Novel Indolyl Aryl Sulfones Active against HIV-1 Carrying NNRTI Resistance Mutations: Synthesis and SAR Studies

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The potent anti-HIV-1 activities of L-737,126 (**2**) and PAS sulfones prompted us to design and test against HIV-1 in acutely infected MT-4 cells a number of novel 1- and 3-benzenesulfonylindoles. Indoles belonging to the 1-benzenesulfonyl series were found poorly or totally inactive. On the contrary, some of the 3-benzenesulfonyl derivatives turned out to be as potent as **2**, being endowed with potencies in the low nanomolar concentration range. In particular, (2-methylphenyl)sulfonyl (**72**) and (3-methylphenyl)sulfonyl (**73**) derivatives showed EC_{50} values of 1 nM. Introduction of two methyl groups at positions 3 and 5 of the phenyl ring of **2** furnished derivatives (**80** and **83**) which showed very potent and selective anti-HIV-1 activity not only against the wt strain, but also against mutants carrying NNRTI-resistant mutations at positions 103 and 181 of the reverse transcriptase gene.

Introduction

Current drugs effective against the HIV-1 reverse transcriptase (RT) are classified according to their structure as nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).[1] NRTIs, such as AZT, ddC, ddI, and 3TC, interfere with the enzyme activity following metabolic activation to the triphosphate forms and incorporation into the growing DNA strand, which causes premature chain termination. On the contrary, NNRTIs do not require preliminary phosphorylation and are less toxic than nucleoside analogues because they do not affect the activity of cellular polymerases. However, NNRTIs give rise to the rapid emergence of drug-resistant strains which are cross-resistant to other inhibitors within the class. Development of new NNRTIs effective against current clinical resistant strains is, therefore, highly pursued.

Following the discovery of the nitrophenyl phenyl sulfone (NNPS, **1**),[2] new derivatives (such as L-737,126, **2**) have been described which were characterized by the substitution of the nitrophenyl moiety with a 5-chloro-1*H*-indol-3-yl-2-carboxyamide[3] (Chart 1). Although L-737,126 turned out to be one of the most potent and selective NNRTIs ever known, its poor solubility hindered further development. Compounds more potent than NNPS have also been obtained following the replacement of the benzene ring with pyrrole[4,5] (e.g., the 1*H*-pyrrol-1-yl aryl sulfones (PASs) **3** and **4**). In this case, the presence of a *p*-chloroanilino moiety was determinant for their potency and selectivity.

Chart 1

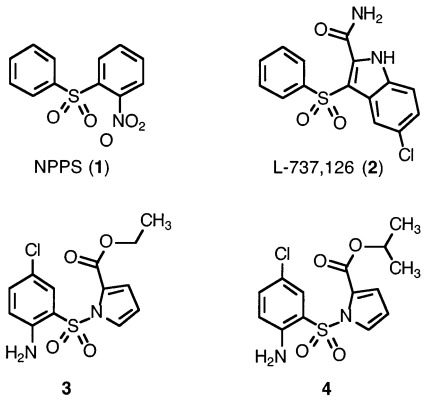
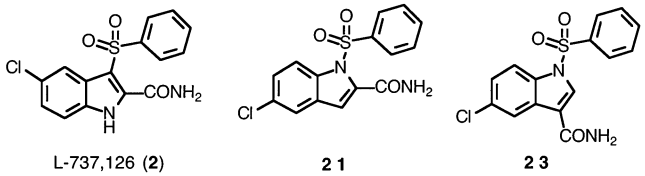


Chart 2



To our knowledge, no attempts have been published reporting SAR investigations on indolyl sulfones. Therefore, we designed, synthesized, and evaluated in vitro the anti-HIV-1 activity of novel indolyl aryl sulfones (IASs). The aim was to investigate the effect of the following structural changes: (i) the shift of the benzene sulfonyl moiety from position 3 to position 1 of the indole ring; (ii) the modification of the carboxyamide side chain and its shift from position 2 to position 3 (Chart 2); (iii) the introduction of different substituents on the phenyl ring; (iv) the replacement of phenyl ring with a *p*-chloroanilino pharmacophore. The most potent derivatives were also tested for activity against HIV-1 strains

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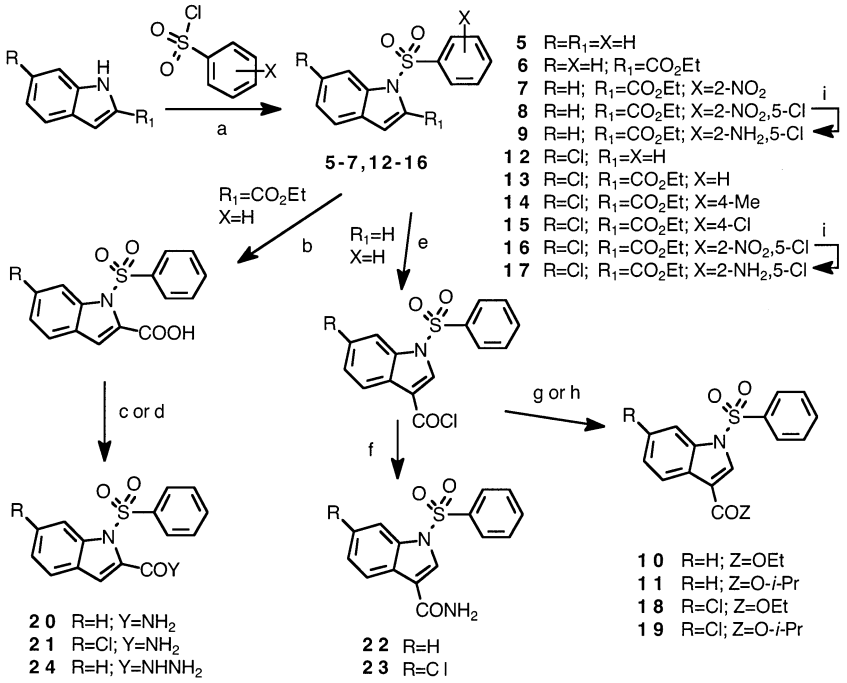
Scheme 1[a]



[a] Reagents and reaction conditions. a: *t*-BuOK, 18-crown-6, THF, r.t., 3.5 h; b: KOH, EtOH−THF 1:1, r.t., 4 h; c: CDI, THF, r.t., 2 h, then NH_3(g), r.t., 1 h; d: CDI, THF, r.t., 2 h, then $NH_2NH_2 \cdot H_2O$, r.t., 1 h; e: $(COCl)_2$, $AlCl_3$, CH_2Cl_2, 0 °C to r.t., 2 h; f: NH_3(g), DMF, r.t., 1 h; g: EtOH, $NaHCO_3$, r.t., overnight; h: *i*-PrOH, $NaHCO_3$, r.t., overnight; i: Fe, MeCOOH, 60 °C, 2 h.

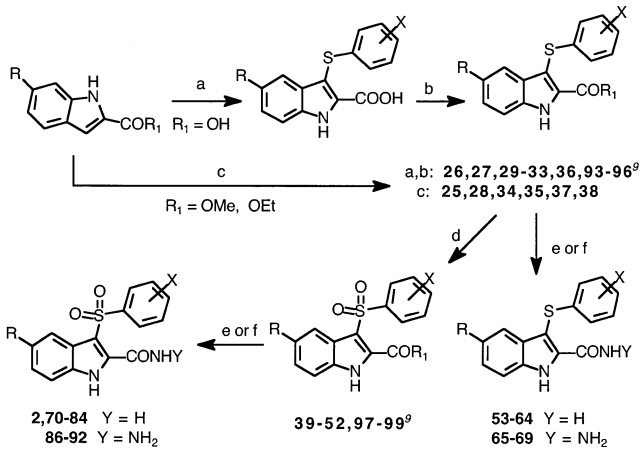
carrying some of the most clinically relevant mutations conferring resistance to NNRTIs.

Chemistry

The synthesis of 1-arylsulfonyl-1*H*-indole derivatives is depicted in Scheme 1. Compounds **5**−**7** and **12**−**16** were prepared by reaction of indole or ethyl indole-2-carboxylate with appropriate arylsulfonyl chlorides in the presence of potassium *tert*-butoxide and 18-crown-6. Amino derivative **17** was obtained by iron powder reduction of **16** in glacial acetic acid. Reaction of 1-phenylsulfonyl-1*H*-indole (**5**) or its 5-chloro derivative **12** with oxalyl chloride in the presence of anhydrous aluminum trichloride[6] afforded the corresponding 3-carbonyl chlorides, which were transformed into **10**, **18**, and **11**, **19** by reaction with ethanol or 2-propanol, respectively, in the presence of sodium hydrogen carbonate, or into amides **22** and **23** by reaction with ammonia. Alkaline hydrolysis of the esters **6** or **13** furnished the corresponding acids which were transformed into amides the **20** and **21** by reaction with 1,1′-carbonyldiimidazole and subsequent displacement of the related imidazolides with gaseous ammonia. The hydrazide **24** was prepared similarly by using hydrazine hydrate.

The synthesis of 3-arylthio-1*H*-indole and the corresponding 3-arylsulfonyl derivatives is depicted in Scheme 2. The required 3-arylthio-1*H*-indole-2-carboxylates were prepared by reaction of proper arylthiodisulfides with 1*H*-indole-2-carboxylic acids in the presence of sodium hydride according to the Atkinson method[7] and subsequent esterification of the 3-arylthio-1*H*-indole-2-carboxylic acids with (trimethylsilyl)diazomethane. Esters **26**, **27**, **29**−**33**, and **36** were prepared according to this procedure. The intermediates 3-arylthio-1*H*-indole-2-carboxylic acids were purified with some difficulty by

Scheme 2[a]

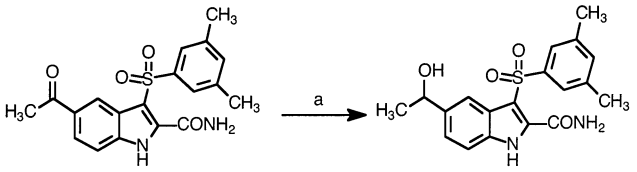


25,**39** R=H, R_1=OEt, X=H
26,**40** R=Cl, R_1=OMe, X=H
27,**41** R=Cl, R_1=OMe, X=2-Me
28,**42** R=Cl, R_1=OMe, X=3-Me
29,**43** R=Cl, R_1=OMe, X=4-Me
30,**44** R=Cl, R_1=OMe, X=4-F
31,**45** R=Cl, R_1=OMe, X=4-Cl
32,**46** R=Cl, R_1=OMe, X=4-*i*-Pr
33,**47** R=Cl, R_1=OMe, X=4-t-Bu
34,**48** R=Cl, R_1=OMe, X=2,4-Me_2
35,**49** R=Cl, R_1=OMe, X=3,5-Me_2
36,**50** R=Cl, R_1=OMe, X=2,6-Cl_2
37,**51** R=BrI, R_1=OEt, X=3,5-Me_2
38,**52** R=$COCH_3$, R_1=OEt, X=3,5-Me_2
93 R = H, R_1=OEt, X=H
94,**97** R=H, R_1=OEt, X=2-NH_2,5-Cl
95,**98** R=Cl, R_1=OEt, X=2-NH_2
96,**99** R=Cl, R_1=OEt, X=2-NH_2,5-Cl

53,**70**,**86** R=H, X=H
54,**71** R=H, X=2-NH_2,5-Cl
55,**65**,**87** R=Cl, X=H
56,**72** R =Cl, X=2-Me
57,**74**,**66**,**88** R=Cl, X=4-Me
58,**75**,**67**,**89** R=Cl, X=4-F
59,**76**,**68**,**90** R=Cl, X=4-Cl
60,**77** R=Cl, X=4-*i*-Pr
61,**78** R=Cl, X=4-*t*-Bu
62,**80**,**91** R=Cl, X=3,5-Me_2
63,**81** R=Cl, X=2,6-Cl_2
64,**82**,**69**,**92** R=Cl, X=2-NH_2,5-Cl
73 R=Cl, X=3-Me
79 R=Cl, X=2,4-Me_2
83 R=Br, X=3,5-Me_2
84 R=COMe, X=3,5-Me_2

[a] Reagents and reaction conditions. a: ArS−SAr, NaH, DMF, 50 °C, overnight, N_2 stream; b: (trimethylsilyl)diazomethane, CH_2Cl_2, r.t., 90 min; c: *N*-(ArS)succinimide, $BF_3 \cdot Et_2O$, CH_2Cl_2, r.t., 2 h, then 45 °C, 2 h, Ar stream; d: MCPBA, $CHCl_3$, r.t., 1 h; e: 30% NH_4OH, NH_4Cl, sealed tube, 100 °C, overnight; f: $NH_2NH_2 \cdot H_2O$, EtOH, 60 °C, 1.5 h.

