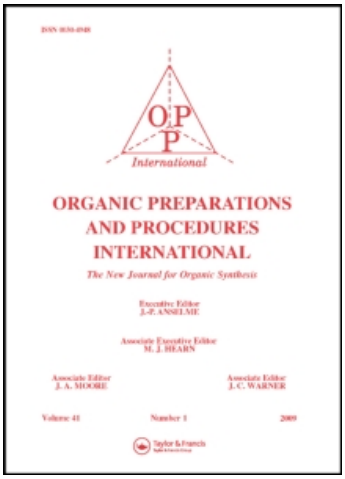

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SYNTHESIS AND CHARACTERIZATION OF NEW 2-SUBSTITUTED ISOINDOLINE DERIVATIVES OF α-AMINO ACIDS

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SYNTHESIS AND CHARACTERIZATION OF NEW 2-SUBSTITUTED ISOINDOLINE DERIVATIVES OF α-AMINO ACIDS

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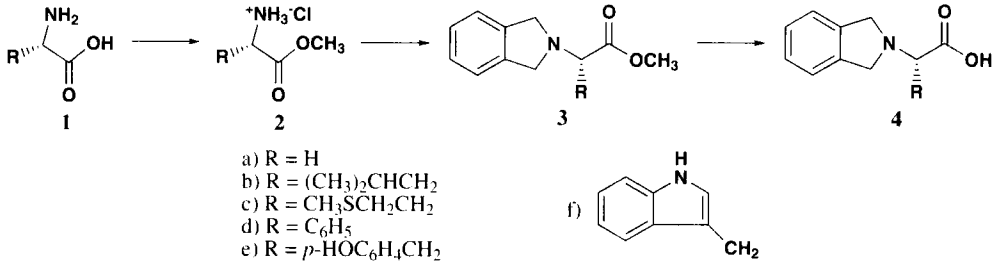
Some isoindolines are important intermediates for the syntheses of novel multidrug resistance reversal agents;[1] they have also shown antiinflammatory[2-4] and diuretic activity.[5,6] They have been used for treating coronary vessel diseases[7,8] and evaluated as alpha-adrenergic and adrenergic neuron blocking agents.[9] 2-Substituted isoindolines have been prepared by a) alkylation of isoindoline,[3,4,7] b) alkylation and reduction of phthalimides[7,8,10] and c) cyclocondensation of α,α'-dibromo-*o*-xylene with primary amines.[1,2,7,11,12] To our knowledge, there are no reports concerning the synthesis of 2-substituted isoindoline derivatives of α-amino acids, which could have important biological properties and be used as ligands to obtain organometallic compounds with antitumor properties.[13] Our current interest in 2-substituted isoindoline **4** derivatives of α-aminoacids prompted us to develop an easy methodology to obtain them from α-amino acid methyl ester hydrochlorides **2** and α,α'-dibromo-*o*-xylene. This paper describes the synthesis and characterization by spectroscopic methods of six new 2-substituted isoindolines **4a-f**. The structure of compound **4b** was further established by a single-crystal X-ray diffraction study.



The known α-aminoacid methyl ester hydrochlorides **2a-f** were prepared by the reaction of α-amino acids **1a-f** with thionyl chloride and methanol and were characterized by ^{1}H NMR spectra. Cyclocondensation of α,α'-dibromo-*o*-xylene with compounds **2a-f** in the presence of potassium bicarbonate under reflux in acetonitrile, gave **3a-f** whichwere used without purification in the final step of the synthesis. The ^{1}H NMR spectra of compounds **3a-f** exhibit the single signal expected for the protons of the OCH_3 group and an AB system for the ring methylene protons (CH_2N), except for compound **3a**, which exhibits a single signal. Compounds **3a-f** were saponified and acidified to obtain the corresponding 2-substituted isoindoline **4a-f** as white solids and the overall yields were between 72% and 85%. Table 1 shows the ^{1}H NMR spectra data for compounds **4a-f**.

