Pergamon

Tetrahedron 57 (2001) 1041–1048

TETRAHEDRON

Synthesis of 5-(sulfamoylmethyl)indoles

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Received 14 September 2000; revised 27 October 2000; accepted 17 November 2000

Abstract—The synthesis of 5-(sulfamoylmethyl)indoles bearing a two-carbon chain at C-3 (aminoethyl, acetate, hydroxyethyl, ethyl) either by the Grandberg modification of the Fischer indolization or by intramolecular Heck reaction of suitable *o*-halotrifluoroacetanilides is reported.

The discovery of the anti-migraine drug sumatriptan (Imigran®)[1] has stimulated the search and design of second-generation 5-HT_{1D} receptor agonists. From the chemical point of view, many of these *tryptamines* (sumatriptan,[1] CP-122,288,[2] avitriptan,[3] almotriptan[4]) have the common feature of possessing a sulfamoyl group attached at the indole 5 position through a methylene spacer (Fig. 1).

In the context of the study of possible almotriptan metabolites it was necessary to synthesize a variety of 5-(sulfamoylmethyl)indoles, including tryptamines and other derivatives bearing a two-carbon chain at the indole 3-position. For this purpose, we had initially planned the introduction of the sulfamoyl moiety from 5-(chloromethyl)-tryptamine **4**, by displacement of the chlorine atom with sodium sulfite, followed by reaction of the resulting sulfonate with thionyl chloride and then with the appropriate amine. Although similar approaches, i.e. the displacement of a leaving group from the benzylic C-5 indole position by a nucleophile, have been employed successfully for the synthesis of related tryptamines,[5] this route proved to be non-viable due to the rapid decomposition of the required (chloromethyl)tryptamine **4**, probably through a reactive conjugate imine intermediate formed by elimination of HCl.[6] This process is assisted by the indole nitrogen lone pair. In fact, attempts to prepare the hydrochloride of tryptamine-methanol **3** also caused complete decomposition.

Alcohol **3** was obtained as shown in Scheme 1, by $LiAlH_4$ reduction of ester **2**.[7] This ester was easily accessible (30% overall yield) by reaction of hydrazine **1** with 4-chlorobutyraldehyde diethyl acetal (following the Grandberg modification of the Fischer indole synthesis[8] whereby the halogen atom undergoes ammonolysis under the reaction conditions), with subsequent reductive alkylation (CH_2O, $NaBH_4$) of the resulting tryptamine. Although it could be expected that an electron-withdrawing group on the indole nitrogen would reduce the leaving group tendency of the benzylic substituent at C-5, the use of the *N*-(benzenesulfonyl)indole **5** did not prove to be satisfactory either.

For this reason, we turned our attention to an alternative approach, involving the elaboration of the indole nucleus[9] from starting materials already incorporating the sulfamoyl moiety. Taking into account that the Grandberg indolization allows the one-pot preparation of tryptamines from readily accessible hydrazines, we selected this procedure, although we were aware that the Fischer indolization from hydrazines bearing a benzylic *para* substituent able to act as a leaving group under acidic conditions usually gives low yields or even fails completely.[10] The required *p*-(sulfamoylmethyl)-phenylhydrazine **7** was prepared in 82% yield from aniline

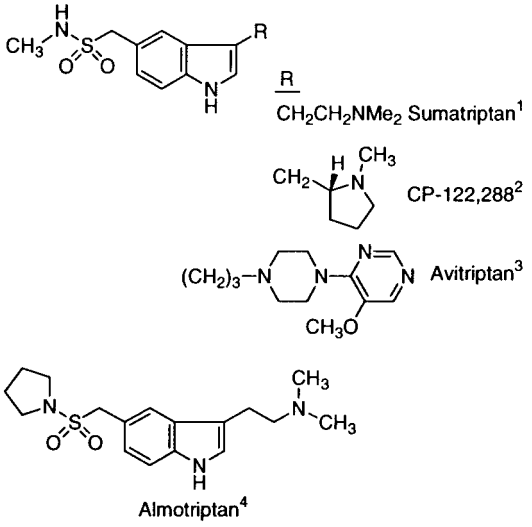

Figure 1.

Keywords: indoles; indolization; Heck reactions; metabolites; drugs.
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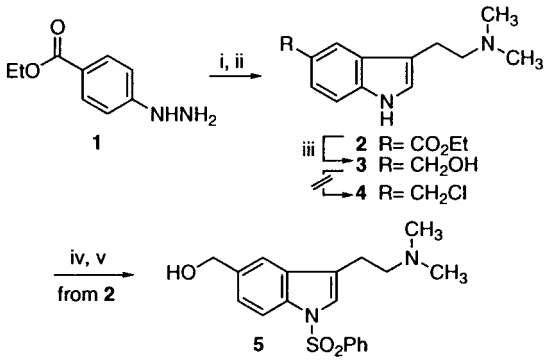
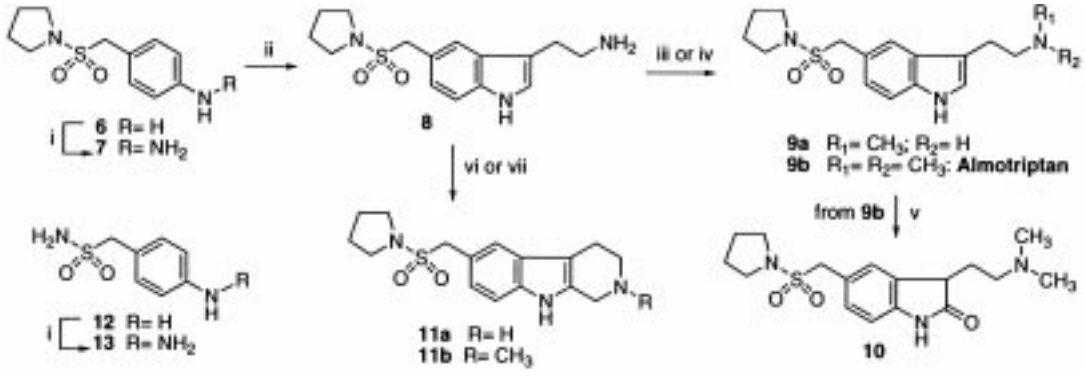


Scheme 1. *Reagents and conditions:* (i) 4-chlorobutyraldehyde diethyl acetal, 2N HCl, then Na_2HPO_4, pH 5, Δ, 32%; (ii) HCHO, $NaBH_4$, 93%; (iii) $LiAlH_4$, THF, Δ, 58%; (iv) $PhSO_2Cl$, 50% NaOH/toluene, TBAHS, 55%; (v) $LiAlH_4$, THF, Δ, 53%.