Scheme 3[a]



[a] Reagents and reaction conditions. a: $NaBH_4$, $THF-H_2O$, 60 °C, 2 h.

Table 1. Cytotoxicities and Anti-HIV-1 Activities of Derivatives **5**−**24**[a]

compd	CC_{50}[b]	EC_{50}[c]	SI[d]
5	15012	>150	-
6	>200	>200	-
7	>200	>200	-
8	>100	>100	-
9	50 ± 6	1.8 ± 0.22	28
10	32 ± 2.5	>32	-
11	54 ± 5	>54	-
12	75 ± 6.2	>75	-
13	>200	>200	-
14	>200	>200	-
15	>200	>200	-
16	31 ± 2	>31	-
17	39 ± 4	8.30 ± 72	4.7
18	42 ± 3.5	>42	-
19	>200	>200	13.3
20	>200	15 ± 1.2	-
21	>200	66 ± 5	>3
22	32 ± 3.1	>32	-
23	200	>200	-
24	>200	>200	-
2	45 ± 5	0.001 ± 0.0002	45 000

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

crystallization. Moreover, as already reported,[7] this procedure furnished poor yields when the preparation of carboxylic esters was attempted. For this reason, an alternative synthetic method was adopted. Compounds **25**, **28**, **34**, **35**, **37**, and **38** were prepared by reaction of methyl or ethyl 1*H*-indole-2-carboxylates with *N*-(arylthio)succinimides in the presence of boron trifluoride diethyl etherate.[8] Oxidation of 3-arylthio-1*H*-indole-2-carboxylates to the related sulfones was performed with 3-chloroperoxybenzoic acid (MCPBA). Esters **25**−**52**, **94**,[9] **96**,[9] **98**,[9] and **99**[9] were transformed into amides **2**, **53**−**64**, **70**−**84** and hydrazides **65**−**69**, **86**−**92** by heating at 100 °C with 30% ammonium hydroxide in a sealed tube or by treatment with hydrazine hydrate at 60 °C, respectively. Sodium borohydride reduction of ketone **84** furnished the related alcohol **85** (Scheme 3).

Results and Discussion

Table 1 reports the results obtained with compounds synthesized to investigate the effect, on the antiretroviral activity, of the shift of the benzenesulfonyl moiety from position 3 (the prototype is L-737,126, **2**) to position 1 of the indole ring. These derivatives are also characterized by the presence of carboxyethyl or carboxyamide groups either at positions 2 or 3 of the indole.

Table 2. Cytotoxicities and Anti-HIV-1 Activities of Sulfides **25**, **93**−**96**, and Sulfones **39**, **97**−**99**[a]

compd	CC_{50}[b]	EC_{50}[c]	SI[d]
25	1.4 ± 0.5	1.4 ± 0.4	-
93[e]	>200	>200	-
94[e]	≥200	≥200	-
95[e]	>200	2.3 ± 0.28	>87
96[e]	>200	2.5 ± 0.22	>80
39	157 ± 12	3.7 ± 0.3	42
97[e]	>200	2.5 ± 0.23	>91
98[e]	>200	>200	-
99[e]	>200	1.9 ± 0.5	105
2	45 ± 5	0.001 ± 0.0002	45 000

[a] Data represent mean values ± SE for three separate experiments. [b] Compound concentration (μM) required to reduce the viability of mock-infected cells by 50% as determined by the MTT method. [c] Compound concentration (μM) required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity as determined by the MTT method. [d] Selectivity index: CC_{50}/EC_{50} ratio. [e] Literature[13]

With the exception of **9** (EC_{50} = 1.8 μM) and **17** (EC_{50} = 8.3 μM), which are 1-benzenesulfonyl-2-carboxyethyl derivatives, and of **20** (EC_{50} = 15 μM) and **21** (EC_{50} = 66 μM), which are 1-benzenesulfonyl-2 carboxyamide derivatives, the other 1-benzenesulfonyl indoles were totally devoid of anti-HIV-1 activity. Noteworthy, **9** and **17** were both characterized by a *p*-chloroanilino pharmacophore, which appears to be determinant for the antiretroviral activity (compare **9** and **17** with **6** and **13**, respectively). As far as 1-benzenesulfonyl-2-carboxyamide derivatives are concerned, the shift of the carboxyamide function to position 3 of the indole (**22**, **23**), or its substitution with a 2-carboxyhydrazide group (**24**), led to loss of activity. Noteworthy, an about 4-fold reduction of antiretroviral activity correlated with the introduction of a chlorine atom at position 5 of the indole ring, no matter whether a carboxyethyl or a carboxyamide group was present at position 2 (compare **9** and **20** with **17** and **21**, respectively).

Tables 2−4 summarize the anti-HIV-1 activity of arylthio and 3-benzenesulfonyl indoles carrying different substituents on the phenyl ring and/or at position 2 of the indolo moiety. With some exceptions, compounds carrying carboxyethyl groups at position 2 of the indole proved weakly active (Table 2). Noteworthy, three of them (**39**, **97**, **99**) were the counterparts of the 1-arylsulfonylindoles **6**, **9**, **17**, respectively. Although structure−activity relationships were not immediately obvious, the 2-carboxyethyl sulfone derivatives **39**, **97**, **99** proved equally or even more potent than sulfur counterparts **25**, **94**, **96** with sole exception of the 2-aminobenzene derivative **95** (compare **98** and **95**).

Substitution of the ester function with an amide function led to a very significant increase of both potency and selectivity (Table 3). Among the monosubstituted sulfones, the introduction of a methyl group at position ortho (**72**), meta (**73**), or para (**74**) of the phenyl ring led to derivatives as potent as the reference compound **2**. When electron-withdrawing (**75**, **76**) or bulky (**77**, **78**) substituents were introduced, a 10- to 100-fold reduction of potency was observed. The positive biological effect of the presence of methyl groups in the phenyl ring was confirmed in the disubstituted series, where 2,4-Me_2 and 3,5-Me_2 derivatives proved fairly potent (**79**, **80**, **83**−**85**), although in some cases also cytotoxic. Unlike what

Table 3. Cytotoxicities and Anti-HIV-1 Activities of Derivatives **53**−**64** and **70**−**85**[a]

compd	CC_{50}[b]	EC_{50}[c]	SI[d]
53	14 ± 2	1.4 ± 0.95	10
54	20 ± 2.8	9 ± 1.2	2.2
55	9 ± 1.5	0.02 ± 0.005	450
56	26 ± 2.5	0.3 ± 0.1	87
57	0.45 ± 0.3	>0.45	-
58	13 ± 2	1.4 ± 0.5	9
59	13 ± 1.6	3.1 ± 0.4	4
60	52 ± 4.2	1.9 ± 0.17	27
61	45 ± 3	8 ± 0.6	6
62	0.7 ± 0.1	0.006 ± 0.0005	117
63	61 ± ± ± 7	1.2 ± 0.6	51
64	33 ± 2.7	1.6 ± 0.2	20
70	>200	0.18 ± 0.05	>1,111
71	3.5 ± 0.18	0.3 ± 0.06	11.7
72	>200	0.001 ± 0.0001	>200 000
73	>200	0.001 ± 0.0002	>200 000
74	>200	0.003 ± 0.0003	>66 667
75	17 ± 2.1	0.014 ± 0.002	1214
76	>200	0.011 ± 0.0009	>18 182
77	>200	0.08 ± 0.006	>2500
78	26 ± 2	0.13 ± 0.02	200
79	37 ± 3.2	0.004 ± 0.0004	9250
80	15 ± 1.2	0.004 ± 0.0003	3750
81	40 ± 5.2	0.1 ± 0.018	400
82	4.6 ± 0.33	0.04 ± 0.005	115
83	18 ± 0.9	0.002 ± 0.0001	9000
84	>200	0.015 ± 0.002	>13 333
85	>200	0.025 ± 0.002	>8000
2	45 ± 5	0.001 ± 0.0002	45 000

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

was observed in the PAS series,[5] replacement of the phenyl ring with a *p*-chloroanilino pharmacophore led to loss of activity (compare **2** with **82**). As a rule, the 2-carboxyamide sulfone derivatives (**70**−**85**) turned out to be less cytotoxic and more potent than sulfur counterparts (**53**−**64**) (compare **55**, **56**, **57**, **62** with **2**, **72**, **74**, **80**, respectively).

To improve the solubility of IAS derivatives, the carboxyamide group was replaced with a carboxyhydrazide chain (Table 4). Unfortunately, this attempt gave compounds considerably less potent then the amide counterparts. Again, sulfone derivatives were less cytotoxic and more potent than sulfur counterparts.

The most potent derivatives were then tested against a panel of HIV-1 strains carrying clinically relevant NNRTI resistance mutations (Table 5) in comparison with Efavirenz, the most potent clinically used NNRTI.[10] The lead compound **2** and its monomethyl-substituted derivatives (**72**, **73**, **74**) were found inhibitory to the Y181C mutant at submicromolar concentrations, whereas they proved inefficient inhibitors of both the K103N-Y181C double mutant and the EFV^R (K103R-V179D-P225H) triple mutant, which is highly resistant to Efavirenz. Interestingly, the potency of monomethyl derivatives against the mutant strains was found to progressively increase as the methyl group was shifted from position 4 (**74**) (in the case of K103N-Y181C and K103R-V179D-P225H), or from position 2 (**72**) (in the case of Y181C), to position 3 (**73**) of the phenyl ring. Among disubstituted derivatives, the 2,4-Me_2 derivative (**79**) confirmed the same low inhibitory potency of the

Table 4. Cytotoxicities and Anti-HIV-1 Activities of Derivatives **65**−**69** and **86**−**92**[a]

compd	CC_{50}[b]	EC_{50}[c]	SI[d]
65	44 ± 3.2	0.5 ± 0.06	88
66	129 ± 2.5	1.5 ± 0.02	86
67	66 ± 7	5 ± 0.6	13
68	30 ± 3.3	10 ± 1.7	3
69	13 ± 2.1	>13	-
86	133 ± 17	0.5 ± 0.06	266
87	>200	0.01 ± 0.004	>20 000
88	>200	0.05 ± 0.006	>4000
89	44 ± 5.2	0.3 ± 0.025	147
90	>200	0.2 ± 0.015	>1000
91	>200	0.1 ± 0.005	>2000
92	19 ± 2.2	0.3 ± 0.02	63
2	45 ± 5	0.001 ± 0.0002	45 000

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

2-methyl derivative (**72**) against all resistant strains. On the contrary, the 3,5-Me_2 derivative (**80**) proved highly potent against Y181C, K103N-Y181C, and K103R-V179D-P225H mutants. Interestingly, the activity of **80** against the two HIV-1 strains carrying mutations at the 103 position of the RT gene was 10-fold superior to that of **2**. Finally, it is worth noting that, when compared to Efavirenz, **80** turned out to be a 4-fold less efficient inhibitor of the double mutant K103N-Y181C, but a 22-fold better inhibitor of the triple mutant K103R-V179D-P225H.