Their spectra exhibit an AB system for the ring methylene protons (CH_2N), except for compound **4a**, which displays a single signal. Table 2 shows the ^{13}C NMR spectra for compounds **4a-f**. Since the signals of C_7 and C_8 for **4c**, C_8 and C_9 for **4d** and C_{12} and C_{14} for **4f** have similar chemical shifts, unambiguous identification was established using HETCOR spectra. Thus for compound **4c**, the signal of C_7 correlates with the coupling pattern system at δ 1.87-2.00 and that of C_8 correlates with the triplet at δ 2.56, while for compound **4d** the signal of C_8 correlates with the doublet at δ 7.50 and that of C_9 correlates with the multiplet at δ 7.33-7.42. Moreover, for compound **4f** the signal of C_{12} correlates with the triplet at δ 6.99 and that of C_{14} correlates with the doublet at δ 7.59. The IR spectra of all compounds show the ν_{as} and ν_s -CO_2 bands in the range between 1626-1636 and 1388-1398 cm^{-1}, respectively. The 70 eV EI mass spectra of compounds **4a-f** exhibit the molecular ion with low relative abundace, except for **4c**,. The fragment ions of m/z = 132, m/z = 188, m/z = 118, m/z = 208, m/z = 176 and m/z = 130 correspond to the base peak for compound **4a-f**, respectively.

X-ray single-crystal diffraction study of compound **4b** allowed establishment of its structure (Fig. 1). The molecule is a zwitterion and the crystal structure shows the following intermolecular contacts: $C{=}O_2....H_{1n}$ 1.698, $C{=}O_1....H_{2a}$ 2.345, $C{=}O_2....H4$ 2.495 and $C{=}O_1....H_{9a}$ 2.585 Å, which are significantly shorter than the sum of the van der Waals radii of oxygen-hydrogen (2.70 Å).[14] In addition the following intramolecular contacts were observed: $N_1....H_{1a}$ 2.049, $N_1....H_{1b}$ 2.048, $N_1...H_{2a}$ 2.055, $N_1....H_{2a}$ 2.074, $N_1....H_{11a}$ 2.666, $N_1....H_{11b}$ 2.543 and $O_2....H_{9a}$ 2.409 Å (sum of the van der Waals radii of nitrogen-hydrogen is 2.75 Å).[14] In general, all bond distances are within the values expected and selected values are: C_{10}-O_2 1.260 (4), C_{10}-O_1 1.229 (5), C_9-N_1 1.494 (4), C_1-N_1 1.499 (4), C_2-N_1 1.517 (4) and N_1-H_{11} 1.013. The 0.031 Å difference between the bond distances for C_{10}-O_2 and C_{10}-O_1 can be due to hydrogen bonding between O_2 and H_{1n}. The conformation of the five-membered ring is not planar, as indicated by the torsion angles: C(8)-C(1)-N(1)-C(2) -14.28°, N(1)-C(1)-C(8)-C(3) 10.47°, C(2)-C(3)-C(8)-C(1) -2.45°, N(1)-C(2)-C(3)-C(8) -6.52° and C(3)-C(2)-N(1)-C(1) 12.87°. In the region of C_1, N_1 and C_2 the difference of the torsion angles are -24.75°, 27.15° and -19.39°, respectively. Inspection of the sequence of the signs and the positive value in the region of nitrogen atom indicate that N_1 is out of the plane and pointing upward,[15] indicating that the ring of the isoindoline has an envelope conformation.

