Brief Articles

Indolyl Aryl Sulfones as HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors: Role of Two Halogen Atoms at the Indole Ring in Developing New Analogues with Improved Antiviral Activity

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Received April 26, 2007

Indolyl aryl sulfones bearing the 4,5-difluoro (**10**) or 5-chloro-4-fluoro (**16**) substitution pattern at the indole ring were potent inhibitors of HIV-1 WT and the NNRTI-resistant strains Y181C and K103N−Y181C. These compounds were highly effective against the 112 and the AB1 strains in lymphocytes and inhibited at nanomolar concentration the multiplication of the $IIIB_{Ba-L}$ strain in macrophages. Compound **16** was exceptionally potent against RT WT and RTs carrying the K103N, Y181I, and L100I mutations.

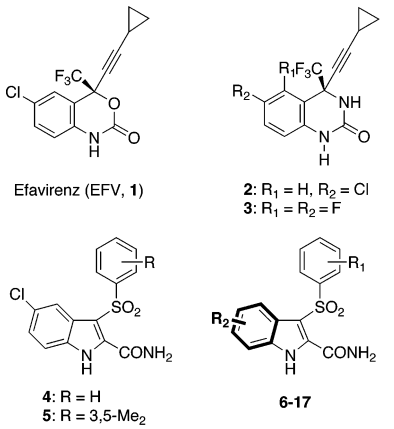
Introduction

Human immunodeficiency virus (HIV)[a] is the etiological agent of acquired immunodeficiency syndrome (AIDS). AIDS and HIV infection caused 2.8 million deaths and 4.1 million newly infected people in 2005.[1] The antiretroviral drugs or an eventual preventive HIV vaccine are the two strategies of combating AIDS/HIV infection.[2] More than 20 antiretroviral drugs are available and fall into four classes: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and fusion inhibitors (FIs).[3] Two new classes of drugs, the entry inhibitors and HIV integrase inhibitors, are expected to be available by the end of 2007.[4] Three (recommended) or four antiretroviral drugs[5] are combined in the highly active antiretroviral therapy (HAART) that, since its introduction in 1996, proved to be effective in reducing morbidity and mortality of HIV-infected people.[6] However, HAART is unable to eradicate the viral infection; the needed long-term or permanent treatments favor the emergence of drug resistance, toxicity, and unwanted side effects.[7]

NNRTIs have received a great amount of attention because of low toxicity and favorable pharmacokinetics properties. Currently, three NNRTIs are approved for AIDS treatment, and more than 30 classes of structurally unrelated NNRTIs have been described.[8] However, the emergence of drug resistance remains a pressing problem. The majority of patients (>90%) treated with efavirenz (EFV, **1**), whose viral loads rebounded after an initial response to the drug, selected the K103N mutation. Furthermore, additional double mutations (K103N−V108N, K103N−P225H) slowly appeared in many patients.[9] Compound **1** was modified by DuPont Laboratories to obtain analogues bearing two halogen atoms at the quinazolinone ring. The new derivatives (for example, **2** and **3**) were active at low nanomolar concentration against HIV-1 WT and viral strains carrying the single mutation K103N and L100I.[10]

Our studies on sulfone NNRTIs[11,12] led to the development of potent indolyl aryl sulfones (IASs) correlated to L-737,126 (**4**).[13,14] The potent activity of **5** against the NNRTI-resistant mutants was correlated to the 3-(3,5-dimethylphenyl)sulfonyl moiety.[13] Continuing our efforts to develop IASs with improved activity against the viral mutants, we planned the synthesis of

Chart 1. Structure of Reference Compounds **1**−**5** and New IASs **6**−**17**



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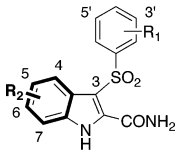
[a] Abbreviations: IAS, indolyl aryl sulfone; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; FI, fusion inhibitor; HAART, highly active antiretroviral therapy; NVP, nevirapine; EFV, efavirenz; WT, wild type; RT, reverse transcriptase; PPA, polyphosphoric acid; MCPBA, 3-chloroperoxybenzoic acid; TC, toxic dose; EC, effective dose; ID, inhibitory dose; SI, selectivity index; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

