2.0 Hz, 1H). IR (nujol): ν 1710 cm^{-1} (CO). Anal. $C_{16}H_{15}ClN_2O_6S$ (398.81): C, H, N, Cl, S.

Cyclohexyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**15**). Yield 52% (alumina/chloroform); m.p. 124–125 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.14–1.61 (m, 6H), 1.61–1.96 (m, 4H), 4.78 (m, 1H), 6.34 (3 line m, 1H), 7.10 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.60 (dd, *J* = 1.8 and 3.3 Hz, 1H), 7.68–7.82 (m, 2H), 8.34 ppm (d, *J* = 8.5 Hz, 1H). IR (nujol): ν 1710 cm^{-1} (CO). Anal. $C_{17}H_{17}ClN_2O_6S$ (412.84): C, H, N, Cl, S.

2-Methoxyethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**16**). Yield 77% (alumina/chloroform); m.p. 83–84 °C (toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 3.35 (s, 3H), 3.58 (t, *J* = 4.6 Hz, 2H), 4.27 (t, *J* = 4.6 Hz, 2H), 6.36 (3 line m, 1H), 7.17 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.64 (dd, *J* = 1.8 and 3.2 Hz, 1H), 7.71 (dd, *J* = 1.9 and 8.6 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 8.28 ppm (d, *J* = 1.9 Hz, 1H). IR (nujol): ν 1700 cm^{-1} (CO). Anal. $C_{14}H_{13}ClN_2O_7S$ (388.78): C, H, N, Cl, S.

1-[(5-Chloro-2-nitrophenyl)sulfonyl]-2-cyano-1H-pyrrole (**17**). Yield 68% (silica gel/dichloromethane–petroleum ether 1:1); m.p. 119–121 °C (toluene/cyclohexane). ^{1}H NMR (DMSO-d_6): δ 6.68 (m, 1H), 7.54 (m, 1H), 7.86 (m, 1H), 8.12 (m, 1H), 8.18–8.34 ppm (m, 2H). IR (nujol): ν 2220 cm^{-1} (CN). Anal. $C_{11}H_6ClN_3O_4S$ (311.70): C, H, N, Cl, S.

Phenyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**18**). Yield 71% (silica gel/chloroform); m.p. 170–171 °C (toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 6.46 (m, 1H), 7.11–7.18 (m, 2H), 7.19–7.45 (m, 4H), 7.60–7.84 (m, 3H), 8.28 ppm (d, *J* = 2.1 Hz, 1H). IR (nujol): ν 1740 cm^{-1} (CO). Anal. $C_{17}H_{11}ClN_2O_6S$ (406.80): C, H, N, Cl, S.

Ethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-3-carboxylate (**19**). Yield 57% (silica gel/chloroform–ethanol 9:1); m.p. 108–109 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.1 Hz, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 6.76 (dd, *J* = 1.5 and 3.4 Hz, 1H), 7.23 (m, 1H), 7.72–7.80 (m, 2H), 7.82 (m, 1H), 7.90 ppm (m, 1H). IR (nujol): ν 1710 cm^{-1} (CO). Anal. $C_{13}H_{11}ClN_2O_6S$ (358.75): C, H, N, Cl, S.

Ethyl 1-[(2,5-dichlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**32**). Yield 74 % (silica gel/chloroform); m.p. 88–89 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, *J* = 7.1 Hz, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 6.33 (m, 1H), 7.10 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 2.5 and 8.0 Hz, 1H), 7.80 (m, 1H), 8.33 ppm (d, *J* = 2.5 Hz, 1H). IR (nujol): ν 1715 cm^{-1} (CO). Anal. $C_{13}H_{11}Cl_2NO_4S$ (348.20): C, H, N, Cl, S.

N,N-Diethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**36**). Yield 62% (silica gel/chloroform–ethanol 9:1); m.p. 113–114 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.04–1.31 (m, 6H), 3.24–3.55 (m, 4H), 6.28–6.41 (m, 2H), 7.35 (dd, *J* = 1.6 and 3.2 Hz, 1H), 7.66 (dd, *J* = 2.0 and 8.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.90 ppm (d, *J* = 2.0 Hz, 1H). IR (nujol): ν 1620 cm^{-1} (CO). Anal. $C_{15}H_{16}ClN_3O_5S$ (385.82): C, H, N, Cl, S.