HIV-1 bearing the K103N mutation are known to be the most frequently emerging variants in patients subjected to HAART based on Nevirapine and Efavirenz as single NNRTIs. Therefore, it was interesting to determine whether the high level resistance of the double mutant K103N-Y181C to the more active indoles was due primarily to the K103N mutation or to the concomitant effect of the two mutations on the RT non-nucleoside binding site. Hence, compounds **80**, **2** and Efavirenz were assayed in MT-4 cells against an HIV-1 strain containing a single K103N mutation. The EC_{50}s were in each case greater than 1.0 μM, suggesting that the high level resistance of the double mutant has to be related to the presence of K103N mutation.

Compounds **74**, **80**, and **2** were then tested against recombinant RTs (rRT) from wt, K103N, and Y181C mutant HIV-1. Consistently with the results obtained in cell-based assays, all compounds inhibited both the wt and Y181C enzymes, but not the rRT carrying the K103 mutation. This confirmed that title compounds target the HIV-1 reverse transcriptase (Table 6).

Conclusions

This study clearly demonstrated that the position of both benzenesulfonyl and carboxyamide moieties on the indole ring were crucial for the anti-HIV-1 activity. In terms of chemical features we found that the best results were obtained with 3-benzenesulfonylindoles carrying a 2-carboxyamide function (Table 3). Related esters (Table 2) and hydrazides (Table 4) were always less potent, whereas the corresponding carboxylic acids were totally inactive (data not shown). The modest anti-

Table 5. Anti-HIV-1 Activities of Derivatives 72−74, 79 and 80 against Some Clinically Relevant HIV-1 Resistant Strains[a]

compd	wt_{IIIB}, EC_{50}[b]	wt_{IIIB}, EC_{90}[c]	Y181C, EC_{50}[b]	K103N-Y181C, EC_{50}[b]	EFV^R, EC_{90}[d]
72	0.001 ± 0.0001	0.005 ± 0.0003	0.16 ± 0.04	10 ± 2	2.6 ± 1
73	0.001 ± 0.0002	0.005 ± 0.0006	0.006 ± 0.001	7 ± 1.5	0.26 ± 0.05
74	0.003 ± 0.0003	0.01 ± 0.005	0.02 ± 0.004	>100	93 ± 12
79	0.004 ± 0.0004	0.01 ± 0.01	0.15 ± 0.08	10 ± 1.8	5.3 ± 1.2
80	0.004 ± 0.0003	0.002 ± 0.0003	0.03 ± 0.008	0.65 ± 0.1	0.08 ± 0.01
2	0.001 ± 0.0002	0.007 ± 0.0007	0.02 ± 0.005	8 ± 1.7	0.9 ± 0.15
EFV[e]	0.004 ± 0.0003	0.008 ± 0.001	0.025 ± 0.005	0.15 ± 0.05	1.8 ± 0.5

[a] Data represent mean values ± SE for three separate experiments. [b] Compound concentration (μM) required to achieve 50% protection of MT-4 cells from the indicated strain HIV-1 induced cytopathogenicity as determined by the MTT method. [c] Compound concentration (μM) required to reduce the amount of p24 by 90% in WT_{IIIB} infected C8166 cells. [d] Compound concentration (μM) required to reduce the amount of p24 by 90% in C8166 cells infected with an efavirenz resistant strain carrying mutations K103R, V179D, and P225H. [e] EFV, Efavirenz.

Table 6. Activities of Derivatives **74**, **80**, **2** and Efavirenz against wt and Mutant Recombinant RTs[a]

compd	wt_{IIIB}, IC_{50}[b]	K103N, IC_{50}[b]	Y181C, IC_{50}[b]
74	0.072 ± 0.0055	>5	0.11 ± 0.010
80	0.031 ± 0.0061	>5	0.13 ± 0.024
2	0.025 ± 0.0032	>5	0.16 ± 0.051
EFV[c]	0.033 ± 0.0023	3.4 ± 0.3	0.085 ± 0.01

[a] Data represent mean values ± SE for two separate experiments. [b] Compound concentration (μM) required to inhibit the HIV-1 rRT activities by 50%. [c] EFV, Efavirenz.

HIV-1 activity of 1-benzenesulfonyl indoles, which has been previously reported by us on structurally similar derivatives,[5] may be due to the fact that they interact with the RT non-nucleoside binding site (NNBS) differently from 3-benzenesulfonyl indoles.

A second interesting aspect of this study is that both potency and spectrum of 3-benzenesulfonyl-2-carboxyamido indoles vary depending on the number and position of the substituents on the phenyl ring. Numerous phenyl-substituted IASs proved as potent as the parent compound **2** against HIV-1 wt (**72**−**74**, **79**, **80**, and **83**) and some of them also showed comparable/slightly lower activity against the Y181C (**73**, **74**, and **80**) and K103N-Y181C (**72**, **73**, **79**, and **80**) strains carrying clinically relevant NNRTI resistance mutations and the K103R-V179D-P225H (**72**, **73**, and **80**) strain highly resistant to Efavirenz. However, it is the 3,5-Me_2 substitution that comes up as the major determinant for the broad spectrum activity against resistant mutants. In fact, derivative **80** turned out as active as **2** and Efavirenz against wt and Y181C, 10- and 20-fold more potent than **2** and Efavirenz, respectively, against K103R-V179D-P225H and, finally, about 10-fold more potent than **2** and only 4-fold less potent than Efavirenz against K103N-Y181C mutant.

Assays against both wt and mutant enzymes confirm that, like Efavirenz, title compounds target the HIV-1 RT. Why in enzyme assays the potency of all the compounds tested is up to 15-fold lower than in cell-based assays is not immediately obvious. Nevertheless, time of addition studies carried out with **80** (data not shown) indicate that, like Efavirenz, it must be added to acutely infected cell cultures within 6 h post infections in order to prevent the HIV-1 multiplication. In addition, **80** is not inhibitory to the HIV-2 multiplication in C8166 cells and lacks activity in enzyme assays with HIV-1 recombinant integrase (data not shown). Taken together, the above results suggest that IASs target the RT of susceptible viruses. Although title compounds potently inhibit wt and mutant HIV-1 carrying the Y181C mutation, but not the variants carrying other clinically relevant NNRTI mutations such as K103N and K103N-Y181C, the results presented herein offer a great stimulus for further improvement of the activity spectrum of novel analogues of **2**.

Experimental Section

Chemistry. Melting points (mp) were determined on a Büchi 510 apparatus and are uncorrected. 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 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 at 254 nm) and silica gel TLC cards (Fluka) (silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for thin-layer chromatography (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 performed by laboratories of Dr. M. Zancato, Dipartimento di Scienze Farmaceutiche, University of Padova (Italy). Analytical results were within ±0.4% of the theoretical values.

General Procedure for the Preparation of the 1-Arylsulfonyl-1*H*-indoles 5−8 and 1-Arylsulfonyl-5-chloro-1*H*-indoles 12−16. Example. 1-Phenylsulfonyl-1*H*-indole (5). To a stirred mixture of potassium *tert*-butoxide (2.58 g, 0.023 mol) and 18-crown-6 (0.45 g, 0.0017 mol) in anhydrous THF (25 mL) was added dropwise a solution of indole (2.00 g, 0.017 mol) in the same solvent (25 mL). After cooling at 0 °C for 15 min, a solution of benzenesulfonyl chloride (3.01 g, 0.017 mol) in anhydrous THF (25 mL) was added dropwise. 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 gave a residue which was purified on silica gel column chromatography (chloroform) to afford **5**, yield 90%, mp 78−79 °C (from ligroin), lit.[12] mp 77−79 °C. Thus, compounds **6**−**8** and **12**−**16** were prepared.

Ethyl 1-phenylsulfonyl-1*H*-indole-2-carboxylate (6), yield 96%, mp 89−90 °C (from ligroin), lit.[12] mp 89−91 °C.

Ethyl 1-[(2-nitrophenyl)sulfonyl]-1*H*-indole-2-carboxylate (7), yield 30%, mp 140−142 °C (from toluene/cyclohexane), ^1H NMR ($CDCl_3$): δ 1.23 (t, J = 7.1 Hz, 3H), 4.22 (q, J = 7.1 Hz, 2H), 7.30−7.42 (m, 2H), 7.49 (m, 1H), 7.62−7.80 (m, 3H), 7.82−7.95 (m, 2H), 8.10 ppm (d, J = 8.5 Hz, 1H). IR (Nujol): ν 1725 cm^{-1}. Anal. ($C_{17}H_{14}N_2O_6S$ (374.36)) C, H, N, S.

Ethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-1*H*-indole-2-carboxylate (8), and **Ethyl 1-[(2-amino-5-chlorophenyl)-sulfonyl]-1*H*-indole-2-carboxylate (9)** were prepared by us previously.[5]

5-Chloro-1-phenylsulfonyl-1*H*-indole (12), yield 73%, mp 73−74 °C (from ligroin), lit.[14] mp 47−48 °C.

Ethyl 5-chloro-1-phenylsulfonyl-1*H*-indole-2-carboxylate (13) yield 84%, mp 104−105 °C (from cyclohexane), lit.[8] ^{1}H NMR ($CDCl_3$): δ 1.38 (t,, J = 7.1 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 7.06 (s, 1H), 7.36 (dd, J = 2.1 and 9.1 Hz, 1H), 7.42−7.63 (m, 4H), 7.95−8.07 (m, 3H). IR (Nujol): ν 1730 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_4S$ (363.81)) C, H, N, Cl, S.

Ethyl 1-[(4-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (14), yield 58%, mp 84−86 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 3H), 2.38 (s, 3H), 4.41 (q, J = 7.1 Hz, 2H), 7.06 (s, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.37 (dd, J = 2.0 and 9.0 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.89 (d, J = 8.3 Hz, 2H), 8.04 ppm (d, J = 9.0 Hz, 1H), IR (Nujol): ν 1730 cm^{-1}. Anal. ($C_{18}H_{16}ClNO_4S$ (377.84)) C, H, N, Cl, S.

Ethyl 1-[(4-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (15), yield 62%, mp 86−88 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.10 (s, 1H), 7.39 (dd, J = 2.0 and 9.0 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 8.7 Hz, 2H), 8.04 ppm (d, J = 9.0 Hz, 1H). IR (Nujol): ν 1730 cm^{-1}. Anal. ($C_{17}H_{13}Cl_2NO_4S$ (398.26)) C, H, N, Cl, S.

Ethyl 1-[(5-chloro-2-nitrophenyl)sulfonyl]-5-chloro-1*H*-indole-2-carboxylate (16), yield 28%, mp 161 °C (from toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H), 4.34 (q, J = 7.2 Hz, 2H), 7.49 (dd, J = 2.1 and 9.1 Hz, 1H), 7.66−7.72 (m, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.86−7.92 (m, 2H), 7.95 ppm (d, J = 9.1 Hz, 1H), IR (Nujol): ν 1710 cm^{-1}. Anal. ($C_{17}H_{12}Cl_2N_2O_6S$ (441.98)) C, H, N, Cl, S.