10.1021/jm070488f CCC: $37.00
Published on Web 09/06/2007

Table 1. Structure, Cytotoxicity, and Antiviral Activity of IASs **6**−**17** and Reference Compounds **4** and **5** in MT-4 and C8166 Cells[a]



4-17

			MT-4			C8166		
compd	R_1	R_2	TC_{50} [b] (nM)	ED_{50} [c] (nM)	SI[d]	TC_{50} [b] (nM)	ED_{50} [c] (nM)	SI [d]
6	H	5,6-Cl_2	>20000	80	>250	>20000	100	>200
7	3′,5′-Me_2	5,6-Cl_2	>20000	10	>2000	>20000	15	>1333
8	3′,5′-Me_2	5,7-Cl_2	>20000	21	>952	>20000	12	>1667
9	H	4,5-F_2	>20000	8	>2500	>20000	10	>2000
10	3′,5′-Me_2	4,5-F_2	>20000	1	>20000	>20000	3	>6667
11	H	5,6-F_2	>20000	16	>1250	>20000	20	>1000
12	3′,5′-Me_2	5,6-F_2	>20000	20	>1000	>20000	30	>667
13	3′,5′-Me_2	5,7-F_2	>20000	7	>2857	>20000	25	>800
14	3′,5′-Me_2	4-Cl, 5-F	>20000	8	>2500	>20000	9	>2222
15	3′,5′-Me_2	6-Cl, 5-F	18000	50	360	>20000	50	>400
16	3′,5′-Me_2	5-Cl, 4-F	>20000	0.5	>40000	>20000	0.8	>25000
17	3′,5′-Me_2	5-Cl, 6-F	>20000	12	>1667	>20000	10	>2000
4	H	5-Cl	>20000	2	>10000	>20000	3	>6667
5	3′,5′-Me_2	5-Cl	12000	6	2000	14000	10	1400

[a] Data are mean values of two experiments performed in triplicate. [b] Cytotoxic concentration (nM) required to reduce the viability (MT-4) or to inhibit the proliferation (C8166) of mock-infected cells by 50% as monitored by the MTT method. [c] Compound concentration (nM) required to inhibit virus-induced cell death by 50% as monitored by the MTT method. [d] Selectivity index: TC_{50}/ED_{50} ratio.

new derivatives **6**−**17** bearing two halogen atoms at the indole ring (Chart 1).

Chemistry

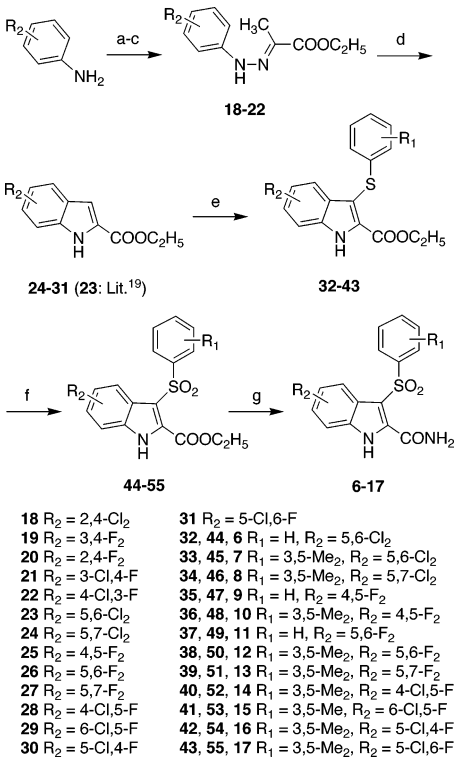
Ethyl 5,7-dichloro-1*H*-indole-2-carboxylate (**24**) was prepared by intramolecular cyclization of the corresponding ethyl pyruvate 2,4-dichlorophenylhydrazone (**18**) in polyphosphoric acid (PPA) as a catalyst, according to Fischer's indole synthesis.[15] By the same procedure, ethyl pyruvate of 3,4-difluorophenylhydrazone (**19**) gave a mixture of ethyl 4,5-difluoro-1*H*-indole-2-carboxylate (**25**) and ethyl 5,6-difluoro-1*H*-indole-2-carboxylate (**26**), which were separated by repeated column chromatography.[16] 3,4-Difluorophenylhydrazone (**19**) was prepared starting from 3,4-difluoroaniline according to the method of Japp−Klingemann.[17] Similarly, ethyl 5,7-difluoro-1*H*-indole-2-carboxylate (**27**), ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate (**28**), ethyl 6-chloro-5-fluoro-1*H*-indole-2-carboxylate (**29**), 5-chloro-4-fluoro-1*H*-indole-2-carboxylate (**30**),[18] and ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate (**31**)[18] were prepared by intramolecular cyclization of the corresponding hydrazones **20**−**22** (Scheme 1).