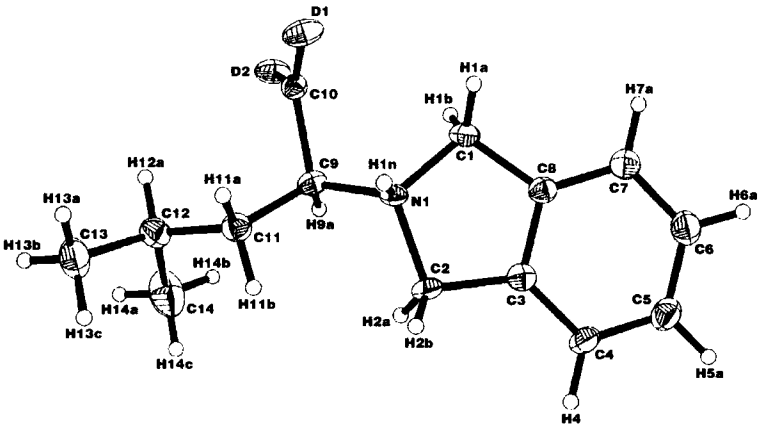


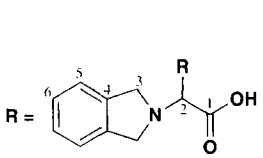
Fig. 1 ORTEP Drawing of Compound **4b**

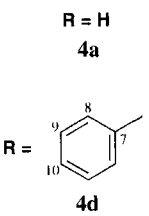
TABLE 1. Yields and ^{1}H NMR Data of Compounds **4**

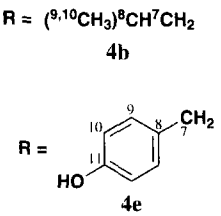
Cmpd	Yield[a] (%)	^{1}H NMR Data[b] CH_2N	CHR	R group	Harom.
4a[c]	80	4.55 (s)	3.80 (s)	4.55 (s)	7.29 (m)
4b[d]	79	4.69 (J_{AB} = 14.1) 4.75 (J_{AB} = 14.1)	4.42 (dd, J = 7.5, J = 3.5)	0.96 (dd, J = 6.4, J = 6.4) 1.80-1.94 (m)	7.37 (m)
4c	80	4.12 (J_{AB}= 13.6) 4.17 (J_{AB} = 13.6)	3.62 (t, J = 7.4)	1.87-2.00 (m) 2.06 (s), 2.56 (t, J = 7.3)	7.22(m)
4d	84	3.87 (J_{AB} = 12.1) 4.05 (J_{AB} = 12.1)	4.46 (s)	7.33-7.42 (m) 7.50 (d, J = 7.3)	7.14-7.24 (m)
4e[c]	82	4.69 (J_{AB} = 14.1) 4.75 (J_{AB} = 14.1)	4.59 (dd, J = 9.6, J = 4.2)	3.13 (dd, J = 13.8, J = 9.6), 3.40 (dd, J = 13.8, J = 4.2) 6.75 (d, J = 8.4) 7.10 (d, J = 8.4)	7.34-7.40 (m)
4f	76	4.15 (J_{AB}= 12.1) 4.23 (J_{AB} = 12.1)	3.81 (t, J = 7.0)	3.14 (dd, J = 13.8, J = 7.0), 3.23 (dd, J = 14.3, J = 7.0) 6.99 (t, J = 7.5) 7.07 (t, J = 7.5) 7.23 (s) 7.35 (d, J = 7.8) 7.59 (d, J = 7.4)	7.18-7-28 (m)

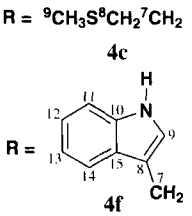
a) Overall yields from cmpd **4**. b) In DMSO-d_6. c) In DMSO-d_6/D_2O. d) Characterized as hydrochloride.