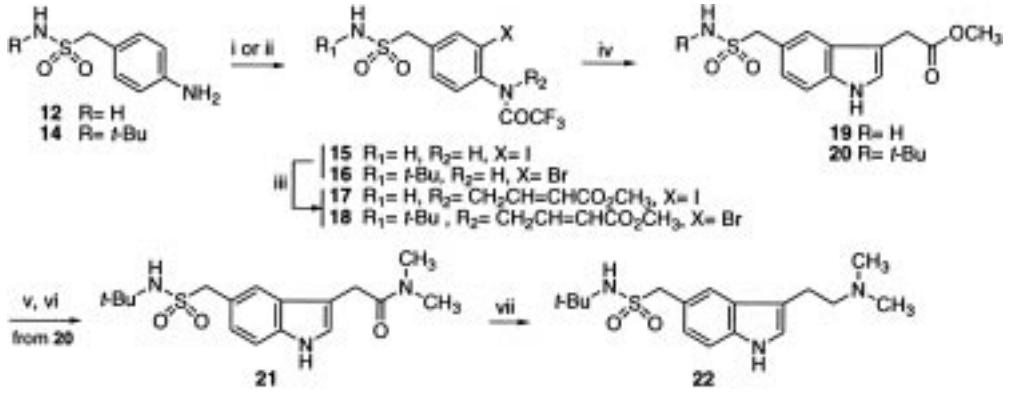
6, by diazotization followed by reduction of the resulting diazonium salt with $SnCl_2$ (Scheme 2). Satisfactorily, treatment of hydrazine **7** with 4-chlorobutyraldehyde diethyl acetal gave the corresponding hydrazone, which underwent rearrangement to tryptamine **8** in 58% overall yield upon treatment with HCl in the presence of Na_2HPO_4 to buffer the reaction to pH 5. These mild reaction conditions, which prevent the decomposition of indole, are probably responsible for the success and relatively high yield of the reaction.[11] Following standard procedures, tryptamine **8** was methylated to **9a**, dimethylated to **9b** (almotriptan), and converted by Pictet–Spengler reaction to tetrahydro-β-carbolines **11a** and **11b**. Finally, although the conversion of tryptamine **9b** to oxindole **10** took place in a yield that was unsatisfactory from the preparative standpoint, it was sufficient for the identification of this potential metabolite.

In spite of the success of the above indolization to a 5-[(dialkylsulfamoyl)methyl]indole, the Grandberg method could not be applied to the synthesis of related *N*-unsubstituted sulfonamides. Hydrazine **13**[12] failed to give the expected tryptamine under a variety of reaction conditions, complex mixtures were formed instead.

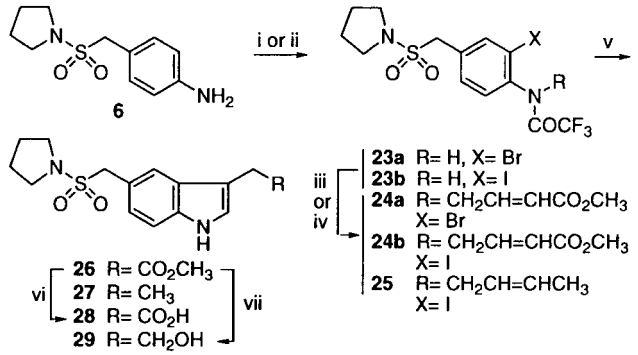
The above results prompted us to use the Pd-catalyzed intramolecular Heck reaction as an alternative method for the construction of the indole ring.[13] This approach required the previous preparation of *N*-protected 2-halo-4-(sulfamoylmethyl)anilines and their allylation with appropriate allyl halides (Scheme 3). As expected, the Heck cyclization of *N*-allyl substituted *o*-iodotrifluoroacetanilide **17** took place in satisfactory yield (60%), with concomitant deprotection of the indole nitrogen, to give indoleacetic ester **19**.[14] The main shortcoming of this route, however, was the low and erratic yield of the allylation step. Thus, although regioselective iodination of 4-(sulfamoylmethyl)aniline **12** with



Scheme 2. *Reagents and conditions:* (i) $NaNO_2$, conc. HCl, then $SnCl_2$, 82%; (ii) 4-chlorobutyraldehyde diethyl acetal, 2N HCl, then Na_2HPO_4, pH 5, Δ, 58%; (iii) HCOOH/Ac_2O, then B_2H_6·DMS, Δ, 40% (**9a**); (iv) HCHO/MeOH, $NaBH_4$, 88% (**9b**); (v) NBS, *t*-BuOH, 5%; (vi) $CH_2(OMe)_2$, AcOH, Δ, 72% (**11a**); (vii) 35% HCHO, AcOH, Δ, 87% (**11b**).



Scheme 3. *Reagents and conditions:* (i) $I(C_5H_5N)_2 \cdot BF_4$, then TFAA, 78% (**15**); (ii) Br_2, MeOH, then TFAA, 33% (**16**); (iii) LDA, $BrCH_2CH{=}CHCO_2CH_3$, 15% (**17**), 63% (**18**); (iv) $Pd(AcO)_2$, Et_3N, TBABr, DMF, 80°C, 60% (**19**), 57% (**20**); (v) 2N KOH/MeOH, 97%; (vi) PCl_5, 0°C, then $Me_2NH \cdot HCl$, TEA, 60%; (vii) $LiAlH_4$, THF, Δ, 33%.



Scheme 4. *Reagents and conditions:* (i) Br_2, MeOH, then TFAA, 26% (**23a**); (ii) $I(C_5H_5N)_2{\cdot}BF_4$, then TFAA, 81% (**23b**); (iii) LDA, $BrCH_2CH{=}CHCO_2CH_3$, 73% (**24a**), 52% (**24b**); (iv) LDA, $BrCH_2CH{=}CHCH_3$, 49% (**25**); (v) $Pd(AcO)_2$, Et_3N, TBABr, DMF, 80°C, 52% (from **24a**) and 60% (from **24b**) for **26**, 57% (from **25**) for **27**; (vi) 2N KOH/MeOH, 83%; vii) $LiBH_4$, THF, Δ, 71%.

IPy_2BF_4[15] followed by protection of the aniline nitrogen with TFAA gave trifluoroacetanilide **15** in 78% overall yield, the subsequent introduction of the crotonate moiety by sequential treatment with LDA and methyl 4-bromocrotonate afforded the desired product **17** in only 15% yield, which was not reproducible when operating on a scale higher than 100 mg. This problem could be circumvented starting from the protected sulfonamide **14**, which was converted to the *N*-protected bromoaniline **16** and then satisfactorily allylated (63% yield) to **18**. In this case, the crucial Heck ring forming reaction took place in 57% yield. The resulting indoleacetic ester **20** was converted to tryptamine **22** via the amide **21**.