N-Benzyl, N-methyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**37**). Yield 80%; m.p. 139–141 °C (toluene/ligroin). ^{1}H NMR ($CDCl_3$): δ 2.98 (s, 3H),

4.66 (s, 2H), 6.32 (m, 1H), 6.44 (m, 1H), 7.10–7.45 (m, 6H), 7.68 (dd, *J* = 1.9 and 8.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 8.01 ppm (d, *J* = 1.9 Hz, 1H). IR (nujol): ν 1640 cm^{-1} (CO). $C_{19}H_{16}ClN_3O_5S$ (433.86): C, H, N, Cl, S.

[(2-Nitrophenyl)sulfonyl]-2-trichloroacetyl-1H-pyrrole (**45**). Yield 42% (silica gel/chloroform–petroleum ether 1:1); m.p. 134–136 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 6.49 (m, 1H), 7.71 (m, 1H), 7.78–7.96 (m, 4H), 8.52 ppm (m, 1H). IR (nujol): ν 1695 cm^{-1} (CO). Anal. $C_{12}H_7Cl_3N_2O_5S$ (397.62): C, H, N, Cl, S.

[(5-Chloro-2-nitrophenyl)sulfonyl]-2-trichloroacetyl-1H-pyrrole (**46**). Yield 38% (silica gel/chloroform-petroleum ether 1:1); m.p. 178–180 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 6.51 (m, 1H), 7.68–7.94 (m, 4H), 8.44 ppm (d, *J* = 2.0 Hz, 1H). IR (nujol): ν 1695 cm^{-1} (CO). Anal. $C_{12}H_6Cl_4N_2O_5S$ (432.06): C, H, N, Cl, S.

*4.1.2. 1-[(2-Nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**33**)*

Gaseous ammonia was bubbled through an ice cooled and stirred solution of **45** (2.38 g, 0.006 mol) in DMF (20 ml) for 1 h, then poured on crushed ice and extracted with ethyl acetate. Organic extracts were washed with brine and dried. Evaporation of the solvent gave the crude product which was purified by column chromatography (silica gel/ethyl acetate) to yield **33** (33%); m.p. 217–218 °C (ethanol). ^1H NMR (DMSO-d_6): δ 6.46 (m, 1H), 7.03 (dd, *J* = 1.5 and 3.5 Hz, 1H), 7.23 (broad s, 2H, disappeared on treatment with D_2O), 7.58 (dd, *J* = 1.5 and 3.1 Hz, 1H), 7.78–7.99 (m, 3H, benzene), 8.07 ppm (m, 1H, benzene). IR (nujol): ν 1660 (CO), 3150, 3270, 3320 and 3450 cm^{-1} (NH_2). Anal. $C_{11}H_9N_3O_5S$ (295.27): C, H, N, S.

1-[(5-Chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**34**). Was prepared as **33** starting from **46**; yield 24% (silica gel/ethyl acetate); m.p. 195–196 °C (ethanol). ^1H NMR ($CDCl_3$): δ 5.60 (broad s, 2H, disappeared on treatment with D_2O), 6.34 (m, 1H), 6.78 (dd, *J* = 1.6 and 3.5 Hz, 1H), 7.60 (dd, *J* = 1.6 and 3.3 Hz, 1H), 7.72 (dd, *J* = 2.1 and 8.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 8.26 ppm (d, *J* = 2.1 Hz, 1H). IR (nujol): ν 1665 cm^{-1} (CO). Anal. $C_{11}H_8ClN_3O_5S$ (329.71): C, H, N, Cl, S.