Table 2 ^{13}C NMR Data of Compounds **4**









Cmpd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}
4a[a]	170.55	58.77	60.40	134.83	124.37	130.40				
4b[b]	169.81	63.65	56.83	134.05	122.66	128.32	24.72	37.41	23.23[c]	21.19[c]
4c	173.52	61.86	54.61	139.20	122.34	126.68	30.07	30.14	14.71	
4d	171.54	71.74	56.71	138.60	122.32	126.86	137.35	128.53	128.39	128.16
4e[a,d]	169.24	66.89	57.21	133.99	122.73	128.44	33.92	124.60	130.36	115.43
4f[e]	173.42	64.89	54.87	139.25	122.32	126.67	26.45	110.47	123.40	127.30

In DMSO-d_6. a) In DMSO-d_6/D_2O. b) Compound characterized as hydrochloride. c) Assignments can be interchanged. d) δ: C_{11} 156.73. e) δ: C_{11} 111.44, C_{12} 118.19, C_{13} 120.88, C_{14} 118.32, C_{15} 136.12.

EXPERIMENTAL SECTION

NMR espectra were recorded on Jeol GLX-270, JEOL Eclipse-400 and Bruker Avance 300-DPX spectrometers. All ^1H and ^{13}C resonances are reported relative to TMS; $CDCl_3$ and DMSO-d_6 being used as solvents. Mass spectra were obtained with a Hewlett-Packard 5994-A instrument, and infrared spectra were recorded as KBr pellets on a Perkin-Elmer 16F PC FT-IR spectrometer. Melting points were taken in open capillary tubes on a Gallenkamp MFB-595 apparatus and are uncorrected. The single-crystal X-ray study was performed on a Enraf Nonius CAD4 diffractometer. Reagents were purchased from Aldrich Chemical Co.

Compound **4b**, $C_{14}H_{19}NO_2$, crystallized in the P2(1)2(1)2(1) space group, orthorhombic, from water/methanol as a colorless rectangular prism with a = 5.675 (10), b = 9.601 (2), c = 22.627 (5) Å, V = 1232.8 (4) Å^3. Lattice constants were determined from least squares refinement on diffractometer angles for 25 automatically centered reflections; ρ 1.262 Mg/m^{-3} Z = 4, μ = 0.084 mm^{-1}, F(000) = 508. Data collection monitoring of check reflectons showed no signs of deacay. A total of 1301 reflections was measured $4.60 \leq 2\theta \leq 50.10°$, 1301 were independent and of these 857 were considered observed $Fo > 4\sigma(Fo)$. Absorption correction was not necessary. Solution and refinement: direct method, all non-hydrogen atoms refined anisotropically, all hydrogen were located by difference Fourier maps and refined with an overall isotropic thermal parameters, R = 0.0441, Rw = 0.1213, $w = 1/\sigma^2$, GOOF = 0.943 parameters to data ratio 1: 8.4, largest residual electron density peack/hole in the final diffrence map: 0.207/-0.189e/Å^3. Atomic scattering factors were taken from the International Tables for X-ray

Crystallography.[16] The data reduction was performed by JANA 98.[17] All calculations were carried out on a VAX 4000 computer using the SHELX 93 (Shedrick G. M.) program package.[18]

The procedure outlined below is general for the preparation of α-amino acid methyl ester hydrochlorides **2a-2f**.

Synthesis of Glycine Methyl Ester Hydrochloride (2a). General Procedure.- To a suspension of 1.00 g (13.3 mmol) of glycine **1a** in 100 mL of methanol was added at room temperature 0.97 mL (13.3 mmol) of thionyl chloride. The mixture was refluxed and stirred during 8 h. After being cooled to room temperature the solvent was evaporated under vacuum. The residue was washed three times with methylene chloride to yield 1.62 g (97%) of compound **2a** as a white solid, mp 173-175° (dec), *lit.*[19] mp 175° (dec). ^{1}H NMR (DMSO-d_6): δ 8.67 (br, 3H), 3.74 (s, 2H), 3.70 (s, 3H).

Synthesis of L-Leucine Methyl Ester Hydrochloride (2b).- The reaction of 1.00 g (7.63 mmol) of L-leucine **1b** with 0.56 mL (7.63 mmol) of thionyl chloride in 100 mL of methanol gave 1.34 g (97%) of compound **2b** as a white solid, mp 148-150° (dec.), *lit.*[20] mp 148-150° (dec.). ^{1}H NMR (DMSO-d_6): δ 8.78 (br, 3H), 3.87 (s, 1H), 3.71 (s, 3H), 1.57-1.84 (m, 3H), 0.83 (d, 6H).