Ethyl 1-[(2-amino-5-chlorophenyl)sulfonyl]-5-chloro-1*H*-indole-2-carboxylate (17) was prepared by iron powder reduction of **16** in glacial acetic acid as previously reported by us,[5] yield 88%, mp 105−106 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.39 (t, J = 7.0 Hz, 3H), 4.38 (q, J = 7.0 Hz, 2H), 5.30 (broad s, 2H, disappeared on treatment with D_2O), 6.61 (d, J = 8.8 Hz, 1H), 7.14 (s, 1H), 7.22 (dd, J = 2.4 and 8.8 Hz, 1H), 7.37 (dd, J = 2.1 and 9.2 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.83 ppm (d, J = 9.2 Hz, 1H), IR (Nujol): ν 1710, 3370, 3480 cm^{-1}. Anal. ($C_{17}H_{14}Cl_2N_2O_4S$ (412.00)) C, H, N, Cl, S.

Synthesis of the 1-(Phenylsulfonyl)-1*H*-indole-3-carboxylic Esters 10, 11, 18, and 19. Example. Ethyl 1-(Phenylsulfonyl)-1*H*-indole-3-carboxylate (10). 1-(Phenylsulfonyl)-1*H*-indole-3-carbonyl chloride was prepared by reaction with 1-phenylsulfonyl-1*H*-indole (**5**) with oxalyl chloride in the presence of anhydrous aluminum trichloride as reported by Ketcha and Gribble.[6] A suspension of 1-(phenylsulfonyl)-1*H*-indole-3-carbonyl chloride (1.0 g, 0.0031 mol), sodium hydrogen carbonate (0.62 g, 0.0031 mol), and absolute ethanol (150 mL) was stirred at room-temperature overnight. After concentration to a small volume, the residue was extracted with ethyl acetate and washed with brine. Evaporation of the solvent gave a residue which was purified on silica gel column chromatography (dichloromethane:petroleum ether 1:1) to afford **10**, yield 78%, mp 113−114 °C (from ligroin), lit.[13] mp 118.5−119.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.1 Hz, 2H), 7.27−7.40 (m, 2H), 7.40−7.64 (m, 3H), 7.88−8.02 (m, 3H), 8.16 (m, 1H), 8.28 ppm (s, 1H). IR (Nujol): ν 1710 cm^{-1}. Thus, compounds **11, 18**, and **19** were prepared.

Isopropyl 1-(phenylsulfonyl)-1*H*-indole-3-carboxylate (11), yield 86%, mp 90−92 °C (from ligroin). ^{1}H NMR ($CDCl_3$): δ 1.40 (d, J = 6.2 Hz, 6H), 5.28 (sp, J = 6.2 Hz, 1H), 7.28−7.42 (m, 2H), 7.42−7.66 (m, 3H), 7.95 (m, 3H), 8.13 (m, 1H), 8.27 ppm (s, 1H). IR (Nujol): ν 1680 cm^{-1}. Anal. ($C_{18}H_{17}NO_4S$ (343.39)) C, H, N, S.

Ethyl 5-chloro-1-(phenylsulfonyl)-1*H*-indole-3-carboxylate (18), yield 97%, mp 145−146 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 7.32 (dd, J = 2.0 and 8.7 Hz, 1H), 7.42−7.67 (m, 3H), 7.83−7.98 (m, 3H), 8.11 (d, J = 2.0 Hz, 1H), 8.28 ppm (s, 1H). IR (Nujol): ν 1705 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_4S$ (363.81)) C, H, N, S, Cl.

Isopropyl 5-chloro-1-(phenylsulfonyl)-1*H*-indole-3-carboxylate (19), yield 54%, mp 121−122 °C (from ligroin). ^{1}H NMR ($CDCl_3$): δ 1.40 (d, J = 6.2 Hz, 6H), 5.27 (sp, J = 6.2 Hz, 1H), 7.32 (dd, J = 2.0 and 8.9 Hz, 1H), 7.43−7.68 (m, 3H), 7.83−7.98 (m, 3H), 5.56 (d, J = 2.0 Hz, 1H), 8.26 ppm (s, 1H). IR (Nujol): ν 1715 cm^{-1}. Anal. ($C_{18}H_{16}ClNO_4S$ (377.84)) C, H, N, S, Cl.

1-(Phenylsulfonyl)-1*H*-indole-2-carboxyamide (20). A mixture of **6** (3.29 g, 0.01 mol), 2 N KOH (20 mL, 2.24 g KOH, 0.04 mol), THF (20 mL), and ethanol (20 mL) was stirred at room temperature for 4 h, then it was quenched on crushed ice and made acidic with 37% HCl. Ethyl acetate was added, and the organic layer was separated, washed with brine, and dried. Removal of the solvent furnished the crude acid (2.1 g, 0.007 mol, 70%) which was dissolved in anhydrous THF (50 mL) and treated portionwise with 1,1′-carbonyldiimidazole (1.62 g, 0.1 mol). After stirring at room temperature for 2 h, gaseous ammonia was bubbled through at 0 °C for 1 h. Water and ethyl acetate were added while shaking. The organic layer was separated, washed with brine, and dried. Removal of the solvent furnished a crude product which was purified on alumina column chromatography (chloroform−ethanol 95:5) to afford **20**, yield 95%, mp 205−206 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 7.03 (s, 1H), 7.21−7.47 (m, 2H), 7.53−7.81 (m, 5H, 4H disappeared on treatment with D_2O), 7.97 (d, J = 8.2 Hz, 1H), 8.08−8.20 (m, 2H), 8.30 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3100, 3420 cm^{-1}. Anal. ($C_{15}H_{12}N_2O_3S$ (300.33)) C, H, N, S.

5-Chloro-1-(phenylsulfonyl)-1*H*-indole-2-carboxyamide (21) was prepared as **20** starting from **13**, yield 50%, mp 193−194 °C (from ligroin). ^{1}H NMR (DMSO-d_6): δ 6.99 (s, 1H), 7.42 (dd, J = 2.0 and 9.0 Hz, 1H), 7.56−7.78 (m, 4H), 7.84 (broad s, 1H, disappeared on treatment with D_2O), 7.99 (d, J = 9.0 Hz, 1H), 8.11−8.22 (m, 2H), 8.34 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3160, 3420 cm^{-1}. Anal. ($C_{15}H_{11}ClN_2O_3S$ (334.77)) C, H, N, S, Cl.

1-(Phenylsulfonyl)-1*H*-indole-2-carboxyhydrazide (24) was prepared as **20** by reaction with hydrazine hydrate, yield 52%, mp 148−150 °C (from aqueous ethanol). ^{1}H NMR (DMSO-d_6): δ 4.63 (broad s, 2H, disappeared on treatment with D_2O), 6.98 (s, 1H), 7.28 (m, 1H), 7.40 (dt, J = 1.2 and 7.5 Hz, 1H), 7.54−7.78 (m, 4H), 7.97 (d, J = 8.1 Hz, 1H), 8.13−8.23 (m, 2H), 10.02 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3340 cm^{-1}. Anal. ($C_{15}H_{13}N_3O_3S$ (315,34)) C, H, N, S.

1-(Phenylsulfonyl)-1*H*-indole-3-carboxyamide (22). Gaseous ammonia was bubbled at 0 °C through a solution of 1-(phenylsulfonyl)-1*H*-indole-3-carbonyl chloride[6] (1.0 g, 0.0031 mol) in DMF (20 mL) for 1 h. Reaction was quenched on crushed ice and extracted with ethyl acetate. Organic layer was washed with brine and dried. Removal of the solvent gave a crude product which was purified on silica gel column chromatography (ethyl acetate) to afford **22**, yield 21%, mp 233−235 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 7.24−7.44 (m, 3H, 2H disappeared on treatment with D_2O), 7.57−7.80 (m, 3H), 7.87−8.09 (m, 4H, 3H disappeared on treatment with D_2O), 8.18 (m, 1H), 8.59 ppm (s, 1H). IR (Nujol): ν 1640, 3330, 3440 cm^{-1}. Anal. ($C_{15}H_{12}N_2O_3S$ (300.33)) C, H, N, S.

5-Chloro-1-(phenylsulfonyl)-1*H*-indole-3-carboxyamide (23). This compound was prepared as reported for **22** starting from 5-chloro-1-(phenylsulfonyl)-1*H*-indole-3-carbonyl chloride, yield 30%, mp 245−247 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 7.37−7.49 (dd, J = 2.0 and 8.9 Hz, 1H, and broad s, 1H, disappeared on treatment with D_2O, overlapped signals), 7.60−7.83 (m, 3H), 7.91−8.10 (m, 4H, after treatment with D_2O showed 3H), 8.19 (d, J = 2.0 Hz, 1H), 8.69 ppm (s, 1H). IR (Nujol): ν 1635, 3180, 3300, 3430 cm^{-1}. Anal. ($C_{15}H_{11}ClN_2O_3S$ (334.77)) C, H, N, S, Cl.

General Procedure for the Synthesis of the 3-Arylthio-1*H*-indole-2-carboxylates 25, 28, 34, 35, 37 and 38. Example. Ethyl 3-(phenylthio)-1*H*-indole-2-carboxylate (25). Boron trifluoride diethyl etherate (0.135 g, 0.12 mL, 0.001 mol) was added to a mixture of ethyl 1*H*-indole-2-carboxylate (0.59 g, 0.003 mol), *N*-(phenylthio)succinimide[11] (0.68 g, 0.0033 mol), and anhydrous dichloromethane (20 mL) under dry argon

atmosphere. After stirring at room temperature for 2 h, boron trifluoride ethyl dietherate (0.27 g, 0.24 mL, 0.002 mol) was added, and then the reaction was heated at 45 °C for 2 h. After cooling, the reaction was diluted chloroform and brine while shaking. The organic layer was separated, washed with saturated solution of sodium hydrogen carbonate and then with brine, and dried. The solvent was evaporated to give a residue which was purified on silica gel column chromatography (chloroform−ethanol 95:5) to give **25**, yield 72%, mp 133−134 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 7.00−7.20 (m, 5H), 7.26−7.50 (m, 3H), 7.59 (m, 1H), 9.52 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1680, 3300 cm^{-1}. Anal. ($C_{17}H_{15}NO_2S$ (297.08)) C, H, N, S. Thus, compounds **28**, **34**, **35**, **37**, and **38** were prepared.

Methyl 5-chloro-3-[(3-methylphenyl)thio]-1*H*-indole-2-carboxylate (28), methyl 5-chloro-1*H*-indole-2-carboxylate was used, yield 80%, mp 179−180 °C (from ethanol). ^{1}H NMR (DMDO-d_6): δ 2.20 (s, 3H), 3.38 (s, 3H), 6.80 (m, 1H), 6.90−7.10 (m, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.38−7.48 (m, 2H), 7.55 (dd, J = 1.2 and 8.3 Hz, 1H), 12.58 ppm (broad, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3370 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_2S$ (331.82)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(2,4-dimethylphenyl)thio]-1*H*-indole-2-carboxylate (34), methyl 5-chloro-1*H*-indole-2-carboxylate was used, yield 60%, mp 191−193 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 2.19 (s, 3H), 2.35 (s, 3H), 3.87 (s, 3H), 6.67 (d, J = 8.0, Hz, 1H), 6.81 (m, 1H), 7.04 (m, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 2.1 and 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 12.52 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670 and 3270 cm^{-1}. Anal. ($C_{18}H_{16}ClNO_2S$ (345.84)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(3,5-dimethylphenyl)thio]-1*H*-indole-2-carboxylate (35), methyl 5-chloro-1*H*-indole-2-carboxylate was used, yield 77%, mp 174−175 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 6H), 3.95 (s, 3H), 6.73−6.82 (m, 3H), 7.28−7.41 (m, 2H), 7.58 (m, 1H), 9.30 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1675, 3280 cm^{-1}. IR (Nujol): ν 1670 and 3270 cm^{-1}. Anal. ($C_{18}H_{16}ClNO_2S$ (345.84)) C, H, N, S, Cl.