The Heck approach also proved to be satisfactory for the preparation of a variety of 3,5-disubstituted indoles bearing the pyrrolidinylsulfonyl moiety of almotriptan and a two-carbon chain at carbon 3. Thus, aniline **6** was converted to the brominated trifluoroacetanilide **23a** (26% overall yield) and, more satisfactorily, to the iodo analogue **23b** (81% overall yield) (Scheme 4). Treatment of either **23a** or **23b** with LDA and then methyl 4-bromocrotonate afforded the respective allylated derivatives **24a** and **24b**, which underwent the Pd-catalyzed Heck cyclization leading to the same indole-3-acetic ester **26**. By simple functional group interconversions ester **26** was converted to indoleacetic acid **28**[16] and tryptophol **29**. Similarly, allylation of *o*-iodotrifluoroacetanilide **23b** with crotyl bromide, followed by Heck cyclization (57% yield) led to 3-ethylindole **27**. In contrast with the above satisfactory results, the Fischer indolization failed to give 3-indoleacetic esters when starting either from hydrazine **7** and ethyl 4-oxobutanoate or from the hydrazone formed by Japp–Klingemann reaction of diethyl 2-acetylglutarate with the diazonium salt derived from **6**.

The above results make evident that the intramolecular Pd-catalyzed Heck reaction of *N*-protected *N*-allyl *o*-haloanilines constitutes a convergent general method for the synthesis of 3-substituted indoles bearing labile substituents, such as sulfamoylmethyl, at the indole 5-position, thus allowing the straightforward preparation of indoles inaccessible by the classical Fischer reaction.

1. Experimental

1.1. General

Melting points were determined in a capillary tube and are uncorrected. NMR spectra were recorded at 200 or 300 (^1H) and 50.3 or 75 MHz (^{13}C). Coupling constants are expressed in hertz and signals are quoted as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; ddd, doublet of doublet of doublets; q, quadruplet; dq, doublet of quadruplets; m, multiplet; br s, broad signal. Analytical thin layer chromatography was carried out on Merck silica gel 60 F_{254} plates, and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Microanalyses were performed on a Carlo Erba 1106 analyzer by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

1.1.1. Ethyl 3-[2-(dimethylamino)ethyl]-5-indolecarboxylate (2). A solution of 4-chlorobutyraldehyde diethyl acetal[17] (20.62 g, 114 mmol) in 35% aqueous HCl (4.5 mL) and H_2O (240 mL) was stirred at rt for 1 h and then added to a solution of **1** hydrochloride[7] (22.6 g,104 mmol) in H_2O (50 mL) and MeOH (265 mL). The mixture was stirred at rt for 1 h and cooled at 0°C. The precipitated yellow solid was collected by filtration and successively washed with 9:1 H_2O–MeOH (100 mL) and cool H_2O (200 mL) to afford the intermediate hydrazone hydrochloride as an orange solid. A solution of this hydrazone and Na_2HPO_4 (13.1 g, 73.6 mmol) in H_2O (150 mL), MeOH (600 mL), and 35% aqueous HCl (6.1 mL) was refluxed overnight. MeOH was evaporated, H_2O (400 mL) was added, and the resulting mixture was saturated with Na_2CO_3 and extracted with CH_2Cl_2 (3×200 mL). The extracts were dried, filtered, and concentrated to give ethyl 3-(2-aminoethyl)-5-indolecarboxylate[7] (7.43 g, 32%) as a brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, *J*=7.1 Hz), 2.94 (t, 2H, *J*=6.4 Hz), 3.04 (t, 2H, *J*=6.4 Hz), 4.40 (q, 2H, *J*=7.1 Hz), 7.07 (s, 1H), 7.35 (d, 1H, *J*=8.6 Hz), 7.90 (d, 1H, *J*=8.6 Hz), 8.38 (s, 1H), 8.80 (br s, 1H). A solution of 35% HCHO (43 mL, 512 mmol) in MeOH (43 mL) and a solution of $NaBH_4$ (6 g, 160 mmol) in H_2O (85 mL) were added dropwise (2 h), simultaneously, to a well-stirred solution of the above tryptamine (7.43 g, 32 mmol) in MeOH (190 mL) cooled at −15°C. The mixture was stirred at −15°C for 0.5 h, 4N aqueous HCl was cautiously added to bring the pH to 3, and the resulting mixture was stirred for 10 min. Then, the pH was adjusted to 6.5–7 with saturated aqueous $NaHCO_3$, MeOH was evaporated, and H_2O (50 mL) was added. The mixture was washed with EtOAc (2×100 mL), basified with Na_2CO_3, and extracted with CH_2Cl_2 (3× 100 mL). The organic extracts were dried, filtered, and concentrated to give **2** as a brown solid: 7.75 g; 93% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, 3H, *J*= 7 Hz), 2.35 (s, 6H), 2.65 (t, 2H, *J*=6.5 Hz), 2.98 (t, 2H, *J*= 6.5 Hz), 4.40 (q, 2H, *J*=7 Hz), 7.06 (s, 1H), 7.35 (d, 1H, *J*=8.4 Hz), 7.88 (d, 1H, *J*=8.5 Hz), 8.38 (s, 1H), 8.50 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 23.3, 45.2, 59.9, 60.5, 110.7, 115.2, 121.1, 121.5, 122.9, 123.0, 126.9, 138.9, 168.0.

1.1.2. 3-[2-(Dimethylamino)ethyl]-5-indolemethanol (3). A solution of **2** (7.75 g, 29.8 mmol) in anhydrous THF (150 mL) was added dropwise under N_2 to a suspension of $LiAlH_4$ (2.27 g, 59.6 mmol) in anhydrous THF (70 mL). The mixture was refluxed for 2 h and cooled to 0–5°C. Then H_2O (2.3 mL), 10% aqueous NaOH (2.3 mL), and H_2O (9.2 mL) were added successively. The resulting suspension was filtered through Celite, and the cake was washed with CH_2Cl_2. H_2O (40 mL) was added to the filtrate, and the mixture was extracted with CH_2Cl_2 (2×100 mL). The combined organic phases were dried, filtered, and concentrated to give alcohol **3**, which was chromatographed (99:1:0.1 CH_2Cl_2–MeOH–NH_4OH): colorless oil, 3.8 g, 58% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 6H), 2.55 (t, 2H, J=6.6 Hz), 2.85 (t, 2H, J=6.6 Hz), 4.30 (br s, 1H), 4.69 (s, 2H), 6.79 (s, 1H), 7.12 (d, 1H, J=8.4 Hz), 7.19 (d, 1H, J=8.5 Hz), 7.48 (s, 1H), 9.17 (br s, 1H). The oxalate precipitated on treating a solution of the base in EtOH with oxalic acid in EtOH; white solid, mp 125–127°C. ^1H NMR (300 MHz, D_2O) δ 2.71 (s, 6H), 3.06 (t, 2H, J=7.4 Hz), 3.27 (t, 2H, J=7.4 Hz), 4.54 (s, 2H), 7.10 (d, 1H, J=8.4 Hz), 7.15 (s, 1H), 7.34 (d, 1H, J=8.4 Hz), 7.46 (s, 1H). ^{13}C NMR (75 MHz, D_2O) δ 21.0, 43.6, 58.5, 65.6, 109.4, 113.1, 118.5, 123.4, 125.5, 127.3, 132.2, 136.9, 166.6. Anal. calcd for $C_{13}H_{18}N_2O{\cdot}C_2H_2O_4$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.34; H, 6.57; N, 8.94.