Synthesis of L-Methionine Methyl Ester Hydrochloride (2c).- The reaction of 1.00 g (6.71 mmol) of L-methionine **1c** with 0.50 mL (6.71 mmol) of thionyl chloride in 100 mL of methanol gave 1.26 g (95%) of compound **2c** as a white solid, mp 152-154° (dec.), *lit.*[21] mp 151-153° (dec.). ^{1}H NMR (DMSO-d_6): δ 8.82 (br, 3H), 4.05 (t, 1H), 3.72 (s, 3H), 2.50-2.68 (m, 2H), 2.06-2.11 (m, 2H), 2.03 (s, 3H).

Synthesis of (S)-(+)-2-Phenylglycine Methyl Ester Hydrochloride (2d).- The reaction of 1.00 g (6.62 mmol) of (S)-(+)-2-phenylglycine **1d** with 0.49 mL (6.62 mmol) of thionyl chloride in 100 mL of methanol gave 1.28 g (97%) of compound **2d** as a white solid, mp 200-202° (dec.), *lit.*[22] mp 200° (dec.). ^{1}H NMR (DMSO-d_6): δ 9.35 (br, 3H), 7.53-7.60 (m, 2H), 7.40-7.47 (m, 3H), 5.23 (s, 1H), 3.70 (s, 3H).

Synthesis of L-Tyrosine Methyl Ester Hydrochloride (2e).- The reaction of 1.00 g (5.53 mmol) of L-tyrosine **1e** with 0.41 mL (5.53 mmol) of thionyl chloride in 100 mL of methanol gave 1.24 g (97%) of compound **2e** as a white solid, mp 189-191° (dec.), *lit.*[23] mp 192° (dec.). ^{1}H NMR (DMSO-d_6): δ 8.71 (br, 3H), 6.86 (d, 1H), 6.83 (d, 1H), 4.11 (br, 1H), 3.64 (s, 3H), 2.94-3.13 (m, 2H).

Synthesis of L-Tryptophan Methyl Ester Hydrochloride (2f).- The reaction of 1.00 g (4.91 mmol) of L-tryptophane **1f** with 0.36 mL (4.91 mmol) of thionyl chloride in 100 mL of methanol gave 1.22 g (98%) of compound **2f** as a white solid, mp 217-219° (dec.), *lit.*[24] mp 220° (dec.). ^{1}H NMR (DMSO-d_6): δ 11.24 (s, 1H), 8.77 (br, 3H), 7.53 (d, 1H), 7.40 (d, 1H), 7.28 (s, 1H), 7.09 (t, 1H), 7.00 (s, 1H), 4.20 (t, 1H), 3.62 (s, 3H), 3.28-3.44 (m, 2H).

The procedure outlined below is general for the preparation of methyl 2(substituted isoindoline)acetates **3a-3f**.

Synthesis of Methyl 2-(1,3-Dihydroisoindol-2-yl)acetate (3a). General Procedure.- To a solution of 0.50 g (1.90 mmol) of α,α'-dibromo-o-xylene in 60 mL of acetonitrile was added at room temperature 0.24 g (1.90 mmol) of compound **2a** and 0.47 g (4.75 mmol) of potassium bicarbonate. The

resulting suspension was refluxed and stirred during 6 hours. After being cooled to room temperature the suspension was filtered and the filtrate evaporated in vacuo to yield 0.34 g of compound **3a** as a yellow liquid. Its ^{1}H NMR spectrum showed a purity of 96% and was used without purification in the following step of the synthesis. ^{1}H NMR ($CDCl_3$): δ 4.08 (s, 4H), 3.72 (s, 3H), 3.59 (s, 2H). ^{13}C NMR ($CDCl_3$): δ170.92 (C_1), 139.39 (C_4), 126.46 (C_6), 121.93 (C_5), 58.44 (C_3), 55.65 (C_2), 51.39 (C_7).