Reaction of the indole esters **23**[19] and **24**−**31** with phenylthiosuccinimide[11] or its 3,5-dimethyl derivative[11] in the presence of boron trifluoride diethyl etherate afforded the 3-arylthioindole-2-carboxylates **22**−**43**. Oxidation of **22**−**43** to the corresponding sulfones **44**−**55** was achieved using 3-chloroperoxybenzoic acid (MCPBA). Esters **44**−**55** were transformed into the corresponding amides **6**−**17** by heating with ammonium hydroxide in a sealed tube.

Cell-Based and Enzymatic Assays

Cytotoxicity (TC_{50}) and antiretroviral activity (ED_{50}) of IAS derivatives **6**−**17** were evaluated against the HIV-1 WT and NNRTI-resistant strains Y181C and K103N−Y181C. IASs **4** and **5**, NVP, and EFV were used as reference compounds.The activity against HIV-1 WT was determined in MT-4 and C8166 cells by means of MTT assay. Against the mutant strains Y181C and K103N−Y181C, the inhibitory activity was determined in MT-4 cells (MTT assay). The activity against the two primary isolates HIV-112 and HIV-AB1 highly resistant to HAART carrying K103N−V108I−M184V and L100I−V108I mutations, respectively, was determined in lymphocytes by means of p24 assay, in parallel with the WT (IIIB) strain. The activity in

Scheme 1. Synthesis of IASs **6**−**17**[a]



18 R_2 = 2,4-Cl_2
19 R_2 = 3,4-F_2
20 R_2 = 2,4-F_2
21 R_2 = 3-Cl,4-F
22 R_2 = 4-Cl,3-F
23 R_2 = 5,6-Cl_2
24 R_2 = 5,7-Cl_2
25 R_2 = 4,5-F_2
26 R_2 = 5,6-F_2
27 R_2 = 5,7-F_2
28 R_2 = 4-Cl,5-F
29 R_2 = 6-Cl,5-F
30 R_2 = 5-Cl,4-F
31 R_2 = 5-Cl,6-F
32, **44**, **6** R_1 = H, R_2 = 5,6-Cl_2
33, **45**, **7** R_1 = 3,5-Me_2, R_2 = 5,6-Cl_2
34, **46**, **8** R_1 = 3,5-Me_2, R_2 = 5,7-Cl_2
35, **47**, **9** R_1 = H, R_2 = 4,5-F_2
36, **48**, **10** R_1 = 3,5-Me_2, R_2 = 4,5-F_2
37, **49**, **11** R_1 = H, R_2 = 5,6-F_2
38, **50**, **12** R_1 = 3,5-Me_2, R_2 = 5,6-F_2
39, **51**, **13** R_1 = 3,5-Me_2, R_2 = 5,7-F_2
40, **52**, **14** R_1 = 3,5-Me_2, R_2 = 4-Cl,5-F
41, **53**, **15** R_1 = 3,5-Me, R_2 = 6-Cl,5-F
42, **54**, **16** R_1 = 3,5-Me_2, R_2 = 5-Cl,4-F
43, **55**, **17** R_1 = 3,5-Me_2, R_2 = 5-Cl,6-F

[a] Reagents and reaction conditions: (a) $NaNO_2$, HCl, 0 °C, 20 min; (b) ethyl 2-methylacetoacetate, MeCOOK, methanol, 0 °C, 3 h; (c) ethanol, room temp, 3 days; (d) PPA, 110 °C, 30 min; (e) (R-Ph)thiosuccinimide (R = H, 3,5-Me_2), $BF_3{\cdot}Et_2O$, dichloromethane, room temp to 45 °C, 4 h, argon stream; (f) MCPBA, chloroform, 0 °C, 1.5 h; (g) NH_4OH, NH_4Cl, 100 °C, overnight, sealed tube.