N-Ethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**35**). Was prepared as **33** starting from **46** and gaseous ethylamine, yield 25% (silica gel/chloroform); m.p. 170–172 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 3.35 (dq, *J* = 1.5 and 7.3 Hz, 2H, showed q when NH was irradiated), 5.94 (broad t, 1H, disappeared on treatment with D_2O), 6.29 (m, 1H, H4-pyrrole), 6.62 (dd, *J* = 1.7 and 3.6 Hz, 1H), 7.49 (dd, *J* = 1.7 and 3.4 Hz, 1H), 7.68 (dd, *J* = 2.1 and 8.6 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 8.16 ppm (d, *J* = 2.1 Hz, 1H). IR (nujol): ν 1630 (CO), 3320 and 3400 cm^{-1} (NH). Anal. $C_{13}H_{12}ClN_3O_5S$ (357.77): C, H, N, Cl, S.

*4.1.3. General procedure for reduction of nitro group to amino, example: n-Butyl 1-[(2-amino-5-chlorophenyl) sulfonyl]-1H-pyrrole-2-carboxylate (**20**)*

A stirred solution of **9** (1.93 g, 0.005 mol) in glacial acetic acid (21 ml) was treated portionwise with iron powder (1.5 g) while heating at 60 °C under stirring. Reaction mixture was maintained at 60 °C for 2 h, then evaporated to dryness. The residue was triturated with ice water and extracted with ethyl acetate. The organic layers were collected, washed with brine and dried. Removal of the solvent gave a residue which was purified by column chromatography (alumina/chloroform) to yield **10** (95%); m.p. 102 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.20–1.50 and 1.50–1.75 (2m, 4H), 4.13 (t, *J* = 6.5 Hz, 2H), 5.27 (broad s, 2H, NH_2, disappeared on treatment with D_2O), 6.28 (m, 1H), 6.55–6.76 (m, 2H), 7.06 (dd, *J* = 1.9 and 3.6 Hz, 1H), 7.56 (d, *J* = 9.4 Hz, 1H), 7.66 ppm (dd, *J* = 1.9 and 3.1 Hz, 1H). IR (nujol): ν 1700 (CO), 3360 and 3450 cm^{-1} (NH_2). Anal. $C_{15}H_{17}ClN_2O_4S$ (356.82): C, H, N, Cl, S.

By this general procedure were prepared sulfones **21–27, 29, 31** and **39–43** *iso-Butyl 1-[(2-amino-5-chlorophenyl) sulfonyl]-1H-pyrrole-2-carboxylate* (**21**). Yield 82% (silica gel/chloroform); m.p. 90–92 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 0.91 (d, *J* = 6.7 Hz, 6H), 1.95 (m, *J* = 6.7 Hz, 1H), 3.92 (d, *J* = 6.7 Hz, 2H), 5.21 (broad s, 2H, disappeared on treatment with D_2O), 6.31 (m, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 7.08 (dd, *J* = 1.9 and 3.7 Hz, 1H), 7.21 (dd, *J* = 2.4 and 8.9 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.67 ppm (dd, *J* = 1.9 and 3.1 Hz, 1H). IR (nujol): ν 1705 (CO), 3370 and 3480 cm^{-1} (NH_2). Anal. $C_{15}H_{17}ClN_2O_4S$ (356.82): C, H, N, Cl, S.

sec-Butyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**22**). Yield 81% (silica gel/chloroform); m.p. 118 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 0.85 (t, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 5.6 Hz, 3H), 1.59 (m, 2H), 4.89 (m, 1H), 5.24 (broad s, 2H, disappeared on treatment with D_2O), 6.29 (m, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 7.04 (dd, *J* = 1.9 and 3.6 Hz, 1H), 7.19 (dd, *J* = 2.4 and 8.8 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.65 ppm (dd, *J* = 1.9 and 3.1 Hz, 1H). IR (nujol): ν 1700 (CO), 3370 and 3480 cm^{-1} (NH_2). Anal. $C_{15}H_{17}ClN_2O_4S$ (356.82): C, H, N, Cl, S.

Cyclopropylmethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**23**). Yield 74% (silica gel/chloroform); m.p. 92–93 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 0.27 (m, 2H), 0.53 (m, 2H), 1.12 (m, 1H), 3.98 (d, *J* = 7.3 Hz, 2H), 5.22 (broad s, 2H, disappeared on treatment with D_2O), 6.31 (m, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 7.12 (dd, *J* = 1.9 and 3.7 Hz, 1H), 7.20 (dd, *J* = 2.4 and 8.9 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.67 ppm (dd, *J* = 1.9 and 3.1 Hz, 1H). IR (nujol): ν 1710 (CO), 3370 and 3480 cm^{-1} (NH_2). Anal. $C_{15}H_{15}ClN_2O_4S$ (354.80): C, H, N, Cl, S.

Propargyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**24**). Yield 57% (alumina/chloroform); m.p. 103–105 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 2.47 (t, *J* = 2.4 Hz, 1H), 4.75 (d, *J* = 2.4 Hz, 2H), 5.22 (broad s, 2H, disappeared on treatment with D_2O), 6.32 (m,

1H), 6.63 (d, *J* = 8.8 Hz, 1H), 7.12–7.27 (m, 2H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.70 ppm (dd, *J* = 1.9 and 3.1 Hz, 1H). IR (nujol): ν 1710 (CO), 3300 (≡C–H), 3380 and 3480 cm^{-1} (NH_2). Anal. $C_{14}H_{11}ClN_2O_4S$ (338.76): C, H, N, Cl, S.

Cyclopentyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**25**). Yield 90% (silica gel/chloroform); m.p. 123–124 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 1.42–1.96 (m, 8H), 5.09–5.38 (overlapped broad s and m, 3H, 2H disappeared on treatment with D_2O), 6.29 (m, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.19 (dd, *J* = 2.3 and 8.8 Hz, 1H), 7.51 (d, *J* = 2.3 Hz, 1H), 7.64 ppm (dd, *J* = 1.8 and 3.0 Hz, 1H). IR (nujol): ν 1700 (CO), 3360 and 3480 cm^{-1} (NH_2). Anal. $C_{16}H_{17}ClN_2O_4S$ (368.83): C, H, N, Cl, S.

Cyclohexyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**26**). Yield 84% (silica gel/chloroform); m.p. 156–157 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 1.12–1.60 (m, 6H), 1.60–1.92 (m, 4H), 4.81 (m, 1H), 5.27 (broad s, 2H, disappeared on treatment with D_2O), 6.27 (m, 1H), 6.62–6.74 (m, 2H), 7.04 (dd, *J* = 1.9 and 3.6 Hz, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.64 ppm (dd, *J* = 1.9 and 3.1 Hz, 1H). IR (nujol): ν 1710 (CO), 3360 and 3480 cm^{-1} (NH_2). Anal. $C_{17}H_{19}ClN_2O_4S$ (382.86): C, H, N, Cl, S.

2-Methoxyethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**27**). Yield 89% (alumina/chloroform); m.p. 127–128 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 3.35 (s, 3H), 3.60 (t, *J* = 4.7 Hz, 2H), 4.29 (t, *J* = 4.7 Hz, 2H), 5.21 (broad s, 2H, disappeared on treatment with D_2O), 6.30 (m, 1H), 6.62 (d, 1H), 7.13 (dd, *J* = 1.8 and 3.6 Hz, 1H), 7.20 (dd, *J* = 2.4 and 8.8 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.67 ppm (dd, *J* = 1.8 and 3.1 Hz, 1H). IR (nujol): ν 1710 (CO), 3320 and 3430 cm^{-1} (NH_2). Anal. $C_{14}H_{15}ClN_2O_5S$ (358.79): C, H, N, Cl, S.

1-[(2-Amino-5-chlorophenyl)sulfonyl]-2-cyano-1H-pyrrole (**29**). Yield 92% (silica gel/chloroform); m.p. 149–150 °C (toluene/cyclohexane). ^1H NMR (DMSO-d_6): δ 6.52 (m, 1H), 6.66 (broad s, 2H, disappeared on treatment with D_2O), 6.89 (d, *J* = 9.0 Hz, 1H), 7.40 (dd, *J* = 1.5 and 3.7 Hz, 1H), 7.46 (dd, *J* = 2.5 and 9.0 Hz, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 8.09 ppm (dd, *J* = 1.5 and 3.0 Hz, 1H). IR (nujol): ν 2220 (CN), 3340 and 3480 cm^{-1} (NH_2). Anal. $C_{11}H_8ClN_3O_2S$ (281.71): C, H, N, Cl, S.

Phenyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxylate (**30**). Yield 61% (silica gel/chloroform); m.p. 125–126 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 5.15 (broad s, 2H, disappeared on treatment with D_2O), 6.40 (m, 1H), 6.50 (d, *J* = 8.9 Hz, 1H), 7.02–7.29 (m, 4H), 7.29–7.44 (m, 3H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.78 ppm (dd, *J* = 1.9 and 3.1 Hz, 1H). IR (nujol): ν 1740 (CO), 3360 and 3460 cm^{-1} (NH_2). Anal. $C_{17}H_{13}ClN_2O_4S$ (376.81): C, H, N, Cl, S.

Ethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-3-carboxylate (**31**). Yield 31% (silica gel/chloroform); m.p. 120 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 1.33 (t, *J* = 7.2 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 5.21 (broad s, 2H, disappeared on treatment with D_2O), 6.60–6.71 (m, 2H), 7.12 (m, 1H), 7.23–7.32 (m, 1H), 7.70 (m, 1H), 7.76 ppm (m, 1H). IR (nujol): ν 1710 (CO), 3350 and 3460 cm^{-1} (NH_2). Anal. $C_{13}H_{13}ClN_2O_4S$ (328.77): C, H, N, Cl, S.

1-[(2-Aminophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**39**). Yield 95% (silica gel/ethyl acetate); m.p. 133–134 °C (ethanol). ^1H NMR (DMSO-d_6): δ 6.30 (m, 1H), 6.42 (broad s, 2H, disappeared on treatment with D_2O), 6.63 (t, *J* = 7.6 Hz, 1H), 6.74–6.88 (m, 2H), 7.18–7.40 (overlapped m and broad s, 2H, 1H disappeared on treatment with D_2O), 7.64 (dd, *J* = 1.6 and 3.1 Hz, 1H), 7.71 (dd, *J* = 1.3 and 8.2 Hz, 1H), 7.83 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1630 and 1660 (CO), 3120, 3200, 3360 and 3440 cm^{-1} ($CONH_2$ and $PhNH_2$). Anal. $C_{11}H_{11}N_3O_3S$ (265.28): C, H, N, S.

1-[(2-Amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**40**). Yield 98% (silica gel/ethyl acetate); m.p. 173–175 °C (ethanol). ^1H NMR ($CDCl_3$): δ 5.31 and 5.76 (2 broad s, 4H, disappeared on treatment with D_2O), 6.29 (m, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 1.7 and 3.6 Hz, 1H), 7.36 (dd, *J* = 2.4 and 8.8 Hz, 1H), 7.50 (dd, *J* = 1.7 and 3.2 Hz, 1H), 7.60 ppm (d, *J* = 2.4 Hz, 1H). IR (nujol): ν 1665 cm^{-1} (CO). Anal. $C_{11}H_{10}ClN_3O_3S$ (299.73): C, H, N, Cl, S.

N-Ethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**41**). Yield 71% (silica gel/chloroform–ethanol 9:1); m.p. 158–160 °C (ethanol). ^1H NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.2 Hz, 3H), 3.39 (m, 2H), 5.43 (broad s, 2H, disappeared on treatment with D_2O), 6.24 (broad s, 1H disappeared on treatment with D_2O), 6.24 (m, 1H), 6.54–6.70 (m, 2H), 7.21 (dd, *J* = 2.2 and 8.8 Hz, 1H), 7.33 (dd, *J* = 1.7 and 3.1 Hz, 1H), 7.65 ppm (d, *J* = 2.2 Hz, 1H). IR (nujol): ν 1650 (CO), 3340, 3400 and 3480 cm^{-1} (NH and NH_2). Anal. $C_{13}H_{14}ClN_3O_3S$ (327.78): C, H, N, Cl, S.