1.1.3. 3-[2-(Dimethylamino)ethyl]-1-(phenylsulfonyl)-5-indolemethanol (5). A solution of tetrabutylammonium hydrogen sulfate (0.24 g, 0.72 mmol) in 50% aqueous NaOH (12 mL) and a solution of benzenesulfonyl chloride (1.3 mL, 10.1 mmol) in toluene (20 mL) were successively added to a solution of **2** (2.5 g, 9.6 mmol) in toluene (20 mL). After stirring at rt for 2 h, the organic phase was washed with H_2O, dried, filtered and concentrated. Flash chromatography (97:3:0.1 CH_2Cl_2–MeOH–NH_4OH) gave the corresponding *N*-(phenylsulfonyl)indole as a yellow oil (2.1 g, 55%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, 3H, J=7 Hz), 2.35 (s, 6H), 2.62 (t, 2H, J=6.5 Hz), 2.95 (t, 2H, J=6.5 Hz), 4.39 (q, 2H, J=7 Hz), 7.2–7.5 (m, 6H), 7.85 (d, 1H, J=8.4 Hz), 8.09 (s, 1H), 8.22 (s, 1H). A solution of the above ester (2.1 g, 5.25 mmol) in anhydrous THF (50 mL) was added dropwise under N_2 to a suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in anhydrous THF (20 mL). The mixture was refluxed for 2 h and cooled to 0–5°C. Then, H_2O (0.4 mL), 10% aqueous NaOH (0.4 mL), and H_2O (1.7 mL) were successively added. The resulting suspension was filtered through Celite, and the cake was washed with CH_2Cl_2. H_2O (20 mL) was added to the filtrate, and the mixture was extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried, filtered, and concentrated to give alcohol **5**, which was chromatographed (95:5:0.1 CH_2Cl_2–MeOH–NH_4OH): colorless oil, 1.5 g, 53% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 2.22 (s, 6H), 2.55 (t, 2H, J=6.6 Hz), 2.76 (t, 2H, J=6.6 Hz), 4.70 (s, 2H), 7.3–7.5 (m, 6H), 7.79 (s, 1H), 7.84 (s, 1H), 7.93 (d, 1H, J=8.4 Hz).

1.1.4. 3-(2-Aminoethyl)-5-(1-pyrrolidinylsulfonylmethyl)-indole (8). A solution of $NaNO_2$ (1.36 g, 19.7 mmol) in H_2O (8 mL) was added dropwise at −20°C to a suspension of aniline **6**[18] (3.5 g, 14.6 mmol) in 35% aqueous HCl (30 mL). The mixture was stirred at −20°C for 15 min and then was added at −20°C to a solution of $SnCl_2{\cdot}2H_2O$ (16.46 g, 73 mmol) in 35% aqueous HCl (12 mL). After stirring at −20°C for 25 min and at −5°C for another 25 min period, the precipitated hydrazine **7** hydrochloride was collected by filtration and successively washed with cool H_2O and Et_2O (3.06 g, 82%). A solution of 4-chlorobutyraldehyde diethyl acetal[17] (21.8 g, 120.5 mmol) in 35% aqueous HCl (5.3 mL) and H_2O (270 mL) was stirred at rt for 1 h and added to a solution of hydrazine **7** (28.0 g, 109.6 mmol) in 35% aqueous HCl (9.8 mL), H_2O (65 mL), and MeOH (300 mL). The mixture was stirred at rt for 1 h and cooled to 0°C. The precipitated yellow solid was collected by filtration and successively washed with 9:1 H_2O–MeOH (150 mL) and cool H_2O (300 mL) to afford the intermediate hydrazone hydrochloride as an orange solid. A solution of this hydrazone and Na_2HPO_4 (12.4 g, 69.6 mmol) in H_2O (70 mL), MeOH (450 mL), and 35% aqueous HCl (9.8 mL) was refluxed overnight. MeOH was evaporated, H_2O (300 mL) was added to the mixture, and the pH was adjusted to 6.5–7 with solid Na_2CO_3. The aqueous solution was washed with CH_2Cl_2 (2×300 mL) and then saturated with Na_2CO_3, extracted with CH_2Cl_2 (3×200 mL), dried, filtered, and concentrated to give **8** (19.6 g, 58%) as a brown solid. ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (br s, 2H), 1.79 (m, 4H), 2.90 (m, 2H), 3.01 (m, 2H), 3.17 (m, 4H), 4.38 (s, 2H), 7.06 (s, 1H), 7.24 (d, 1H, J=8.4 Hz), 7.33 (d, 1H, J=8.4 Hz), 7.60 (s, 1H), 8.30 (br s, 1H).

1.1.5. 3-[(2-Methylamino)ethyl]-5-(1-pyrrolidinylsulfonylmethyl)indole (9a). A mixture of 98% HCO_2H (5.6 mL, 150 mmol) and Ac_2O (14.1 mL, 150 mmol) was stirred at 60°C for 1 h. After cooling to rt, a solution of tryptamine **8** (9.2 g, 30 mmol) in anhydrous CH_2Cl_2 (50 mL) was added. The mixture was stirred at rt for 1.5 h and then concentrated to dryness. The residue was basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3×200 mL). The organic extracts were dried, filtered, and concentrated to give the corresponding *N*-formyltryptamine, which was chromatographed (96:4:1 CH_2Cl_2–MeOH–NH_4OH): 6.63 g, 66% yield. A solution of 95% B_2H_6–DMS (13 mL, 136 mmol) was added dropwise at rt under N_2 to a solution of the above *N*-formyltryptamine (5.7 g, 17 mmol) in anhydrous THF (25 mL). The mixture was stirred at reflux for 2 h. After cooling to 0–5°C, MeOH (45 mL) was added, and the solution was refluxed for 8 h. The mixture was concentrated, and the resulting residue was chromatographed (90:10:1 CH_2Cl_2–MeOH–NH_4OH): 3.23 g, 60% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 1.79 (m, 4H), 1.95 (br s, 1H), 2.44 (s, 3H), 2.93 (m, 4H), 3.15 (m, 4H), 4.36 (s, 2H), 7.03 (s, 1H), 7.20 (d, 1H, J=8.5 Hz), 7.31 (d, 1H, J=8.5 Hz), 7.60 (s, 1H), 8.65 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.1, 25.7, 35.9, 48.0, 51.8, 56.4, 111.5, 113.0, 119.3, 120.9, 123.3, 124.0, 127.4, 136.4. The oxalate precipitated on treating a solution of the base in EtOH with oxalic acid in EtOH; mp 194–195°C. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 1.74 (m, 4H), 2.59 (s, 3H), 3.10 (m, 8H), 4.43 (s, 2H), 7.12 (dd, 1H, J=8.4, 1.5 Hz), 7.25 (d, 1H, J=2.0 Hz), 7.35 (d, 1H, J=8.4 Hz), 7.59 (s, 1H), 11.10 (br s, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 21.8, 25.6, 32.6, 47.9, 48.7, 54.4, 109.6, 111.6, 119.8, 120.9, 124.2, 124.3, 126.9, 136.2, 165.1. Anal. calcd for $C_{16}H_{25}N_3O_2S{\cdot}C_2H_2O_4$: C, 52.55; H, 6.57; N, 10.20. Found: C, 52.54; H, 6.37; N, 9.92.