Table 2. Antiviral Activity of IASs **6**−**17** and Reference Compounds **4**, **5**, NVP, and EFV against the HIV-1 WT (IIIB) and the Y181C and the K103N−Y181C Resistant Strains in MT-4 Cells[a]

	ED_{50} [b] (nM)		
compd	WT (IIIB)	Y181C	K103N−Y181C
6	80	1700	>20000
7	10	1000	>20000
8	21	4200	>20000
9	8	600	18000
10	1	50	1200
11	16	8200	>20000
12	20	400	>20000
13	7	1500	>20000
14	8	2200	>20000
15	50	700	12000
16	0.5	4	300
17	12	50	>20000
4	2	30	10000
5	6	50	800
NVP	50	14000	>20000
EFV	3	10	200

[a] Data are mean values of two experiments performed in triplicate. [b] Compound concentration (nM) required to achieve 50% protection of MT-4 cells from HIV-1 WT (IIIB), Y181C, and K103N−Y181C resistant strains cytopathogenicity as monitored by MTT method.

Table 3. Activities of Derivatives **10** and **16** and Reference Compounds **4**, **5**, NVP, and EFV against the HIV-1 WT (IIIB) and the Primary Isolates HIV-112 and HIV-AB1 in Lymphocytes[a]

		ED_{50}[b] (nM)			SI[c]		
compd	TC_{50}	IIIB	112	AB1	IIIB	112	AB1
10	>20000	20	130	84	>1000	>154	>238
16	>20000	8	10	12	>2500	>2000	>1667
4	>20000	160	2300	2500	>125	>9	>8
5	18000	200	300	220	90	60	82
NVP	>20000	90	>20000	>20000	>222		
EFV	>20000	7	>20000	>20000	>2857		

[a] Data are mean values of two experiments performed in triplicate. [b] Compound concentration (nM) required to reduce the amount of p24 by 50% in the indicated strain. HIV-p24 antigen production in control HIV-1 infected lymphocytes was 118 900 and 247 200 pg/mL in HIV-112 and HIV-AB1 infected lymphocytes, respectively. [c] Selectivity index: TC_{50}/ED_{50} ratio.

Table 4. Activities of Derivatives **10** and **16** and Reference Compounds **4** and **5** against the HIV-1 WT ($IIIB_{Ba-L}$) in Macrophages[a]

compd	TC_{50} (nM)	ED_{50} [b] (nM)	SI [c]
10	>20000	23	>870
16	>20000	10	>2000
4	>20000	2000	>10
5	20000	115	174

[a] Data are mean values of two experiments performed in triplicate. [b] Compound concentration (nM) required to reduce the amount of p24 by 50% in the HIV-1 WT ($IIIB_{Ba-L}$). HIV-p24 antigen production in control HIV-1 infected macrophages was 83 400 pg/mL. [c] Selectivity index: TC_{50}/ED_{50} ratio.

macrophages infected by HIV-1 WT ($IIIB_{Ba-L}$) was measured by means of a p24 assay. Enzymatic assay was carried out against the RT WT and RTs containing the K103N, Y181I, and L100I single amino acid mutations.

Results and Discussion

IAS derivatives **6**−**17** bearing two halogen atoms at the indole nucleus (dihalo-IASs) were generally highly active against the HIV-1 WT and not cytotoxic up to 20 000 nM. The ED_{50} ranged from 0.5 nM (**16** in MT-4 cells) to 100 nM (**6** in C8166 cells), and selectivity indexes (SI) ranged from >40000 (**16** in MT-4 cells) to >200 (**6** in C8166 cells). Derivatives **10** and **16** potently inhibited the HIV-1 WT multiplication in the low nanomolar range of concentration (ED_{50} = 1 and 0.5 nM, respectively) (Table 1).