Synthesis of (S)-Methyl 2-(1,3-Dihydroisoindol-2-yl)-4-methylpentanoate (3b).- The reaction of 0.50 g (1.90 mmol) of α,α'-dibromo-o-xylene with 0.35 g (1.90 mmol) of compound **2b** and 0.47 g (4.75 mmol) of potassium bicarbonate gave 0.45 g (96%) of compound **3b**. Its ^{1}H NMR spectrum showed a purity of 96% and it was used without purification in the following step of the synthesis. ^{1}H NMR ($CDCl_3$): δ 7.21 (s, 4H), 4.25 (d, 1H, J = 10.6), 4.11 (d, 1H, J = 10.6), 3.73 (s, 3H), 3.63 (t, 1H, J = 7.4), 1.80-1.94 (m, 2H), 1.69-1.80 (m, 1H), 1.01 (d, 3H), 0.99 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 173.70 (C_1), 139.33 (C_4), 126.50 (C_6), 122.19 (C_5), 62.16 (C_2), 54.97 (C_3), 51.11 (C_{11}), 39.90 (C_8), 24.65 (C_7), 22.41 and 22.27 ($C_{9,10}$ assignments can be interchanged).

Synthesis of (S)-Methyl 2-(1,3-Dihydroisoindol-2-yl)-4-ethylsulfanylpropanoate (3c).- The reaction of 0.50 g (1.90 mmol) of α,α'-dibromo-o-xylene with 0.38 g (1.90 mmol) of compound **2c** and 0.47 g (4.75 mmol) of potassium bicarbonate gave 0.48 g (95%) of compound **3c** as a viscous yellow liquid. Its ^{1}H NMR spectrum showed a purity of 96% and was used without purification in the following synthesis step. ^{1}H NMR ($CDCl_3$): δ 7.18 (s, 4H), 4.13 (d, 1H, J = 10.9), 4.09 (d, 1H, J = 10.9), 3.73 (dd, 1H, J = 8.0, J = 6.5), 3.64 (s, 3H), 2.62 (t, 2H, J = 7.3), 2.03-2.18 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.83 (C_1), 139.13 (C_4), 126.49 (C_6), 122.14 (C_5), 63.95 (C_2), 55.14 (C_3), 51.22 (C_{10}), 30.49 (C_8), 30.13 (C_7), 15.31 (C_9).

Synthesis of (S)-Methyl 2-(1,3-Dihydroisoindol-2-yl)-2-phenylacetate (3d).- The reaction of 0.50 g (1.90 mmol) of α,α'-dibromo-o-xylene with 0.38 g (1.90 mmol) of compound **2d** and 0.47 g (4.75 mmol) of potassium bicarbonate gave 0.49 g (96%) of compound **3d** as a light yellow liquid. Its ^{1}H NMR spectrum showed a purity of 96% and was used without purification in the following step of the synthesis . ^{1}H NMR ($CDCl_3$): δ 7.51-7.55 (m, 2H), 7.34-7.40 (m, 3H), 7.12-7.17 (m, 4H), 4.40 (s, 1H), 4.01 (d, 1H, J = 11.1), 3.89 (d, 1H, J = 11.1), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.88 (C_1), 139.23 (C_4), 136.86 (C_7), 128.68 (C_8), 128.51 (C_9), 128.45 (C_{10}), 126.72 (C_6), 122.24 (C_5), 72.60 (C_2), 57.29 (C_3), 52.12 (C_{11}).