1.1.6. 3-[(2-Dimethylamino)ethyl]-5-(1-pyrrolidinylsulfonylmethyl)indole (9b). A solution of 35% formaldehyde (35 mL, 416 mmol) in MeOH (35 mL) and a solution of $NaBH_4$ (5 g, 132 mmol) in H_2O (70 mL) were added dropwise, simultaneously, at 15°C to a well-stirred solution of tryptamine **8** (8.1 g, 26 mmol) in MeOH (150 mL). The mixture was stirred at 15°C for 0.5 h, 2N aqueous HCl was cautiously added to bring the pH to 3, and the resulting mixture was stirred for 10 min. Then, the pH was adjusted to 6.5–7 with saturated aqueous $NaHCO_3$, MeOH was evaporated, and H_2O (50 mL) was added. The mixture was washed with EtOAc (2×150 mL), basified with K_2CO_3, and extracted with EtOAc (2×130 mL). The organic extracts were dried, filtered, and concentrated to give **9b**[4] (7.70 g, 88%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (m, 4H), 2.35 (s, 6H), 2.63 (t, 2H, J=7.8 Hz), 2.93 (t, 2H, J=7.8 Hz), 3.14 (m, 4H), 4.37 (s, 2H), 6.99 (s, 1H), 7.19 (d, 1H, J=8.4 Hz), 7.27 (d, 1H, J=8.4 Hz), 7.56 (s, 1H), 8.60 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 25.7, 45.3, 48.0, 56.6, 60.1, 111.4, 113.7, 119.3, 120.8, 122.6, 123.9, 127.4, 136.2.

1.1.7. 3-[(2-Dimethylamino)ethyl]-2-oxo-5-(1-pyrrolidinylsulfonylmethyl)-2,3-dihydroindole (10). NBS (0.53 g, 3 mmol) was added in small portions under Ar during a 15 min period to a solution of **9b** (0.5 g, 1.50 mmol) in 95% *t*-BuOH (10 mL). After stirring at rt for 18 h, the mixture was concentrated to dryness. The residue was dissolved in CH_2Cl_2, and the organic phase was washed with saturated aqueous Na_2CO_3, dried, filtered, and concentrated to give crude oxindole **10**, which was purified twice by flash chromatography (98:2:0.1 CH_2Cl_2–MeOH–NH_4OH): 25 mg, 5% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.83 (m, 4H), 2.05 (m, 2H), 2.21 (s, 6H), 2.42 (m, 2H), 3.21 (m, 4H), 3.57 (t, 1H) 4.21 (s, 2H), 6.93 (d, 1H, J=8.4 Hz), 7.22 (d, 1H, J=8.4 Hz), 7.30 (s, 1H), 9.0 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.8, 28.2, 43.8, 45.1, 48.0, 55.4, 55.8, 109.6, 122.9, 126.5, 130.0, 130.3, 142.2, 180.1. The oxalate precipitated on treating a solution of the base in 1:1 EtOH–Et_2O with oxalic acid in 1:1 EtOH–Et_2O; mp decomposed above 125°C. Anal. calcd for $C_{17}H_{25}N_3O_3S{\cdot}C_2H_2O_4$: C, 51.70; H, 6.10; N, 9.52. Found: C, 51.67; H, 6.33; N, 9.79.

1.1.8. 6-(1-Pyrrolidinylsulfonylmethyl)-1,2,3,4-tetrahydro-β-carboline (11a). A solution of tryptamine **8** (3.1 g, 10 mmol) and $CH_2(OMe)_2$ (3.5 mL, 40 mmol) in AcOH (amount sufficient to dissolve) was stirred at 100°C for 96 h. The mixture was basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×70 mL). The organic extracts were dried, filtered, and concentrated to give β-carboline **11a** as a yellow oil (2.30 g, 72%). The oxalate precipitated on treating a solution of the base in EtOH with oxalic acid in EtOH; mp 250–252°C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 1.74 (m, 4H), 2.91 (m, 2H), 3.08 (m, 4H), 3.42 (m, 2H), 4.34 (s, 2H), 4.44 (s, 2H), 7.13 (d, 1H, J=8.5 Hz), 7.35 (d, 1H, J=8.5 Hz), 7.48 (s, 1H), 11.23 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.4, 25.6, 39.9, 41.6, 47.8, 54.2, 105.7, 111.3, 120.3, 120.5, 124.7, 126.1, 127.9, 135.9, 164.8. Anal. calcd for $C_{16}H_{21}N_3O_2S{\cdot}C_2H_2O_4{\cdot}1/2H_2O$: C, 51.55; H, 5.73; N, 10.03. Found: C, 51.16; H, 5.57; N, 9.80.

1.1.9. 2-Methyl-6-(1-pyrrolidinylsulfonylmethyl)-1,2,3,4-tetrahydro-β-carboline (11b). A solution of tryptamine **8** (4 g, 13 mmol) in 35% HCHO (5 mL) and AcOH (18 mL) was refluxed for 6 h. After cooling to rt, saturated aqueous Na_2CO_3 was added, and the mixture was extracted with 95:5 CH_2Cl_2–MeOH. The residue was dissolved in THF (20 mL) and saturated aqueous Na_2CO_3 (20 mL). After stirring at rt overnight, the mixture was extracted with CH_2Cl_2 (2×30 mL). The organic extracts were washed with H_2O (2×20 mL), dried, filtered, and concentrated to give β-carboline **11b** as a yellow oil (3.60 g, 87%). The oxalate precipitated on treating a solution of the base in EtOH with oxalic acid in EtOH; mp decomposed above 145°C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 1.75 (m, 4H), 2.88 (s, 3H), 2.93 (m, 2H), 3.09 (m, 4H), 3.42 (m, 2H), 4.31 (s, 2H), 4.44 (s, 2H), 7.15 (d, 1H, J=8.5 Hz), 7.34 (d, 1H, J=8.5 Hz), 7.48 (s, 1H), 11.15 (s, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 18.4, 25.2, 42.2, 47.6, 50.1, 51.3, 54.6, 105.0, 111.1, 120.1, 120.2, 124.2, 125.9, 128.1, 136.1, 164.1.