As a rule, derivatives bearing two halogen atoms at positions 4 and 5 of the indole and the 3-(3,5-dimethylphenyl)sulfonyl moiety were more potent than the corresponding 5,6- or 5,7-dihalo-IAS counterparts in both cell lines (compare **10** (ED_{50} = 1 and 3 nM) with **12**, **14** (ED_{50} = 8 and 9 nM) with **15**, and **16** (ED_{50} = 0.5 and 0.8 nM) with **17**). The 4,5-difluoro-IAS (**10**) and 5-chloro-4-fluoro-IAS (**16**) (ED_{50} = 1 and 0.5 nM, respectively, in MT-4 cells) were the most potent and selective HIV-1 WT inhibitors within the series. The 4,5-dihaloindole was an optimal substitution pattern for the antiviral activitiy of IASs. The antiviral potency was particularly correlated to the presence of the fluorine atom at position 4.

Against the Y181C mutant strain, derivatives **9**, **10**, **12**, and **15**−**17** showed inhibitory potencies in the nanomolar range of concentration. IASs **10** and **17** were as active as the reference compounds **4** and **5**. The most potent derivative **16** (ED_{50} = 4 nM) was as active as EFV in inhibiting the Y181C mutant strain (Table 2).

Compounds **10** (ED_{50} = 1200 nM) and **16** (ED_{50} = 300 nM) effectively inhibited the K103N−Y181C double-mutant strain, which is highly resistant to NVP. Against this strain, **16** was as active as EFV and >667-fold more active than NVP.

The most potent derivatives **10** and **16** were evaluated in lymphocytes against HIV-1 WT (IIIB) and primary isolates HIV-112 and HIV-AB1 obtained from two HIV-1-Ab seropositive individuals who had experienced therapeutic failure after treatment with HAART regimens. The 112 strain was selected after treatment with NRTIs and NNRTIs and carried mutations at K103N−V108I−M184V positions that showed >99% resistance to NVP and EFV. The AB1 strain was selected after treatment with NRTIs, NNRTIs, and at least one PI and carried L100I−V108I mutations that were >90% and >85% resistant to NVP and EFV, respectively. Compounds **10** and **16** inhibited the 112 and the AB1 strains in lymphocytes (Table 3) and the multiplication of the $IIIB_{Ba-L}$ strain in macrophages (Table 4) at nanomolar concentrations.

Derivatives **10** and **16** were tested against RT WT and RTs containing the K103N, Y181I, and L100I single amino acid mutations responsible for resistance to NNRTIs (Table 5). Against RT WT, **10** and **16** were more potent than NVP (235 and 133 times, respectively) and EFV (47 and 27 times, respectively). Compound **16** proved to be an exceptionally potent inhibitor of the RTs carrying the K103N, Y181I, and L199I mutations (K103N, 1167 and >3333 times more potent than NVP and EVF, respectively; Y181I, >690 and 14 times more potent than NVP and EVF, respectively; L100I, 4500 times more potent than NVP). The recombinant HIV-1 RT carrying the Y181I mutation was absolutely comparable to the Y181C

Table 5. HIV-1 RT Inhibitory Activity of Compounds **10** and **16** against the WT and Mutant Enzymes Carrying Single Amino Acid Substitutions[a]

	ID_{50} [b] (nM)			
compd	WT	K103N	Y181I	L100I
10	1.7	1000	2050	90
16	3	6	29	2
NVP	400	7000	>20000	9000
EFV	80	>20000	400	nd[c]

[a] Data represent mean values of at least three separate experiments. [b] Compound dose (K_i, nM) required to inhibit by 50% the RT activity of the indicated strain. [c] nd, no data.

substitution in terms of drug resistance, as we previously characterized in our laboratory from an enzymological point of view.