N,N-Diethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-1H-pyrrole-2-carboxyamide (**42**). Yield 92% (silica gel/chloroform–ethanol 9:1); m.p. 142–145 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 1.14 and 1.24 (2t, *J* = 7.0 Hz, 6H), 3.29 and 3.51 (2q, *J* = 7.0 Hz, 4H), 5.58 (broad s, 2H, disappeared on treatment with D_2O), 6.24 (m, 2H), 6.54 (d, *J* = 8.9 Hz, 1H), 7.03 (m, 1H, pyrrole), 7.18 (dd, *J* = 2.4 and 8.9 Hz, 1H), 7.74 ppm (d, *J* = 2.4 Hz, 1H). Anal. $C_{15}H_{18}ClN_3O_3S$ (355.84): C, H, N, Cl, S.

N-Benzyl, N-methyl 1-[(2-amino-5-chlorophenyl) sulfonyl]-1H-pyrrole-2-carboxyamide (**43**). Yield 100%; m.p. 134–136 °C (toluene/cyclohexane). ^1H NMR ($CDCl_3$): δ 2.92 and 3.00 (2s, 3H), 4.54 and 4.74 (2s, 2H), 5.53 (broad s, 2H, disappeared on treatment with D_2O), 6.15–6.38 (m, 2H), 6.58 (d, *J* = 8.8 Hz, 1H), 7.02–7.42 (m, 7H), 7.81 ppm (m, 1H). IR (nujol): ν 1610 (CO), 3320 and 3450 cm^{-1} (NH_2). Anal. $C_{19}H_{18}ClN_3O_3S$ (403.88): C, H, N, Cl, S.

*4.1.4. 2-Hydroxyethyl 1-[(2-amino-5-chlorophenyl) sulfonyl]-1H-pyrrole-2-carboxylate (**28**)*

Chlorotrimethylsilane (0.54 g, 0.005 mol) was added at room temperature to a stirred mixture of **27** (0.90 g, 0.0025

mol), sodium iodide (0.75 g, 0.005 mol) and acetonitrile (30 ml) while flushing continuously with anhydrous nitrogen, then reaction was refluxed for 24 h under nitrogen atmosphere. After cooling the mixture was diluted with water and extracted with ethyl acetate. Organic layer was shaken with brine, 5% sodium thiosulfate, then with brine and dried. After concentration to a small volume, the mixture was passed trough an alumina column eluting with the same solvent. First fractions afforded traces of starting material, further elution furnished **28** (35%); m.p. 110–111 °C (toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 2.07 (t, J = 6.6 Hz, 1H, disappeared on treatment with D_2O), 3.84 (m, 2H), 4.32 (m, 2H), 5.17 (broad s, 2H, disappeared on treatment with D_2O), 6.34 (m, 1H), 6.66 (d, J = 8.8 Hz, 1H), 7.15 (dd, J = 1.9 and 3.7 Hz, 1H), 7.25 (dd, J = 2.4 and 8.8 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.68 ppm (dd, J = 1.9 and 3.2 Hz, 1H). IR (nujol): ν 1720 cm^{-1} (CO). Anal. $C_{13}H_{13}ClN_2O_5S$ (344.77): C, H, N, Cl, S.

4.1.5. Synthesis of pyrrole-2-carboxylates and carboxyamides

sec-Butyl 1H-pyrrole-2-carboxylate. A mixture of 2-trichloroacetyl-1*H*-pyrrole [17] (6.00 g, 0.028 mol), potassium carbonate (4.00 g, 0.029) and *sec*-butanol (2.30 g, 0.031 mol) was stirred at 60 °C for 17 h. After cooling the mixture was dissolved in chloroform, filtered and evaporated to a residue which was passed through a silica gel column (dichloromethane), yield 87%; b.p. 100–102 °C/0.16 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.65 (t, J = 7.4 Hz, 3H), 1.30 (d, J = 6.2 Hz, 3H), 1.70 (m, 2H), 5.03 (m, 1H), 6.26 (m, 1H), 6.92 (m, 2H), 9.50 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (neat): ν 1690–1710 (CO), 3160 cm^{-1} (NH). Anal. $C_9H_{13}NO_2$ (167.21): C, H, N.