1.1.10. [3-Iodo-4-(trifluoroacetamido)phenyl]methanesulfonamide (15). Bis(pyridine)iodonium(I) tetrafluoroborate[19] (2.37 g, 6.4 mmol) was added at rt to a suspension of aniline **14**[18] (1.19 g, 6.4 mmol) in CH_2Cl_2 (15 mL). After stirring at rt for 2 h, the mixture was filtered, and the filtrate was concentrated to dryness. TFAA (0.9 mL, 6.8 mmol) was added under Ar to a solution of the resulting crude *o*-iodoaniline in anhydrous THF (40 mL). The mixture was stirred at rt for 4 h, and then concentrated approximately to 2 mL. A 1:1 mixture of Et_2O–hexane was added, and the precipitated crude product was collected by filtration (2.04 g, 78%); white solid, mp 126–128°C. ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ 4.32 (s, 2H), 7.02 (s, 2H), 7.38 (d, 1H, J= 8.2 Hz), 7.46 (d, 1H, J=8.2 Hz), 7.95 (s, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 58.9, 98.3, 116.5 (q, J=296 Hz), 128.4, 131.8, 132.8, 136.9, 141.3, 155.8 (q, J=36 Hz). Anal. calcd for $C_9H_8F_3IN_2O_3S$: C, 26.49; H, 1.97; N, 6.86. Found: C, 26.61; H, 1.93; N, 6.76.

1.1.11. [3-Bromo-4-(trifluoroacetamido)phenyl]-*N*-*tert*-butyl-methanesulfonamide (16). A solution of Br_2 (0.15 mL, 2.2 mmol) in MeOH (3 mL) was added dropwise to an ice-cooled suspension of aniline **14**[18] (0.48 g, 2 mmol) in MeOH (5 mL). The mixture was stirred at rt for 1 h, and then Na_2CO_3 (0.5 g) was added. Solvent was evaporated, and the resulting residue was digested with CH_2Cl_2. The organic extracts were dried, filtered, and evaporated. Flash chromatography (9:1 CH_2Cl_2–Et_2O) gave pure *o*-bromoaniline (0.27 g, 43%). ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ 1.23 (s, 9H), 4.07 (s, 2H), 6.73 (br s, 1H), 6.78 (d, 1H, J= 8.8 Hz), 7.04 (d, 1H, J=8.8 Hz), 7.34 (s, 1H). TFAA (0.94 μL, 0.67 mmol) was added under Ar to a solution of the above bromoaniline (0.2 g, 0.62 mmol) in anhydrous THF (4 mL), and the mixture was stirred at rt for 2 h. Solid Na_2CO_3 (60 mg) was added, and the mixture was concentrated to dryness. The resulting residue was digested with EtOAc, and the organic extracts were dried, filtered and concentrated. Flash chromatography (CH_2Cl_2) gave pure **16** (0.2 g, 77%); white solid, mp 118–120°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 9H), 4.15 (br s, 1H), 4.21 (s, 2H), 7.42 (d, 1H, J=8.2 Hz), 7.68 (s, 1H), 8.36 (d, 1H, J=8.2 Hz), 8.55 (br s, 1H).

1.1.12. {4-[*N*-(3-Methoxycarbonyl-2-propenyl)trifluoroacetamido]-3-iodophenyl}methanesulfonamide (17). A

solution of 1.5N LDA in cyclohexane (0.16 mL, 0.24 mmol) and methyl 4-bromocrotonate (0.03 mL, 0.29 mmol) were added successively at −78°C under N_2 to a solution of trifluoroacetanilide **15** (90 mg, 0.22 mmol) in anhydrous THF (5 mL), and the resulting solution was allowed to rise to rt. After being stirred at reflux for 20 h, the mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. Concentration of the dried extracts gave a residue, which was chromatographed (99:1 CH_2Cl_2–MeOH) to give **17** (17 mg, 15%) as an orange oil. ^1H NMR (200 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.77 (m, 1H), 4.31 (s, 2H), 4.95 (br s, 2H), 5.02 (ddd, 1H, *J*=15.8, 5.6, 1.8 Hz), 5.92 (dt, 1H, *J*=15.8, 1.4 Hz), 6.85 (m, 1H), 7.25 (d, 1H, *J*=8.2 Hz), 7.47 (d, 1H, *J*=8.2 Hz), 8.03 (s, 1H).

1.1.13. {3-Bromo-4-[*N*-(3-methoxycarbonyl-2-propenyl)-trifluoroacetamido]phenyl}-*N*-*tert*-butyl-methanesulfonamide (18). Operating as above, from methyl 4-bromocrotonate (2 mL, 16.8 mmol) and trifluoroacetanilide **16** (5 g, 12 mmol) was obtained **18** (3.9 g, 63%) as orange oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 9H), 3.74 (s, 3H), 3.85 (dd, 1H, *J*=15.8, 7.6 Hz), 4.25 (s, 2H), 5.01 (ddd, 1H, *J*=15.8, 5.6, 1.8 Hz), 5.92 (dt, 1H, *J*=15.8, 1.4 Hz), 6.88 (m, 1H), 7.25 (d, 1H, *J*=8.2 Hz), 7.41 (d, 1H, *J*=8.2 Hz), 7.78 (s, 1H).

1.1.14. Methyl 5-(sulfamoylmethyl)-3-indoleacetate (19). Bu_4NBr (16 mg, 0.05 mmol), freshly distilled Et_3N (0.02 mL, 0.125 mmol), and $Pd(OAc)_2$ (2 mg) were added under Ar to a solution of **17** (24 mg, 0.05 mmol) in anhydrous DMF (0.5 mL). After stirring at 80°C for 3 h, EtOAc (5 mL) was added, and the mixture was successively washed with brine (5×5 mL) and 1N aqueous HCl (2×5 mL). Evaporation of the dried organic extracts gave a residue, which was chromatographed (95:5 CH_2Cl_2–MeOH) to give indole **19** (14 mg, 60%) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.79 (s, 2H), 4.42 (s, 2H), 7.20 (s, 1H), 7.23 (d, 1H, *J*=8.4 Hz), 7.38 (d, 1H, *J*=8.4 Hz), 7.62 (s, 1H), 8.8 (br s, 1H).

1.1.15. Methyl 5-(*tert*-butylsulfamoylmethyl)-3-indoleacetate (20). Operating as above, from Bu_4NBr (2.4 g, 7.5 mmol), $Pd(OAc)_2$ (35 mg), Et_3N (2.6 mL, 18.75 mmol), and **18** (3.9 g, 7.5 mmol) was obtained indole **20** (1.45 g, 57%) as a white solid. mp 94–96°C. ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 9H), 3.71 (s, 3H), 3.79 (s, 2H), 3.87 (br s, 1H), 4.36 (s, 2H), 7.20 (s, 1H), 7.24 (d, 1H, *J*=8.4 Hz), 7.35 (d, 1H, *J*=8.4 Hz), 7.63 (s, 1H), 8.2 (br s, 1H). Anal. calcd for $C_{16}H_{22}N_2O_4S{\cdot}1/4\ H_2O$: C, 56.03; H, 6.56; N, 8.16. Found: C, 56.01; H, 6.54; N, 7.84.