Ethyl 5-bromo-3-[(3,5-dimethylphenyl)thio]-1*H*-indole-2-carboxylate (37), ethyl 5-bromo-1*H*-indole-2-carboxylate was used, yield 93%, mp 162−165 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 1.25 (t, J = 7.1 Hz, 3H), 2.14 (s, 6H), 4.29 (q, J = 7.1 Hz, 2H), 6.72 (m, 2H), 6.76 (m, 1H), 7.43 (dd, J = 1.8 and 8.8 Hz, 1H), 7.51 and 7.53 (two d, J = 1.8 and 8.8 Hz, overlapped signals, 2H), 12.65 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3270 cm^{-1}. Anal. ($C_{19}H_{18}BrNO_2S$ (404.32)) C, H, N, S, Br.

Ethyl 5-acetyl-3-[(3,5-dimethylphenyl)thio]-1*H*-indole-2-carboxylate (38), ethyl 5-acetyl-1*H*-indole-2-carboxylate was used, yield 70%, mp 164−166 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 1.25 (t, J = 7.1 Hz, 3H), 2.14 (s, 6H), 2.48 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 6.80 (m, 3H), 7.58 (d, J = 8.8 Hz, 1H), 7.90 (m, 1H), 8.02 (m, 1H), 8.02 (m, 1H), 12.80 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3270 cm^{-1}. Anal. ($C_{21}H_{21}NO_3S$ (367.46)) C, H, N, S.

General Procedure for the Synthesis of the 3-Arylthio-1*H*-indole-2-carboxylates 26, 27, 29−33 and 36. Example. Methyl 5-chloro-3-(phenylthio)-1*H*-indole-2-carboxylate (26). 5-Chloro-1*H*-indole-2-carboxylic acid (2.93 g, 0.015 mol) was added by portions to a mixture of sodium hydride (60% dispersion in mineral oil, 1.80 g, 0.045 mol) in anhydrous DMF (35 mL) under a nitrogen stream at 0 °C. After 15 min, 1,1′-diphenyl disulfide (4.37 g, 0.020 mol) was added portionwise, and then the reaction was heated at 50 °C overnight under a nitrogen atmosphere. After cooling, the mixture was poured on crushed ice, made acidic with 2 N HCl, and extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried. Removal of the solvent gave a residue which was triturated with cyclohexane, filtered, and then crystallized by the same solvent to give satisfactory pure 5-chloro-3-(phenylthio)-1*H*-indole-2-carboxylic acid (2.27 g, 45%). The acid was dissolved in dichloromethane (120 mL) and methanol (30 mL) and treated with trimethylsilyldiazomethane (10.5 mL of a 2 N solution in hexane, 0.015 mol) while stirring at room temperature for 90 min. After concentration to a small volume, the residue was extracted with ethyl acetate, washed with 0.1 N acetic acid and then with brine, and dried. Removal of the solvent gave the crude product which was purified by passing through a silica gel column chromatography to furnish **26**, 1.95 g, yield 91%, (overall yield 41%), mp 195−195 °C (from toluene cyclohexane). ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H), 7.03−7.12 (m, 5H), 7.30 (dd, J = 1.9 and 8.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.56 (m, 1H), 9.30 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1675, 3270 cm^{-1}. Anal. ($C_{16}H_{12}ClNO_2S$ (317.78)) C, H, N, S, Cl. Thus, compounds **27**, **29**−**33**, and **36** were prepared.

Methyl 5-chloro-3-[(2-methylphenyl)thio]-1*H*-indole-2-carboxylate (27), overall yield 47%, mp 188−190 °C (from toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 3.91 (s, 3H), 6.78 (dd, J = 1.2 and 7.8 Hz, 1H), 6.93 (m, 1H), 7.04 (dt, J = 1.3 and 7.1 Hz, 1H), 7.16 (d, J = 7.1 Hz, 1H), 7.29 (dd, J = 1.8 and 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 1.8 Hz, 1H), 9.26 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3300 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_2S$ (331.82)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-methylphenyl)thio]-1*H*-indole-2-carboxylate (29), overall yield 52%, mp 220−222 °C (from toluene). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H), 3.94 (s, 3H), 7.02 and 7.10 (two d, J = 8.3 Hz, 4H), 7.30 (dd, J = 1.8 and 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 9.21 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1680 and 3270 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_2S$ (331.82)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-fluorophenyl)thio]-1*H*-indole-2-carboxylate (30), overall yield 54%, mp 176−177 °C (from toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 3.96 (s, 3H), 6.84−6.98 (m, 2H), 7.12−7.42 (m, 4H), 7.56 (d, J = 1.6 Hz, 1H), 9.38 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1680, 3290 cm^{-1}. Anal. ($C_{16}H_{11}ClFNO_2S$ (335.78)) C, H, N, S, Cl, F.

Methyl 5-chloro-3-[(4-chlorophenyl)thio]-1*H*-indole-2-carboxylate (31), overall yield 60%, mp 203−204 °C (from toluene/cyclohexane). ^{1}H NMR (DMSO-d_6): δ 3.87 (s, 3H), 7.09 and 7.30 (two d, J = 8.5 Hz, 4H), 7.33−7.43 (m, 2H), 7.57 (d, J = 8.6 Hz, 1H), 12.77 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1675, 3270 cm^{-1}. IR (Nujol): ν 1680, 3290 cm^{-1}. Anal. ($C_{16}H_{11}Cl_2NO_2S$ (352.23)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-isopropylphenyl)thio]-1*H*-indole-2-carboxylate (32), overall yield 41%, mp 172−173 °C (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.12 (d, J = 7.0 Hz, 6H), 2.83 (sp, J = 7.0 Hz, 1H), 3.93 (s, 3H), 7.06 and 7.13 (two d, J = 8.3 Hz, 4H), 7.28−7.38 (m, 2H), 7.51 (m, 1H), 9.23 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1680, and 3280 cm^{-1}. Anal. ($C_{19}H_{18}ClNO_2S$ (359.87)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-*tert*-butylphenyl)thio]-1*H*-indole-2-carboxylate (33), overall yield 58%, mp 237−238 °C (from toluene/cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 9H), 3.93 (s, 3H), 7.22 and 7.13 (two d, J = 8.7 Hz, 4H), 7.27 (dd, J = 1.9 and 8.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 1.9 Hz, 1H), 9.21 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1675 and 3280 cm^{-1}. Anal. ($C_{20}H_{20}Cl_2NO_2S$ (373.89)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(2,6-dichorophenyl)thio]-1*H*-indole-2-carboxylate (36), overall yield 55%, mp 241−243 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 3.89 (s, 3H), 6.92 (dd, J = 0.6 and 2.0 Hz, 1H), 7.26 (dd, J = 2.0 and 8.8 Hz, 1H), 7.40 (dd, J = 6.8 and 9.1 Hz, 1H), 7.48 (dd, J = 0.6 and 8.8 Hz,1H), 7.52−7.60 (m, 2H), 12.43 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1680, 3280 cm^{-1}. Anal. ($C_{16}H_{10}Cl_3NO_2S$ (386.67)) C, H, N, S, Cl.

General Procedure for Oxidation of the 3-Arylthio-1*H*-indole-2-carboxylates 25−38 to Sulfones 39−52. Example. Ethyl 3-(phenysulfonyl)-1*H*-indole-2-carboxylate

(39). 3-Chloroperoxybenzoic acid (1.32 g, 0.00766 mol) was added to an ice-cooled solution of ethyl 3-(phenylthio)-2-carboxylate (**25**) (0.78 g, 0.00264 mol) in chloroform (42 mL). Reaction was stirred at room temperature for 1.5 h, poured on crushed ice, and extracted with chloroform. The organic solution was shaken with saturated solution of sodium hydrogen carbonate and then with brine. After concentration to a small volume, the solution was passed through a silica gel column chromatography (ethyl acetate) to afford **39**, yield 75%, mp 148−149 °C (from toluene/cyclohexane). ^{1}H NMR (DMSO-d_6): δ 1.30 (t, J = 7.0 Hz, 3H), 4.36 (q, J = 7.0 Hz, 2H), 7.28−7.47 (m, 2H), 7.52−7.70 (m, 4H), 7.95−8.07 (m, 2H), 8.24 (m, 1H), 13.03 ppm (broad s, 1H, disappeared on treatment with D_2O). Anal. ($C_{17}H_{15}NO_4S$ (329.37)) C, H, N, S. Thus, compounds **40**−**52** were prepared.

Methyl 5-chloro-3-(phenysulfonyl)-1*H*-indole-2-carboxylate (40), yield 48%, mp 254−255 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H), 7.44 (dd, J = 1.6 and 8.9 Hz, 1H), 7.53−7.71 (m, 4H), 7.97−8.07 (m, 2H), 8.26 (d, J = 1.6 Hz, 1H), 13.39 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1715, 3250 cm^{-1}. Anal. ($C_{16}H_{12}ClNO_4S$ (349.78)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(2-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (41), yield 33%, mp 275−276 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H), 3.78 (s, 3H), 7.35 (d, J = 6.9 Hz, 1H), 7.42−7.66 (m, 3H), 7.70 (d, J = 8.8 Hz, 1H), 8.17 (dd, 1H), 8.32 (m, 1H), 13.49 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1710, 3220 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_4S$ (363.81)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(3-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (42), yield 81%, mp 181−182 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H), 3.88 (s, 3H), 7.08−7.30 (m, 1H), 7.40−7.55 (m, 2H), 7.61 (d, J = 8.8 Hz, 1H), 7.91 (m, 2H), 8.26 (d, J = 1.8 Hz, 1H), 13.33 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1735, 3700 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_4S$ (363.81)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-methylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (43), yield 50%, mp 229−231 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H), 3.91 (s, 3H), 7.40 (d, J = 8.4 Hz, 2H), 7.45 (dd, J = 1.8 and 8.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 8.27 (d, J = 1.8 Hz, 1H), 13.4 ppm (very broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1715 and 3260 cm^{-1}. Anal. ($C_{17}H_{14}ClNO_4S$ (363.81)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-fluorophenyl)sulfonyl]-1*H*-indole-2-carboxylate (44), yield 74%, mp 211−213 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 3.90 (s, 3H), 7.36−7.51 (m, 3H), 7.51 (d, J = 8.9 Hz, 1H), 8.03−8.16 (m, 2H), 8.26 (m, 1H), 13.44 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1735, 3390 cm^{-1}. Anal. ($C_{16}H_{11}ClFNO_4S$ (367.77)) C, H, N, S, Cl, F.