Cyclopropylmethyl 1H-pyrrole-2-carboxylate. Was prepared *sec*-butyl ester using cyclopropanemethanol; purification on silica gel column (chloroform), yield 96%; b.p. 107–108/0.025–0.030 mmHg, m.p. 49–50 °C (petroleum ether, +4 °C). ^{1}H NMR ($CDCl_3$): δ 0.34 (m, 2H), 0.58 (m, 2H), 1.20 (m, 1H), 6.27 (m, 1H), 6.96 (m, 2H), 9.36 ppm (broad s, 1H, disappeared on treatment with D_2O). Anal. $C_9H_{11}NO_2$ (165.19): C, H, N.

Propargyl 1H-pyrrole-2-carboxylate. Was prepared as the *sec*-butyl ester using propargyl alcohol; purification on alumina column (chloroform), yield 85%; m.p. 60–61 °C (ligroin/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ 2.50 (t, J = 2.4 Hz, 1H), 4.86 (d, J = 2.4 Hz, 2H), 6.28 (m, 1H), 6.99 (m, 2H), 9.27 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1680 (CO), 3270 and 3340 cm^{-1} (NH and ≡CH). Anal. $C_8H_7NO_2$ (149.15): C, H, N.

Cyclopentyl 1H-pyrrole-2-carboxylate. Was prepared as *sec*-butyl ester using cyclopentanol; purification on silica gel column (chloroform), yield 96%; b.p. 119–120/0.035–0.040 mmHg, m.p. 61 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 1.52–2.06 (m, 8H), 5.34 (m, 1H), 6.23 (m, 1H), 6.84–6.96 (m, 2H), 9.55 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1670 (CO), 3240 cm^{-1} (NH). Anal. $C_{10}H_{13}NO_2$ (179.22): C, H, N.

Cyclohexyl 1H-pyrrole-2-carboxylate. Was prepared as *sec*-butyl ester using cyclohexanol; purification on silica gel column (chloroform), yield 90%; m.p. 46–50 °C (petroleum ether, –25 °C). ^{1}H NMR ($CDCl_3$): δ 1.08–1.68 (m, 6H), 1.68–1.86 (m, 2H), 1.86–2.04 (m, 2H), 4.96 (m, 1H), 6.24 (m, 1H), 6.93 (m, 2H), 9.48 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1670 (CO), 3280 cm^{-1} (NH). Anal. $C_{11}H_{15}NO_2$ (193.24): C, H, N.

2-Methoxyethyl 1H-pyrrole-2-carboxylate. Was prepared as the *sec*-butyl ester using 2-methoxyethanol; purification on silica gel column (dichloromethane), yield 95%; b.p. 108–110/0.15 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.42 (s, 3H), 3.69 and 4.43 (2t, J = 4.7 Hz, 4H), 6.25 (m, 1H), 6.95 (m, 2H), 9.60 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (neat): ν 1710–1720 (CO), 3280–3300 cm^{-1} (NH). Anal. $C_8H_{11}NO_3$ (169.18): C, H, N.

N-Benzyl, N-methyl 1H-pyrrole-2-carboxyamide. A mixture of 2-trichloroacetyl-1*H*-pyrrole [17] (5.31 g, 0.025 mol), triethylamine (3.03 g, 0.03 mol) and *N*-benzylmethylamine (15.73 g, 0.13 mol) was heated at 60 °C for 20 h. Removal of the excess of *N*-benzylmethylamine gave the crude amide which was purified on silica gel column (ethyl acetate), yield 97%; m.p. 98–100 °C (ligroin). ^{1}H NMR ($CDCl_3$): δ 3.19 (s, 3H), 4.83 (s, 2H), 6.20 (m, 1H), 6.53 (broad, 1H), 6.92 (m, 1H), 7.25–7.38 (m, 5H), 10.19 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1605 (CO), 3260 cm^{-1} (NH). Anal. $C_{13}H_{14}N_2O$ (214.26): C, H, N.