Conclusions

The dihalo-IASs showed potent antiviral activity and were not cytotoxic up to 20 000 nM. The 4,5-difluoro- (**10**) and 5-chloro-4-fluoro (**16**) derivatives were the most potent inhibitors of HIV-1 WT (ED_{50} = 1 and 0.5 nM, respectively, in MT-4 cells) and the Y181C and K103N−Y181C NNRTI-resistant strains. These potent derivatives were characterized by the presence of a fluorine atom at position 4 of the indole nucleus. Compounds **10** and **16** were highly effective against the 112 and the AB1 strains in lymphocytes and inhibited at nanomolar concentration the multiplication of the III_{BBa-L} strain in macrophages. Compound **16** proved to be an exceptionally potent inhibitor of the RTs carrying the K103N, Y181I, and L100I mutations. These results suggest that, similar to EFV's analogues, IAS derivatives may successfully adopt the 4,5-dihaloindole substitution pattern. Compound **16** is a very robust lead compound for the development of new second-generation NNRTIs that should be effective against the viral mutant strains arising in patients whose viral loads rebounds after an initial response to the drug.[10] These results serve as basis for the design of new IAS derivatives.

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 (400 MHz) FT spectrometers in the indicated solvent. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Chromatography columns were packed with Merck alumina (70−230 mesh) and Merck silica gel (70−230 mesh). Aluminum oxide TLC cards from Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator at 254 nm) and silica gel TLC cards from Fluka (silica gel precoated aluminum cards with fluorescent indicator at 254 nm) were used for thin layer chromatography (TLC). Developed plates were visualized by a Spectroline ENF 260C/F UV apparatus. Organic solutions were dried over anhydrous sodium sulfate. Concentration and evaporation of the solvent after reaction were carried out on a Büchi Rotavapor R-210 equipped with a Büchi V-850 vacuum controller and Büchi V-700 and V-710 vacuum pumps. Elemental analysis results were within ±0.4% of the theoretical values.

General Procedure for the Synthesis of Derivatives 6−17. Example. 5,6-Dichloro-3-(phenylsulfonyl)-1*H*-indole-2-carboxamide (6). Compound **44** (0.56 g, 0.0014 mol) was heated at 100 °C with 30% ammonium hydroxide (25 mL) and ammonium chloride (40 mg) in a sealed tube 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 was evaporated. The crude residue was purified by silica gel column chromatography (95:5 chloroform−ethanol as eluent) to afford **6** (0.45 g, 87%), mp 292−295 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 7.58 (m, 3H), 7.76 (s, 1H), 8.06 (m, 2H), 8.17 (s, 1H), 8.32 (broad s, 1H, disappeared on treatment with D_2O), 8.50 (broad s, 1H, disappeared on treatment with D_2O), 13.17 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1130, 1280, 1660, 3100, 3300 cm^{-1}. Anal. ($C_{15}H_{10}Cl_2N_2O_3S$ (369.22)) C, H, N, Cl, S.

General Procedure for the Synthesis of Derivatives 18−22. Example. Ethyl Pyruvate 2,4-Dichlorophenylhydrazone (18). From 2,4-Dichloroaniline. A solution of sodium nitrite (11.2 g, 0.16 mol) in water (14.7 mL) was dropped onto an ice-cooled mixture of 2,4-dichloroaniline (20.9 g, 0.16 mol), 37% HCl (39 mL), and water (39 mL). Sodium acetate trihydrate (18.2 g, 0.22 mol) was added while stirring on an ice bath for 20 min. This mixture was added to an ice-cooled and well-stirred solution of ethyl 2-methylacetoacetate (90%, 25.6 g, 0.162 mol) and potassium acetate (31.7 g, 0.32 mol) in methanol (157 mL). The mixture was stirred at 0 °C for 3 h and then extracted with diethyl ether. The organic layer was separated, washed with brine, and dried. Evaporation of the solvent gave a residue that was dissolved in ethanol (250 mL) and stirred at room temperature for 3 days. The resulting suspension was cooled at 4 °C overnight and filtered to give compound **18** as crystals (11.8 g, 27%), mp 118−120 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 1.30 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 4.29 (q, J = 7.1 Hz, 2H), 7.38 (dd, J = 2.2 and 8.9 H z, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 12.3 ppm (broad s, disappeared on treatment with D_2O, 1H). IR (nujol): ν 760, 850, 1110, 1160, 1290, 1660, 3200 cm^{-1}.