Methyl 5-chloro-3-[(4-chlororophenyl)sulfonyl]-1*H*-indole-2-carboxylate (45), yield 54%, mp 218−219 °C (from toluene/cyclohexane). ^{1}H NMR (DMSO-d_6): δ 3.90 (s, 3H), 7.46 (dd, J = 2.0 and 8.8 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.6 Hz, 2H), 8.26 (d, J = 2.0 Hz, 1H), 13.49 ppm (broad s, 1H, disappeared on treatment with D_2O). Anal. ($C_{16}H_{11}Cl_2NO_4S$ (384.23)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-isopropylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (46), yield 100%, mp 204−206 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 1.18 (d, J = 7.0 Hz, 6H), 2.94 (sp, J = 7.0 Hz, 1H), 3.90 (s, 3H), 7.40−7.52 (m, 3H), 7.60 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 8.23 (d, J = 1.4 Hz, 1H), 13.33 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1735 and 3240 cm^{-1}. Anal. ($C_{19}H_{18}ClNO_4S$ (391.86)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(4-*tert*-butylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (47), yield 96%, mp 240−241 °C (from toluene).^{1}H NMR (DMSO-d_6): δ 1.26 (s, 9H), 3.91 (s, 3H), 7.43 (dd, J = 1.9 and 8.6 Hz, 1H), 7.54−7.67 (m, 3H), 7.96 (d, J = 8.5 Hz, 2H), 8.23 (d, J = 1.9 Hz, 1H), 13.28 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1740 and 3260 cm^{-1}. Anal. ($C_{20}H_{20}ClNO_4S$ (405.89)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(2,4-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (48), yield 58%, mp 241−242 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H), 2.33 (s, 3H), 3.75 (s, 3H), 7.11 (m, 1H), 7.28 (m, 1H), 7.45 (dd, J = 1.7 and 8.7 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 1.7 Hz, 1H), 13.36 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1700 and 3235 cm^{-1}. Anal. ($C_{18}H_{16}ClNO_4S$ (377.84)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (49), yield 74%, mp 234−236 °C (from toluene/cyclohexane). ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 6H), 3.88 (s, 3H), 7.28 (m, 1H), 7.43 (dd, J = 2.0 and 8.6 Hz, 1H), 7.55−7.67 (m, 3H), 8.24 (d, J = 2.0 Hz, 1H), 13.33 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1740, 3200 cm^{-1}. Anal. ($C_{18}H_{16}ClNO_4S$ (377.84)) C, H, N, S, Cl.

Methyl 5-chloro-3-[(2,6-dichlorophenyl)sulfonyl]-1*H*-indole-2-carboxylate (50), yield 100%, mp 273−276 °C (from toluene).^{1}H NMR (DMSO-d_6): δ 3.72 (s, 3H), 7.46 (dd, J = 2.1 and 8.9 Hz, 1H), 7.53−7.68 (m, 4H), 8.28 (m, 1H), 12.42 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3240 cm^{-1}. Anal. ($C_{16}H_{10}Cl_3NO_4S$ (418.67)) C, H, N, S, Cl.

Ethyl 5-bromo-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (51), yield 77%, mp >300 °C (from aqueous ethanol). ^{1}H NMR (DMSO-d_6): δ 1.28 (t, J = 7.1 Hz, 3H), 2.32 (s, 6H), 4.35 (q, J = 7.1 Hz, 2H), 7.28 (m, 1H), 7.55 (d, J = 1.2 Hz, 2H), 7.60 (m, 2H), 8.38 ppm (t, J = 1.2 Hz, 1H). IR (Nujol): ν 1690, 3260 cm^{-1}. Anal. ($C_{19}H_{18}BrNO_4S$ (436.32)) C, H, N, S, Br.

Ethyl 5-acetyl-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxylate (52), yield 62%, mp 193−195 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 1.31 (t, J = 7.1 Hz, 3H), 2.32 (s, 6H), 2.68 (s, 3H), 4.38 (q, J = 7.1 Hz, 2H), 7.28 (m, 1H), 7.60−7.71 (m, 3H), 8.01 (dd, J = 1.7 and 8.8 Hz, 1H), 8.89 (m, 1H), 12.7 ppm (very broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1665, 1700, 3280 cm^{-1}. Anal. ($C_{21}H_{21}NO_5S$ (399.46)) C, H, N, S.

General Procedure for the Synthesis of Amides 2, 53−64, and 70−84. Example. 3-(Phenylthio)-1*H*-indole-2-carboxyamide (53). Ethyl 3-(phenylthio)-*1H*-indole-2-carboxylate (**25**) (0.50 g, 0.0017 mol) was heated with 30% ammonium hydroxide (25 mL) and ammonium chloride (40 mg) in a sealed tube at 100 °C overnight. After cooling, the reaction mixture was poured on ice water, stirred for 15 min, and extracted with ethyl acetate. The organic layer was washed with brine and dried and the solvent evaporated to afford a residue which was purified on silica gel column chromatography (chloroform−ethanol 95:5) to give **53**, yield 69%, mp 197 °C (from toluene). ^{1}H NMR (CD_3COCD_3): δ 7.00−7.38 (m, 8H, 7H, after treatment with D_2O), 7.51−7.73 (m, 2H), 8.02 (broad s, 1H, disappeared on treatment with D_2O),11.58 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1730, 3280, 3400 cm^{-1}. Anal. ($C_{15}H_{12}N_2OS$ (368.33)) C, H, N, S. Thus, compounds **2**, **54**−**64** and **70**−**84** were prepared.

3-[(2-Amino-5-chlorophenyl)thio]-1*H*-indole-2-carboxyamide (54), yield 64%, mp 200−202 °C (from toluene/cyclohexane). ^{1}H NMR (DMSO-d_6): δ 5.63 (broad s, 2H, disappeared on treatment with D_2O), 6.65−6.78 (m, 2H), 6.94 (dd, J = 2.3 and 8.6 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.43−7.65 (m, 2H), 7.83 and 7.99 (two broad s, 2H, disappeared on treatment with D_2O) 12.21 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1655, 3280, 3380 cm^{-1}. Anal. ($C_{15}H_{12}ClN_3OS$ (317.79)) C, H, N, S.

5-Chloro-3-(phenylthio)-1*H*-indole-2-carboxyamide (55), yield 51%, mp 212−213 °C (from toluene/cyclohexane), lit.[8] mp 213−215 °C. ^{1}H NMR (DMSO-d_6): δ 7.05−7.35 (m, 6H), 7.44 (d, J = 1.9 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.77 and 8.05 (two broad s, 2H, disappeared on treatment with D_2O), 12.53 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1635, 3120, 3385 cm^{-1}.

5-Chloro-3-[(2-methylphenyl)thio]-1*H*-indole-2-carboxyamide (56), yield 94%, mp 222−224 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 2.47 (s, 3H), 6.47 (d, J = 7.8 Hz, 1H),

6.89−7.12 (m, 2H), 7.18−7.41 (m, 2H), 7.60 (d, J = 8.7 Hz, 1H), 7.70 and 7.96 (two broad s, 2H, disappeared on treatment with D_2O), 8.79 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1645, 3260, 3300, 3420 cm^{-1}. Anal. ($C_{16}H_{13}ClN_2OS$ (316.80)) C, H, N, S, Cl.

5-Chloro-3-[(4-methylphenyl)thio]-1*H*-indole-2-carboxyamide (57), yield 69%, mp 232−235 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 2.21 (s, 3H), 6.99 and 7.08 (two d, J = 8.4 Hz, 4H), 7.30 (dd, J = 1.8 and 8.7 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.79 and 8.09 (two broad s, disappeared on treatment with D_2O), 12.51 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1650, 3200, 3300, and 3440 cm^{-1}. Anal. ($C_{16}H_{13}ClN_2OS$ (316.80)) C, H, N, S, Cl.

5-Chloro-3-[(4-fluorophenyl)thio]-1*H*-indole-2-carboxyamide (58), yield 52%, mp 210−212 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 7.12 (s, 2H), 7.16 (s, 2H), 7.31 (dd, J = 1.9 and 8.6 Hz, 1H), 7.46 (d, J = 1.9 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.81 and 8.10 (two broad s, 2H, disappeared on treatment with D_2O), 12.55 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1675, 3120, 3360, and 3440 cm^{-1}. Anal. ($C_{15}H_{10}ClFN_2OS$ (320.76)) C, H, N, S, Cl, F.

5-Chloro-3-[(4-chlorophenyl)thio]-1*H*-indole-2-carboxyamide (59), yield 57%, mp 232−233 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 7.06 (d, J = 8.5 Hz, 2H), 7.24−7.38 (m, 3H), 7.43 (m, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.75 and 8.08 (two broad s, 2H, disappeared on treatment with D_2O), 12.58 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3200, 3320, and 3460 cm^{-1}. Anal. ($C_{15}H_{10}Cl_2N_2OS$ (337.22)) C, H, N, S, Cl.

5-Chloro-3-[(4-isopropylphenyl)thio]-1*H*-indole-2-carboxyamide (60), yield 75%, mp 195 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 1.12 (d, J = 6.7 Hz, 6H), 2.79 (sp, J = 6.7 Hz, 1H), 7.02 and 7.14 (two d, J = 8.2 Hz, 4H), 7.29 (dd, J = 1.6 and 8.7 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.79 and 8.02 (two broad s, 2H, disappeared on treatment with D_2O), 12.48 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1640, 3280, and 3370 cm^{-1}. Anal. ($C_{18}H_{17}ClN_2OS$ (344.85)) C, H, N, S, Cl.

5-Chloro-3-[(4-*tert*-butylphenyl)thio]-1*H*-indole-2-carboxyamide (61), yield 100%, mp 234−235 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 1.20 (s, 9H), 7.01 (d, J = 8.5 Hz, 2H), 7.22−7.34 (m, 3H), 7.47 (d, J = 1.9 Hz, 1H), 7.55 (d, J = 8.7 Hz,1H), 7.78 and 8.00 (two broad s, 2H, disappeared on treatment with D_2O), 12.46 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1630−50, 3160, 3280, 3420 cm^{-1}. Anal. ($C_{19}H_{19}ClN_2OS$ (358.82)) C, H, N, S, Cl.

5-Chloro-3-[(3,5-dimethylphenyl)thio]-1*H*-indole-2-carboxyamide (62), yield 91%, mp 201−203 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 2.14 (s, 6H), 6.69 (m, 2H), 6.79 (m, 1H), 7.30 (dd, J = 1.6 and 8.6 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.73 and 8.01 (two broad s, 2H, disappeared on treatment with D_2O), 12.46 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1650, 3260, and 3440 cm^{-1}. Anal. ($C_{17}H_{15}ClN_2OS$ (330.83)) C, H, N, S, Cl.

5-Chloro-3-[(2,6-dichlorophenyl)thio]-1*H*-indole-2-carboxyamide (63), yield 97%, mp 242−245 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 7.12 (dd, J = 0.6 and 2.0 Hz, 1H), 7.20 (dd, J = 2.0 and 8.7 Hz, 1H), 7.38 (dd, J = 7.0 and 8.9 Hz, 1H), 7.46 (dd, J = 0.6 and 8.7 Hz, 1H), 7.52−7.59 (two d, J = 7.0 and 8.9 Hz, 2H), 7.74 and 8.03 (two broad s, 2H, disappeared on treatment with D_2O), 12.25 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1630, 3180, and 3380 cm^{-1}. Anal. ($C_{15}H_9Cl_3N_2OS$ (371.66)) C, H, N, S, Cl.