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Appendix A

Elemental analyses of derivatives **9–32**

Compound	Elemental analyses calculated/found				
	C	H	N	Cl	S
9	46.58	3.91	7.24	9.17	8.29
	46.42	3.88	7.18	9.20	8.35
10	46.58	3.91	7.24	9.17	8.29
	46.72	3.98	7.20	9.21	8.30
11	46.58	3.91	7.24	9.17	8.29
	46.42	3.88	7.30	9.20	8.16
12	46.82	3.41	7.28	9.21	8.33
	46.73	3.38	7.35	9.29	8.28
13	45.60	2.46	7.60	9.61	8.69
	45.38	2.39	7.72	9.80	8.55
14	48.19	3.79	7.02	8.89	8.04
	48.01	3.80	6.89	8.97	7.95
15	49.46	4.15	6.79	8.59	7.77
	49.52	4.12	6.85	8.60	7.71
16	43.25	3.37	7.21	9.12	8.25
	43.09	3.42	7.20	9.06	8.30
17	42.39	1.94	13.48	11.37	10.29
	42.51	2.16	13.55	11.21	10.16
18	50.19	2.73	6.89	8.72	7.88
	50.36	2.80	6.90	8.68	7.80
19	43.52	3.09	7.81	9.88	8.94
	43.48	2.97	7.68	9.91	8.80
20	50.49	4.80	7.85	9.94	8.98
	50.18	4.81	7.79	9.97	8.90
21	50.49	4.80	7.85	9.94	8.98
	50.60	4.71	7.83	10.09	8.97
22	50.49	4.80	7.85	9.94	8.98
	50.56	4.81	7.73	10.12	8.87
23	50.78	4.26	7.90	9.99	9.04
	50.84	4.09	7.79	10.02	9.01
24	49.64	3.27	8.27	10.47	9.46
	49.82	3.10	8.21	10.65	9.41
25	52.10	4.65	7.60	9.61	8.69
	52.11	4.48	7.45	9.73	8.60
26	53.33	5.00	7.32	9.26	8.37
	53.57	5.07	7.39	9.21	8.42
27	46.87	4.21	7.81	9.88	8.94
	46.86	4.10	7.76	9.81	8.85
28	45.29	3.80	8.13	10.28	9.30
	45.43	3.77	8.05	10.41	9.47
29	46.90	2.86	14.92	12.58	11.38
	47.08	2.78	15.13	12.89	11.19
30	54.19	3.48	7.43	9.41	8.51
	54.21	3.44	7.43	9.40	8.35
31	47.49	3.99	8.52	10.78	9.75
	47.56	4.17	8.38	10.65	9.84
32	47.86	3.40	17.17	21.74	9.83
	47.77	3.88	17.04	21.56	9.81

Appendix B

Elemental analyses of derivatives **33–37** and **39–43**

Compound	Elemental analyses calculated/found				
	C	H	N	Cl	S
33	44.75	3.07	14.23	–	10.86
	44.48	2.90	14.06	–	10.77
34	40.07	2.45	12.74	10.75	9.72
	39.74	2.37	12.83	10.66	9.50
35	43.64	3.38	11.75	9.91	8.96
	43.45	3.31	11.66	9.73	9.02
36	46.70	4.18	10.89	9.19	8.31
	46.81	4.20	10.82	9.15	8.30
37	52.60	3.72	9.69	8.17	7.39
	52.38	3.66	9.70	8.11	7.40
39	49.80	4.18	15.84	–	12.09
	49.57	4.09	15.48	–	11.83
40	44.08	3.36	14.02	11.83	10.70
	44.26	3.27	13.92	11.99	10.56
41	47.64	4.30	12.82	10.82	9.78
	47.77	4.17	12.77	10.84	9.76
42	50.63	5.10	11.81	9.96	9.01
	50.82	5.13	11.86	9.82	9.04
43	56.50	4.49	10.40	8.78	7.94
	56.41	4.48	10.37	8.80	7.87

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