1.1.16. 5-(*tert*-Butylsulfamoylmethyl)-*N*,*N*-dimethyl-3-indoleacetamide (21). A solution of ester **20** (1.45 g, 4.3 mmol) in a 1:1 mixture of 2N aqueous KOH–MeOH (60 mL) was stirred at rt for 1 h. The MeOH was evaporated, and the mixture was acidified with 1N aqueous HCl and extracted with EtOAc (3×30 mL). The organic extracts were dried, filtered, and concentrated to give the corresponding 3-indoleacetic acid (1.35 g, 97%) as a yellow solid; 190–192°C. ^1H NMR (200 MHz, CD_3OD) δ 1.41 (s, 9H), 3.84 (s, 2H), 4.45 (s, 2H), 7.26 (d, 1H, *J*=8.4 Hz), 7.29 (s, 1H), 7.44 (d, 1H, *J*=8.4 Hz), 7.69 (s, 1H). PCl_5 (0.7 g, 3.3 mmol) was added to an ice-cooled suspension of the above acid (1 g, 3.1 mmol) in CH_2Cl_2 (20 mL) and DMF (2 mL). After stirring at 0°C for 3 h, a suspension of $Me_2NH{\cdot}HCl$ (0.5 g, 6.2 mmol) and Et_3N (1.7 mL, 12.4 mmol) in CH_2Cl_2 (10 mL) was added, and the resulting mixture was stirred at rt for 4 h. The mixture was successively washed with 1N aqueous HCl (3×20 mL), 2N aqueous Na_2CO_3 (3×20 mL), and H_2O (7×20 mL). The organic extracts were dried, filtered, and concentrated to give amide **21** (0.65 g, 60%) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.98 (s, 3H), 3.06 (s, 3H), 3.80 (s, 2H), 4.33 (s, 2H), 7.10 (s, 1H), 7.21 (d, 1H, *J*=8.4 Hz), 7.31 (d, 1H, *J*=8.4 Hz), 7.62 (s, 1H), 8.42 (br s, 1H).

1.1.17. *N*-*tert*-Butyl-{3-[2-(dimethylamino)ethyl]-5-indolyl}methanesulfonamide (22). Operating as in the above preparation of alcohol **3**, from amide **21** (0.66 g; 1.8 mmol) was obtained crude tryptamine **22**. Flash chromatography (9:1 CH_2Cl_2–MeOH) afforded pure **22** as a white foam (0.2 g, 33%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.35 (s, 6H), 2.64 (t, 2H, *J*=9.2 Hz), 2.93 (t, 2H, *J*=9.2 Hz), 4.36 (s, 2H), 7.05 (s, 1H), 7.23 (d, 1H, *J*=8.4 Hz), 7.34 (d, 1H, *J*=8.4 Hz), 7.61 (s, 1H), 8.10 (br s, 1H).

1.1.18. 1-{[3-Bromo-4-(trifluoroacetamido)phenyl]methylsulfonyl}pyrrolidine (23a). A solution of Br_2 (2.3 mL, 45.8 mmol) in MeOH (30 mL) was added dropwise (40 min) to a suspension of aniline **6**[18] (10 g, 41.6 mmol) in MeOH (100 mL). The mixture was stirred at rt for 1 h, and then concentrated to dryness. The residue triturated with CH_2Cl_2 to give a white solid (12.7 g) as a 1:1:2 mixture of starting material, dibromoaniline, and *o*-bromoaniline. TFAA (5.8 mL, 41.2 mmol) was added under Ar to a suspension of the above mixture in anhydrous THF (275 mL). The mixture was stirred at rt for 0.5 h and then concentrated to dryness. The resulting residue was triturated with 1:1 hexane–Et_2O (200 mL) to give a white solid. Flash chromatography (97:3 CH_2Cl_2–hexane) afforded pure **23a** (4.5 g, 26%); mp 175–177°C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.88 (m, 4H), 3.23 (m, 4H), 4.19 (s, 2H), 7.42 (d, 1H, *J*=8.2 Hz), 7.70 (s, 1H), 8.32 (d, 1H, *J*=8.2 Hz), 8.52 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 48.2, 54.8, 114.0, 115.9 (q, *J*=290 Hz), 121.7, 128.7, 130.9, 133.3, 134.4, 155.1 (q, *J*=35 Hz). Anal. calcd for $C_{13}H_{14}BrF_3N_2O_3S{\cdot}1H_2O$: C, 36.06; H, 3.72; N, 6.46. Found: C, 36.03; H, 3.33; N, 6.24.

1.1.19. 1-{[3-Iodo-4-(trifluoroacetamido)phenyl]methylsulfonyl}pyrrolidine (23b). Bis(pyridine)iodonium(I) tetrafluoroborate[19] (4.6 g, 12.36 mmol) was added at rt to a solution of aniline **6**[18] (2.9 g, 12.1 mmol) in CH_2Cl_2 (30 mL). After stirring at rt for 5 h, the mixture was washed with H_2O (30 mL) and 0.1N aqueous $Na_2S_2O_3$ (2×30 mL). The organic extract was dried, filtered, and concentrated to give the corresponding *o*-iodoanaline. TFAA (1.8 mL, 12.84 mmol) was added under Ar to a solution of this iodoaniline (4.1 g) in anhydrous THF (85 mL). The mixture was stirred at rt for 1 h and then concentrated to dryness. The resulting residue was redissolved in CH_2Cl_2 and successively washed with 1N aqueous HCl and saturated aqueous Na_2CO_3. The organic phase was dried, filtered, and concentrated to give **23b** (4.6 g, 81%) as a white solid; mp 149–151°C. ^1H NMR (200 MHz, $CDCl_3$) δ 1.88 (m, 4H), 3.23

(m, 4H), 4.17 (s, 2H), 7.45 (d, 1H, *J*=8.2 Hz), 7.92 (s, 1H), 8.25 (d, 1H, *J*=8.2 Hz), 8.35 (br s, 1H).

1.1.20. 1-{[3-Bromo-4-[*N*-(3-methoxycarbonyl-2-propenyl)trifluoroacetamido]phenyl]methylsulfonyl}pyrrolidine (24a). Operating as in the above preparation of **17**, from **23a** (1 g, 2.4 mmol) and methyl 4-bromocrotonate (0.4 mL, 3.36 mmol) was obtained **24a** (0.9 g, 73%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.86 (m, 4H), 3.19 (m, 4H), 3.74 (s, 3H), 3.85 (dd, 1H, *J*=15.8, 7.6 Hz), 4.23 (s, 2H), 5.01 (ddd, 1H, *J*=15.8, 5.6, 1.8 Hz), 5.90 (dt, 1H, *J*=15.8, 1.4 Hz), 6.88 (dq, 1H, *J*=15.7, 7.5, 5.6 Hz), 7.25 (d, 1H, *J*=8.2 Hz), 7.45 (d, 1H, *J*=8.2 Hz), 7.78 (s, 1H).