5-Chloro-3-[(2-amino-5-chlorophenyl)thio]-1*H*-indole-2-carboxyamide (64), yield 85%, mp 233−235 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 5.70 (broad s, 2H, disappeared on treatment with D_2O), 6.71 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 2.4 and 8.6 Hz, 1H), 7.29 (dd, J = 1.9 and 8.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.88 and 8.10 (two broad s, 2H, disappeared on treatment with D_2O), 12.40 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3100, 3310, 3370, and 3420 cm^{-1}. Anal. ($C_{15}H_{11}Cl_2N_3OS$ (352.24)) C, H, N, S, Cl.

3-(Phenylsulfonyl)-1*H*-indole-2-carboxyamide (70), yield 40%, mp 226−227 °C (from ethanol). ^1H NMR (CD_3COCD_3): δ 7.24−7.72 (m, 8H, 7H, 6H, after treatment with D_2O), 7.96−8.12 (m, 2H), 8.24 (m, 1H), 9.11 (broad s, 1H, disappeared on treatment with D_2O), 11.88 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3170, 3270, 3370 cm^{-1}. Anal. ($C_{15}H_{12}N_2O_3S$ (300.05)) C, H, N, S.

3-[(2-Amino-5-chlorophenyl)sulfonyl]-1*H*-indole-2-carboxyamide (71), yield 40%, mp 238−239 °C (from aqueous ethanol). ^1H NMR ($CDCl_3$): δ 4.99 (broad s, 2H, disappeared on treatment with D_2O), 6.12 (broad s, 1H, disappeared on treatment with D_2O), 6.58 (d, J = 8.8 Hz, 1H), 7.15−7.55 (m, 4H), 7.76 (d, J = 2.3 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 9.15 (broad s, 1H, disappeared on treatment with D_2O), 10.19 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1645, 3225, and 3380 cm^{-1}. Anal. ($C_{15}H_{12}ClN_3O_3S$ (349.79)) C, H, N, S, Cl.

5-Chloro-3-[(2-methylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (72), yield 82%, mp 260−261 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 2.39 (s, 3H), 7.27−7.64 (m, 5H), 7.81 (d, J = 1.7 Hz, 1H), 8.03 (dd, J = 1.1 and 7.9 Hz, 1H), 8.23 and 8.29 (two partially overlapped broad s, 2H, disappeared on treatment with D_2O), 13.11 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3290, 3220, 3410 cm^{-1}. Anal. ($C_{16}H_{13}ClN_2O_3S$ (348.80)) C, H, N, S, Cl.

5-Chloro-3-[(3-methylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (73), yield 87%, mp 265−268 °C (from aqueous ethanol). ^1H NMR (DMSO-d_6): δ 2.36 (s, 3H), 7.34 (m, 1H), 7.40−7.58 (m, 3H), 7.77−7.88 (m, 2H), 7.95 (m, 1H), 8.24 and 8.47 (two broad s, 1H, disappeared on treatment with D_2O), 13.02 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1650, 3180, 3380 cm^{-1}. Anal. ($C_{16}H_{13}ClN_2O_3S$ (348.80)) C, H, N, S, Cl.

5-Chloro-3-[(4-methylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (74), yield 90%, mp >300 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 2.33 (s, 3H), 7.28−7.46 (m, 3H), 7.54 (d, J = 8.7 Hz, 1H), 7.86−7.99 (m, 3H), 8.27 and 8.51 (two broad s, disappeared on treatment with D_2O), 13.08 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3200, and 3380 cm^{-1}. Anal. ($C_{16}H_{13}ClN_2O_3S$ (348.80)) C, H, N, S, Cl.

5-Chloro-3-[(4-fluorophenyl)sulfonyl]-1*H*-indole-2-carboxyamide (75), yield 94%, mp 229−230 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 7.29−7.58 (m, 4H), 7.95 (m, 1H), 8.07−8.21 (m, 2H), 8.24 and 8.47 (two broad s, 2H, disappeared on treatment with D_2O), 13.11 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1650, 3150, 3230 cm^{-1}. Anal. ($C_{15}H_{10}ClFN_2O_3S$ (352.76)) C, H, N, S, Cl, F.

5-Chloro-3-[(4-chlorophenyl)sulfonyl]-1*H*-indole-2-carboxyamide (76), yield 90%, mp >300 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 7.36 (m, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.94 (m, 1H), 8.07 (d, J = 8.2 Hz, 2H), 8.23 and 8.45 (two broad s, 2H, disappeared on treatment with D_2O), 13.15 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1650, 3150, 3230, and 3440 cm^{-1}. Anal. ($C_{15}H_{10}Cl_2N_2O_3S$ (369.22)) C, H, N, S, Cl.

5-Chloro-3-[(4-isopropylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (77), yield 79%, mp 272−275 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 1.15 (d, J = 6.8 Hz, 6H), 2.92 (sp, J = 6.8 Hz, 1H), 7.35 (dd, J = 1.9 and 8.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.6 Hz, 1H), 7.90 and 8.02 (m, 3H), 8.24 and 8.50 (two broad s, 2H, disappeared on treatment with D_2O), 13.03 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3140, and 3380 cm^{-1}. Anal. ($C_{18}H_{17}ClN_2O_3S$ (376.66)) C, H, N, S, Cl.

5-Chloro-3-[(4-*tert*-butylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (78), yield 100%, mp 276−277 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 1.25 (s, 9H), 7.44 (dd, J = 1.9 and 8.7 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.61 and 7.94 (two d, J = 8.6 Hz, 4H), 7.98 (d, J = 1.9 Hz, 1H), 8.22 and 8.48 (two broad s, 2H, disappeared on treatment with D_2O), 12.99 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3180, 3280, and 3430 cm^{-1}. Anal. ($C_{19}H_{19}ClN_2O_3S$ (390.88)) C, H, N, S, Cl.

5-Chloro-3-[(2,4-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (79), yield 89%, mp 217−220 °C (from aqueous ethanol). ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 6H), 7.16 (s, 1H), 7.22−7.40 (m, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 9.94 (d, J = 8.1 Hz, 1H), 8.26 and 8.32 (two broad s, 2H, disappeared on treatment with D_2O), 13.07 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3180, 3280 and 3420 cm^{-1}. Anal. ($C_{17}H_{15}ClN_2O_3S$ (362.83)) C, H, N, S, Cl.

5-Chloro-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (80), yield 85%, mp 274−277 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 6H), 7.26 (m, 1H), 7.34 (dd, J = 1.6 and 8.7 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.63 (m, 2H), 7.96 (d, J = 1.6 Hz, 1H), 8.21 and 8.46 (two broad s, 2H, disappeared on treatment with D_2O), 13.02 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1680, 3220, and 3340 cm^{-1}. Anal. ($C_{17}H_{15}ClN_2O_3S$ (362.83)) C, H, N, S, Cl.

5-Chloro-3-[(2,6-dichlorophenyl)sulfonyl]-1*H*-indole-2-carboxyamide (81), yield 100%, mp 288−290 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 7.37 (dd, J = 2.1 and 8.8 Hz, 1H), 7.54−7.66 (m, 4H), 7.94 (dd, J = 0.4 and 2.1 Hz,1H), 8.14 (broad s, 2H, disappeared on treatment with D_2O), 13.16 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3160, 3300, and 3440 cm^{-1}. Anal. ($C_{15}H_9Cl_3N_2O_3S$ (403.66)) C, H, N, S, Cl.

5-Chloro-3-[(2-amino-5-chlorophenyl)sulfonyl]-1*H*-indole-2-carboxyamide (82), yield 87%, mp 225−227 °C (from aqueous ethanol). ^{1}H NMR (DMSO-d_6): δ 6.54 (broad s, 2H, disappeared on treatment with D_2O), 6.73 (d, J = 8.9 Hz, 1H), 7.20−7.39 (m, 2H), 7.53 (d, J = 8.6 Hz, 1H), 7.64 (m, 1H), 7.80 (d, J = 2.3 Hz, 1H), 8.27 and 8.48 (two broad s, 2H, disappeared on treatment with D_2O), 13.00 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3280, 3360, cm^{-1}. Anal. ($C_{15}H_{11}Cl_2N_3O_3S$ (384.24)) C, H, N, S, Cl.

5-Bromo-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (83), yield 42%, mp >300 °C (from aqueous DMF). ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 6H), 7.26 (m, 1H), 7.46 (m, 2H), 7.62 (m, 2H), 8.10 (m, 1H), 8.31 and 8.46 (two broad s, 1H, disappeared on treatment with D_2O), 13.05 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1680, 3210, 3360 cm^{-1}. Anal. ($C_{17}H_{15}BrN_2O_3S$ (407.28)) C, H, N, S, Br.

5-Acetyl-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxyamide (84), yield 54%, mp >300 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 6H), 2.64 (s, 3H), 7.26 (m, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.49 (m, 2H), 7.91 (dd, J = 1.7 and 8.7 Hz, 1H), 8.31 and 8.50 (two broad s, 1H, disappeared on treatment with D_2O), 8.60 (d, J = 1.7 Hz, 1H), 13.1 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1670, 3150, 3250, 3350 cm^{-1}. Anal. ($C_{19}H_{18}N_2O_4S$ (370.42)) C, H, N, S.

5-Chloro-3-(phenylsulfonyl)-1*H*-indole-2-carboxyamide (2), yield 65%, mp 254−255 °C (from toluene), lit.[8] mp 255−257 °C. ^{1}H NMR (DMSO-d_6): δ 7.35 (m, 1H), 7.48−7.62 (m, 4H), 7.94−8.12 (m, 3H), 8.25 and 8.49 (two broad s, 2H, disappeared on treatment with D_2O), 12.80 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3220, 3380 cm^{-1}.

General Procedure for the Synthesis of Hydrazides 65−69 and 86−92. Example. 5-Chloro-3-(phenylthio)-1*H*-indole-2-carboxyhydrazide (65). A mixture of methyl 5-chloro-3-(phenylthio)-1*H*-indole-2-carboxylate (**26**) (0.54 g, 0.0017 mol), hydrazine hydrate (4 mL), and ethanol (4 mL) was heated at 60 °C for 1.5 h. After quenching on crushed ice, the solid which formed was filtered, washed with water, and dried to afford **65**, yield 80%, mp 231 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.73 (broad s, 2H, disappeared on treatment with D_2O), 6.98−7.34 (m, 6H), 7.39 (m, 1H), 7.55 (d, J = 8.7 Hz, 1H), 4.38 (broad s, 1H, disappeared on treatment with D_2O), 12.55 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1630, 3210 cm^{-1}. Anal. ($C_{15}H_{12}ClN_3OS$ (317.79)) C, H, N, S, Cl. Thus, compounds **66**−**69** and **86**−**92** were prepared.

5-Chloro-3-[(4-methylphenyl)thio]-1*H*-indole-2-carboxyhydrazide (66), yield 90%, mp 249−250 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H), 4.74 (broad s, 2H, disappeared on treatment with D_2O), 6.96 and 7.07 (two d, J = 8.2 Hz, 4H), 7.28 (dd, 1H, J = 1.9 and 8.2 Hz), 7.39 (d, J = 1.9 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 4.37 (broad s, 1H, disappeared on treatment with D_2O), 12.52 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1630, 3300 and 3380 cm^{-1}. Anal. ($C_{15}H_{14}ClN_3OS$ (331.81)) C, H, N, S, Cl.

5-Chloro-3-[(4-fluorophenyl)thio]-1*H*-indole-2-carboxyhydrazide (67), yield 90%, mp 235−236 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.74 (broad s, 2H, disappeared on treatment with D_2O), 7.10 (s, 2H), 7.13 (s, 2H), 7.28 (dd, J = 2.0 and 8.7 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 9.43 (broad s, 1H, disappeared on treatment with D_2O) 12.55 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1635, 3240 cm^{-1}. Anal. ($C_{15}H_{11}ClFN_3OS$ (335.78)) C, H, N, S, Cl, F.