Synthesis of (S)-Methyl 2-(1,3-Dihydroisoindol-2-yl)-3-(4-hydroxyphenyl)propanoate (3e).- The reaction of 0.50 g (1.90 mmol) of α,α'-dibromo-o-xylene with 0.44 g (1.90 mmol) of compound **2e** and 0.47 g (4.75 mmol) of potassium bicarbonate gave 0.54 g (96%) of compound **3e** as a light yellow solid. Its ^{1}H NMR spectrum showed a purity of 96% and was used without purification in the following step of the synthesis . ^{1}H NMR ($CDCl_3$): δ 7.19 (s, 4H), 7.01 (d, 2H, J = 8.4), 6.66 (d, 2H, J = 8.4), 4.23 (d, 1H, J = 11.2), 4.12 (d, 1H, J = 11.2), 3.73 (t, 1H, J = 7.2), 3.58 (s, 3H), 3.01-3.11 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.76 (C_1), 155.10 (C_{11}), 138.99 (C_4), 128.71 (C_8) 129.94 (C_9), 126.78 (C_6), 122.30 (C_5), 115.54 (C_{10}), 67.16 (C_2), 55.53 (C_3), 51.38 (C_{17}), 36.52 (C_7).

Synthesis of (S)-Methyl 2-(1,3-Dihydroisoindol-2-yl)-3-(1H-indol-3-yl)propanoate (3f).- The reac-

tion of 0.50 g (1.90 mmol) of α,α'-dibromo-o-xylene with 0.48 g (1.90 mmol) of compound **2f** and 0.47 g (4.75 mmol) of potassium bicarbonate gave 0.58 g (95%) of compound **3e** as a light yellow solid (≈96% pure by ^{1}H NMR). It was used without purification in the following step of the synthesis. ^{1}H NMR ($CDCl_3$): δ 8.75 (s, 1H), 7.71 (d, 1H, J= 7.3), 7.30 (s, 5H), 7.21-7.20 (br d, 3H), 6.92 (br, 1H), 4.32 (d, 1H, J = 11.4), 4.26 (d, 1H, J = 11.4), 3.97 (dd, 1H, J = 6.2, J = 8.6), 3.44 (dd, 1H, J = 14.5, J = 8.6), 3.35 (dd, 1H, J = 14.5, J= 6.2). ^{13}C NMR ($CDCl_3$): δ 172.91 (C_1), 139.00 (C_4), 135.90 (C_{15}), 127.06 (C_{10}), 126.63 (C_6), 122.74 (C_9), 122.17 (C_5), 121.45 (C_{13}) 118.86 (C_{14}), 118.10 (C_{12}), 111.16 (C_{11}), 110.55 (C_8), 66.08 (C_2), 55.50 (C_3), 51.66 (C_{16}), 26.83 (C_7).

The procedure outlined below is general for the preparation of 2-substituted isoindolines **4a-4f**.

Synthesis of 2-(1,3-Dihydroisoindol-2-yl)acetic Acid (4a). General Procedure.- To a stirred solution of compound **3a** (0.34 g, 1.78 mmol) in water/methanol (1:1) was added at room temperature a 2.2 M KOH solution (2.4 mL). The reaction mixture was refluxed for 3 h. After being cooled to room temperature the solution was acidified with a 2.5 M aqueous HCl solution (2.1 mL) and stirred for 10 min. until white precipitates were formed. The suspension was filtered and the precipitate washed with cold distilled water, and was recrystallized from water/methanol to yield 0.27 g (85%) of compound **4a** as a white solid, mp 274-276° (dec.). IR: 3042, 3014, 2976, 2948, 2872, 1636, 1398, 768, 510 cm^{-1}(KBr). MS: m/z (%): 177 (M^+, 9.0), 176 (15.0), 132 (100.0), 130 (24.0), 118 (57.0), 117 (9.0), 105 (71.0).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21; N, 7.91. Found: C, 67.72; H, 6.18; N, 7.94