From 2,4-Dichlophenylhydrazine. A mixture of 2,4-dichlorophenylhydrazine (13.3 g, 0.075 mol), ethyl pyruvate (13.9 g, 10.3 mL, 0.12 mol), glacial acetic acid (0.9 mL), and absolute ethanol (105 mL) was refluxed for 2 h. After the mixture was cooled at room temperature, the solid was filtered and recrystallized from ethanol to afford **18** (17.1 g, 83%). The melting point and spectral data were identical to those of the sample prepared from 2,4-dichloroaniline.

General Procedure for the Synthesis of Derivatives 24−31. Example. Ethyl 5,7-Dichloro-1*H*-indole-2-carboxylate (24). Compound **18** (16.5 g, 0.06 mol) was added by portions to PPA (165 g) preheated at 110 °C. The mixture was stirred at 110 °C for 30 min and then quenched on ice−water. The solid was filtered, washed with water, and dried. The crude product was purified by silica gel column chromatography (chloroform as eluent) to give **24** (5.0 g, 37%), mp 143−145 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 1.31 (t, J = 7.2 Hz, 3H), 4.37 (q, J = 7.2 Hz, 2H), 7.23 (s, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.76 (d, J = 1.5 Hz, 1H), 12.4 ppm (broad s, 1H, disappeared on treatment with D_2O). IR (nujol): ν 1000, 1180, 1240, 1300, 1680, 3240 cm^{-1}.

General Procedure for the Synthesis of Derivatives 32−43. Example. Ethyl 5,6-Dichloro-3-(phenylthio)-1*H*-indole-2-carboxylate (32). Boron trifluoride diethyl etherate (0.28 g, 0.24 mL, 0.002 mol) was added under a dry argon atmosphere to a mixture of **23** (1.54 g, 0.006 mol), *N*-(phenylthio)succinimide[11] (1.37 g, 0.0066 mol), and anhydrous dichloromethane (40 mL). After the mixture was stirred at room temperature for 2 h, boron trifluoride diethyl etherate (0.56 g, 0.48 mL, 0.004 mol) was added and the mixture was heated at 45 °C for 2 h. After cooling, the mixture was diluted with chloroform and brine while shaking. The organic layer was separated, washed with sodium hydrogen carbonate solution and brine, and dried. Removal of the solvent afforded **32** (2.17 g, 96%), mp 192−195 °C (from ethanol). ^1H NMR (DMSO-d_6): δ 1.25 (t, J = 6.9 Hz, 3H), 4.34 (q, J = 6.9 Hz, 2H), 7.10−7.33 (m, 5H), 7.55 (s, 1H), 7.74 ppm (s,1H). IR (nujol): ν 700, 1240, 1660, 3210 cm^{-1}.

General Procedure for the Synthesis of Derivatives 44−55. Example. Ethyl 5,6-Dichloro-3-(phenylsulfonyl)-1*H*-indole-2-carboxylate (44). 3-Chloroperoxybenzoic acid (0.87 g, 0.005 mol) was added to an ice solution of **32** (0.62 g, 0.0017 mol) in chloroform (30 mL). The mixture was stirred at room temperature for 1.5 h and then poured on crushed ice and extracted with chloroform. The organic solution was shaken with sodium hydrogen carbonate solution and brine and dried. After concentration to a small volume, the solution was passed through an alumina column chromatography (ethyl acetate as eluent) to furnish **44** (0.55 g, 82%), mp 196−197 °C (from aqueous ethanol). ^1H NMR (DMSO-d_6): δ 1.30 (t, J = 7.1 Hz, 3H), 4.43 (q, J = 7.1 Hz, 2H), 7.61 (m, 3H), 7.85 (s, 1H), 8.06 (m, 2H), 8.47 ppm (s, 1H). IR (nujol): ν 700, 840, 1120, 1280, 1700, 3500 cm^{-1}.

Acknowledgment. We are thankful for the financial support of the Italian MUR (PRIN 2006, Grant 2006030809) and Istituto Pasteur−Fondazione Cenci Bolognetti.

Supporting Information Available: Additional chemical and biological information. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM070488F