5-Chloro-3-[(4-chlorophenyl)thio]-1*H*-indole-2-carboxyhydrazide (68), yield 100%, mp 247−248 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.74 (broad s, 2H, disappeared on treatment with D_2O), 7.03 (d, J = 8.5 Hz, 2H), 7.25−7.36 (m, 3H), 7.39 (m, 1H), 7.55 (d, J = 8.7 Hz, 1H), 9.42 (broad s, 1H, disappeared on treatment with D_2O) 12.60 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1630, 3240 cm^{-1}. Anal. ($C_{15}H_{11}Cl_2N_3OS$ (352.23)) C, H, N, S, Cl.

5-Chloro-3-[(2-amino-5-chlorophenyl)thio]-1*H*-indole-2-carboxyhydrazide (69), yield 87%, mp 265−268 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.78 (broad s, 2H, disappeared on treatment with D_2O), 5.74 (broad s, 2H, disappeared on treatment with D_2O), 6.71 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.97 (dd, J = 2.2 and 8.4 Hz, 1H), 7.27 (dd, J = 1.9 and 8.7 Hz, 1H), 7.45−7.56 (m, 2H), 9.57 (broad s, 1H, disappeared on treatment with D_2O), 12.38 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1630, 3250, 3300, 3420 cm^{-1}. Anal. ($C_{15}H_{12}Cl_2N_4OS$ (367.25)) C, H, N, S, Cl.

3-(Phenylsulfonyl)-1*H*-indole-2-carboxyhydrazide (86), yield 100%, mp 225−227 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.79 (broad s, 2H, disappeared on treatment with D_2O), 7.18−7.38 (m, 2H), 7.43−7.69 (m, 4H), 7.70−8.12 (m, 3H), 10.06 (broad s, 1H, disappeared on treatment with D_2O), 12.81 ppm (s, 1H). Anal. ($C_{15}H_{13}N_3O_3S$ (301.34)) C, H, N, S.

5-Chloro-3-(phenylsulfonyl)-1*H*-indole-2-carboxyhydrazide (87), yield 100%, mp > 300 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.77 (broad s, 2H, disappeared on treatment with D_2O), 7.34 (m, 1H), 7.50−7.67 (m, 4H), 7.93 (m, 1H), 8.02−8.14 (m, 2H), 10.11 (broad s, 1H, disappeared on treatment with D_2O), 13.29 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1635, 3180, 3280 cm^{-1}. Anal. ($C_{15}H_{12}ClN_3O_3S$ (349.79)) C, H, N, S, Cl.

5-Chloro-3-[(4-methylphenyl)sulfonyl]-1*H*-indole-2-carboxyhydrazide (88), yield 100%, mp >300 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H), 4.81 (broad s, 2H, disappeared on treatment with D_2O), 7.30−7.43 (m, 3H), 7.52 (d, J = 7.9 Hz, 1H), 7.78−8.02 (m, 3H), 10.08 (broad s, 1H, disappeared on treatment with D_2O), 13.07 ppm (very broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1640, 3310 and 3390 cm^{-1}. Anal. ($C_{16}H_{14}ClN_3O_3S$ (363.81)) C, H, N, S, Cl.

5-Chloro-3-[(4-fluorophenyl)sulfonyl]-1*H*-indole-2-carboxyhydrazide (89), yield 90%, mp 252−253 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.81 (broad s, 2H, disappeared on treatment with D_2O), 7.28−7.58 (m, 4H), 7.94 (m, 1H), 8.12−8.24 (m, 2H), 10.10 (broad s, 1H, disappeared on treatment with D_2O), 13.13 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1640, 3190, 3280 cm^{-1}. Anal. ($C_{15}H_{11}ClFN_3O_3S$ (367.78)) C, H, N, S, Cl, F.

5-Chloro-3-[(4-chlorophenyl)sulfonyl]-1*H*-indole-2-carboxyhydrazide (90), yield 100%, mp 247−248 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 4.80 (broad s, 2H, disappeared on treatment with D_2O), 7.35 (dd, J = 1.6 and 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 1.6 Hz, 1H), 8.11 (d, J = 8.5 Hz, 2H), 10.07 (broad s, 1H,

disappeared on treatment with D_2O) 13.15 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1640, 3180, 3300 cm^{-1}. Anal. ($C_{15}H_{11}Cl_2N_3O_3S$ (384.23)) C, H, N, S, Cl.

5-Chloro-3-[(3,5-dimethylphenyl)sulfonyl]-1*H*-indole-2-carboxyhydrazide (91), yield 82%, mp >300 °C (from ethanol).^{1}H NMR (DMSO-d_6): δ 2.27 (s, 6H), 4.80 (very broad s, 2H, disappeared on treatment with D_2O), 7.20 (s, 1H), 7.28 (dd, J = 2.0 and 8.7 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.65 (s, 2H), 7.89 (d, J = 2.0 Hz, 1H), 10.05 ppm (broad s, 1H, disappeared on treatment with D_2O). Anal. ($C_{17}H_{16}ClN_3O_3S$ (377.84)) C, H, N, S, Cl.

5-Chloro-3-[(2-amino-5-chlorophenyl)sulfonyl]-1*H*-indole-2-carboxyhydrazide (92), yield 92%, mp 218−220 °C (from aqueous ethanol).^{1}H NMR (DMSO-d_6): δ 4.82 (broad s, 2H, disappeared on treatment with D_2O), 6.63 (broad s, 2H, disappeared on treatment with D_2O), 6.74 (d, J = 8.9 Hz, 1H), 7.23−7.38 (m, 2H), 7.53 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 10.20 (broad s, 1H, disappeared on treatment with D_2O), 13.04 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1640, 3300, 3450 cm^{-1}. Anal. ($C_{15}H_{12}Cl_2N_4O_3S$ (399.35)) C, H, N, S, Cl.

5-(1-Hydroxyethyl)-3-(3,5-dimethylphenylsulfonyl)-1*H*-indole-2-carboxyamide (85) Sodium borohydride (0.03 g, 0.0008 mol) was added to a mixture of 5-acetyl-3-(3,5-dimethylphenylsulfonyl)-1*H*-indole-2-carboxyamide (**84**) (0.30 g, 0.0008 mol) in THF (8.5 mL) containing 0.1 mL of water, and then the reaction was refluxed for 1 h. After cooling, water was added while stirring for a few minutes, and then the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried, and evaporated to dryness to give **85**, yield 83%, mp 260−262 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 1.36 (d, J = 6.4 Hz, 3H), 4.80 (m, 1H, showed q, J = 6.4 Hz after treatment with D_2O), 5.21 (d, J = 4.1 Hz, disappeared on treatment with D_2O), 7.19 (m, 1H), 7.25 (dd, J = 1.5 and 8.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.54 (m, 2H), 7.91 (m, 1H), 8.16 and 8.54 (two broad s, 1H, disappeared on treatment with D_2O), 12.7 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (Nujol): ν 1660, 3160, 3250, 3350, 3530 cm^{-1}. Anal. ($C_{19}H_{20}N_2O_4S$ (372.43)) C, H, N, S.

***N*-(3,5-Dimethylphenylthio)succinimide.** 3,5-Dimethylthiophenol (2.76 g, 0.02 mol) was added by a syringe to an ice-cooled mixture of *N*-chlorosuccinimide (3.34 g, 0.025 mol) and anhydrous dichloromethane (30 mL) under argon atmosphere. After 1 h, *N*-chlorosuccinimide (0.4 g, 0.003 mol) was added, and then the reaction was stirred for 2.5 h. Triethylamine (3.9 mL, 0.028 mol) was added while stirring for 15 min, and then dichloromethane and 1 N HCl were added. After shaking, the organic layer was dried, concentrated to a small volume, and passed through a Celite column. After evaporation of the solvent, the residue was triturated with diethyl ether to give 3.0 g (64%) of title compound, mp 131−134 °C. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 6H), 2.83 (s, 4H), 6.98 (s, 1H), 7.25 ppm (s, 2H).

***N*-(3-Methylphenylthio)succinimide** was prepared as *N*-(3,5-dimethylphenylthio)succinimide by using 3-methylthiophenol, yield 48%, mp 98−100 °C. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 6H), 2.83 (s, 4H), 6.98 (s, 1H), 7.25 ppm (s, 3H).

Antiviral Assay Procedures. Compounds. Compounds were solubilized in DMSO at 200 mM and then diluted in culture medium.

Cells and Viruses. MT-4, C8166, and H9/IIIB cells were grown at 37°C in a 5% CO_2 atmosphere in RPMI 1640 medium and 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, IIIB strain) was obtained from supernatants of persistently infected H9/IIIB cells. The HIV-1 stock solutions had titers of 4.5×10^6 50% cell culture infectious dose ($CCID_{50}$)/mL. The K103R-V179D-P225H mutant was derived from an IIIB strain passaged in C8166 cells in the presence of Efavirenz (up to 2 μM). The Y181C mutant (NIH N119) derives from an AZT-sensitive clinical isolate passaged initially in CEM, and then in MT-4 cells, in the presence of nevirapine (10 μM). The K103N-Y181C (NIH A17) derives from the IIIB strain passaged in H9 cells in the presence of BI−RG 587 (1 μM). K103R-V179D-P225H, Y181C and K103N-Y181C stock solutions had titers of 3.0×10^5 $CCID_{50}$/mL, 1.3×10^6 $CCID_{50}$/mL and 2.5×10^5 $CCID_{50}$ / 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 titer was determined by light microscope scoring of syncytia after 4 days of incubation. Virus titers were expressed as $CCID_{50}$/mL.

Anti-HIV Assays. The activity of test compounds against multiplication of wt HIV-1, Y181C, and K103N-Y181C in acutely infected cells was based on inhibition of virus-induced cytopathicity in MT-4 cells. The activity of the compounds against the K103R multiplication in acutely infected cells was based on inhibition of p24 antigen in C8166 cells. Briefly, 50 μL of culture medium containing 1×10^4 cells were added to each well of flat-bottom microtiter trays containing 50 μL of culture medium with or without various concentrations of test compounds. Then 20 μL of HIV suspensions (containing the appropriate amount of $CCID_{50}$ to cause complete cytopathicity at day 4) were added. After incubation at 37°C, cell viability was determined by the 3-(4,5-dimethylthiazol-1-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[15] Alternatively, p24 levels were determined by an immunoenzymatic kit (Abbott). The cytotoxicity of test compounds was evaluated in parallel with their antiviral activity and was based on the viability of mock-infected cells, as monitored by the MTT method.

RT Assays. Assays were performed as previously described.[16] Briefly, purified rRTs were assayed for their RNA-dependent DNA polymerase activity in a 50 μL volume containing 50 mM Tris-HCl (pH 7.8), 80 mM KCl, 6mM $MgCl_2$, 1 mM DTT, 0.1 mg mL^{-1} BSA, 0.5 OD_{260} unit mL^{-1} template: primer [poly(rC)-oligo$(dG)_{12-18}$], and 10 mM [^{3}H]dGTP (1 Ci $mmol^{-1}$). After incubation for 30 min at 37 °C, the samples were spotted on glass fiber filters (Whatman GF/A), and the acid-insoluble radioactivity was determined.

Statistical Analysis. Means ± SE for triplicate (cell-based assays) or duplicate (enzyme assays) determinations are reported. The statistical significance of differences was determined by a nonparametric Mann−Whitney test. $P < 0.05$ was the criterion for significance.

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