Synthesis of (S)-2-(1,3-Dihydroisoindol-2-yl)-4-methylpentanoic Acid (4b).- The reaction of 0.45 g (1.82 mmol) of compound **3b** gave a white solid, which was recrystallized from water/methanol to yield 0.36 g (85%) of compound **4b**, mp 201-203° (dec). $[\alpha]^{25}_D$ +15.5 (C 2, HCl 5N). IR: 3060, 2998, 2956, 2944, 2932, 2870, 1608, 1398, 750, 510 cm^{-1}(KBr). MS: m/z (%) 233 (M^+, 1.0), 232 (2.0), 188 (100.0), 176 (7.0), 132 (13.0), 130 (18.0), 118 (31.0), 117 (14.0), 105 (28.0).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found: C, 71.87; H, 8.17; N, 6.14

Synthesis of (S)-2-(1,3-Dihydroisoindol-2-yl)-4-methylsulfanylbutanoic Acid (4c).- The reaction of 0.48 g (1.81 mmol) of compound **3c** gave a white solid, which was recrystallized from water/methanol to yield 0.40 g (88%) of compound **4c**, mp 179-181° (dec). $[\alpha]^{20}_D$ +21 (C 1, HCl 1N). IR : 3030, 2998, 2918, 2866, 1626, 1398, 750, 520 cm^{-1} (KBr). MS: m/z (%): 251 (M^+. abs.), 250 (1.0), 206 (29.0), 176 (6.0), 132 (8.0), 118 (100), 117 (14.0), 105 (8.0).

Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.15; H, 6.77; N, 5.58; S, 12.75. Found: C, 62.23; H, 6.94; N, 5.50; S, 12.65

Synthesis of (S)-2-(1,3-Dihydroisoindol-2-yl)-4-phenylpentanoic Acid (4d).- The reaction of 0.49 g (1.83 mmol) of compound **3d** gave a white solid, which was recrystallized from water/methanol to yield 0.42 g (90%) of compound **4d**, mp 242-244° (dec). $[\alpha]^{25}_D$ +16.4 (C 1, HCl 1N). IR: 3042, 3010, 2954, 2918, 2870, 1628, 1398, 750, 540 cm^{-1}(KBr). MS: m/z (%) 253 (M^+, 1.0), 252 (1.0), 208 (100), 130 (41.0), 118 (20.0), 117 (7.0), 105 (41.0).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93; N, 5.53. Found: C, 75.69; H, 5.96; N, 5.64

Synthesis of (S)-2-(1,3-Dihydroisoindol-2-yl)-3-(4-hydroxyphenyl)propanoic Acid (4e).- The reaction of 0.54 g (1.81 mmol) of compound **3e** gave a white solid, which was recrystallized from water/methanol to yield 0.45 g (89%) of compound **4e**, mp 236-238° (dec). $[\alpha]^{25}_{D}$ -11 (C 4, HCl 1N). IR : 3020, 2934, 2860, 1630, 1388, 750, 540 cm^{-1}(KBr). MS: m/z (%) 283 (M^+, 1.8), 282 (1.5), 238 (19.2), 176 (100), 132 (11.4), 130 (41.6), 118 (21.3), 117 (10.3), 105 (6.4).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.24; H, 6.06; N, 4.83

Synthesis of (S)-2-(1,3-Dihydroisoindol-2-yl)-3-(1H-indol-3-yl)propanoic Acid (4f).- The reaction of 0.58 g (1.81 mmol) of compound **3f** gave a white solid, which was recrystallized from water/methanol to yield 0.45 g (81%) of compound **4f**, mp 207-209° (dec). $[\alpha]^{20}_{D}$ -29 (C 1, H_2O). IR : 3054, 2928, 2864, 1626, 1388, 744, 520 cm^{-1} (KBr). MS: m/z (%) 306 (M^+, 3.5), 261 (9.6), 176 (36.1), 132 (11.2), 130 (100), 118 (9.2), 117 (11.7), 105 (2.4).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.57; H, 5.92; N, 9.15. Found: C, 74.43; H, 5.97; N, 9.26

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