1.1.21. 1-{[4-[*N*-(3-methoxycarbonyl-2-propenyl)trifluoroacetamido]-3-iodophenyl]methylsulfonyl}pyrrolidine (24b). Operating as in the above preparation of **17**, from **23b** (4.5 g, 9.7 mmol) and methyl 4-bromocrotonate (1.6 mL, 13.5 mmol) was obtained **24b** (2.8 g, 52%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.86 (m, 4H), 3.19 (m, 4H), 3.74 (s, 3H), 3.75 (m, 1H), 4.21 (s, 2H), 5.02 (ddd, 1H, *J*=15.8, 5.6, 1.8 Hz), 5.91 (dt, 1H, *J*=15.8, 1.4 Hz), 6.88 (dq, 1H, *J*=15.8, 7.5, 5.6 Hz), 7.24 (d, 1H, *J*=8.2 Hz), 7.45 (d, 1H, *J*=8.2 Hz), 8.0 (s, 1H).

1.1.22. 1-{[4-(*N*-2-Butenyltrifluoroacetamido)-3-iodophenyl]methylsulfonyl}pyrrolidine (25). Operating as in the above preparation of **17**, from **23b** (1.34 g, 2.9 mmol) and crotyl bromide (0.69 g, 4.3 mmol) was obtained **25** (0.74 g, 49%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.0 (d, 3H, *J*=6.6 Hz), 1.85 (m, 4H), 3.17 (m, 4H), 3.57 (dd, 1H, *J*=15.7, 7.5 Hz), 4.22 (s, 2H), 4.85 (dd, 1H, *J*=15.7, 5.6 Hz), 5.5 (m, 1H), 7.17 (d, 1H, *J*=8.2 Hz), 7.45 (d, 1H, *J*=8.2 Hz), 7.98 (s, 1H).

1.1.23. Methyl 5-(1-pyrrolidinylsulfonylmethyl)-3-indoleacetate (26). Operating as in the above preparation of **19**, from **24a** (0.15 g, 0.29 mmol) was obtained indole **26** (51 mg, 52%) as a yellow oil. From **24b** the yield arose to 57%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (m, 4H), 3.14 (m, 4H), 3.70 (s, 3H), 3.76 (s, 2H), 4.37 (s, 2H), 7.16 (s, 1H), 7.21 (d, 1H, *J*=8.4 Hz), 7.31 (d, 1H, *J*=8.4 Hz), 7.59 (s, 1H), 8.35 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 31.0, 48.1, 51.9, 56.7, 108.4, 111.5, 120.3, 121.2, 124.0, 124.6, 127.3, 136.0, 172.3.

1.1.24. 3-Ethyl-5-(1-pyrrolidinylsulfonylmethyl)indole (27). Operating as in the above preparation of **19**, from **25** (0.74 g, 1.4 mmol) was obtained the indole **27** (0.24 g, 57%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J*=7.2 Hz), 1.76 (m, 4H), 2.75 (q, 2H, *J*=7.2 Hz), 3.14 (m, 4H), 4.38 (s, 2H), 6.98 (s, 1H), 7.21 (d, 1H, *J*=8.4 Hz), 7.30 (d, 1H, *J*=8.4 Hz), 7.59 (s, 1H), 8.30 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 18.2, 25.8, 48.1, 56.7, 111.3, 118.5, 119.4, 121.1, 121.5, 124.1, 127.8, 136.6.

1.1.25. 5-(1-Pyrrolidinylsulfonylmethyl)-3-indoleacetic acid (28). A suspension of ester **26** (0.63 g, 1.87 mmol) in a 1:1 mixture of 2N aqueous KOH–MeOH (20 mL) was stirred at rt for 1 h. The mixture was filtered, MeOH was evaporated, and the aqueous residue was acidified with 1N aqueous HCl and extracted with EtOAc (3×15 mL). The organic extracts were dried, filtered, and concentrated to give indoleacetic acid **28** (0.51 g, 83%) as an orange solid. An analytical sample was obtained by flash chromatography (99:1 CH_2Cl_2–MeOH); mp 95–97°C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 1.74 (m, 4H), 3.09 (m, 4H), 3.63 (s, 2H), 4.44 (s, 2H), 7.13 (d, 1H, *J*=8.5 Hz), 7.26 (s, 1H), 7.33 (d, 1H, *J*=8.5 Hz), 7.52 (s, 1H), 10.99 (s, 1H), 12.18 (br s, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 25.5, 31.1, 47.8, 54.4, 107.9, 111.4, 119.8, 121.2, 124.2, 124.9, 127.3, 135.9, 173.2. Anal. calcd for $C_{15}H_{18}N_2O_4S\cdot H_2O$: C, 52.98; H, 5.92; N, 8.24. Found: C, 52.95; H, 5.90; N, 8.16.

1.1.26. 5-(1-Pyrrolidinylsulfonylmethyl)-3-indolemethanol (29). $LiBH_4$ (8 mg, 0.37 mmol) was added under N_2 to a solution of ester **26** (0.22 g, 0.65 mmol) in anhydrous THF (3 mL) and toluene (0.5 mL). After being stirred at 100°C for 2 h, the mixture was poured into saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2×10 mL). Concentration of the dried extracts gave a residue, which was chromatographed (99:1 CH_2Cl_2–MeOH). Crystallization from 8:2 H_2O–MeOH gave alcohol **29** (0.14 g, 71%) as a white solid; mp 103–105°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 1H), 1.79 (m, 4H), 3.02 (t, 2H, *J*=7.2 Hz), 3.17 (m, 4H), 3.88 (m, 2H), 4.36 (s, 2H), 7.08 (s, 1H), 7.21 (d, 1H, *J*=8.5 Hz), 7.32 (d, 1H, *J*=8.5 Hz), 7.60 (s, 1H), 8.37 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 28.8, 48.3, 56.7, 62.8, 111.7, 112.5, 120.1, 121.3, 123.6, 124.7, 127.8, 136.5. Anal. calcd for $C_{15}H_{20}N_2O_3S\cdot H_2O$: C, 55.26; H, 6.80; N, 8.59. Found: C, 55.20; H, 6.74; N, 8.56.

Acknowledgements

This work was supported by the CICYT (Spain)-European Comission (project 2FD97-1086). Thanks are also due to the Comissionat per Universitats i Recerca (Generalitat de Catalunya) for Grant 1999SGR-00079.

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