Synthesis of New 4,5,6,7-Tetrahydro-3*H*-imidazo[4,5-*c*]pyridine Derivatives

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The synthesis of new ligands for the H_3 histamine receptor is described. These new compounds are spinacine derivatives obtained by alkylation or Michael reaction at C6 position.

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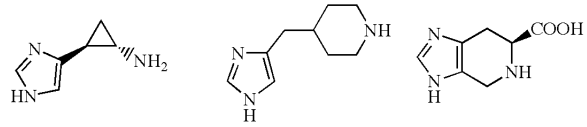
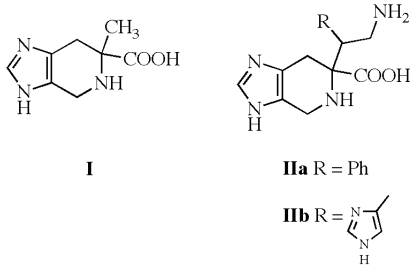
The H_3 histamine receptor was demonstrated to be located presynaptically on histaminergic neurons in the central nervous system (CNS) where it regulates histamine synthesis and release as autoreceptor [1,2]. Inhibition of this negative feedback mechanism by H_3 receptor antagonists, thus, increases concentration of the histamine released [3].

Moreover, H_3 receptors function as heteroreceptors on nonhistaminergic neurons in the brain and the periphery, inhibiting the release of neuropeptides [4] and several other neurotransmitters such as acetylcholine, dopamine, serotonin and noradrenaline [5]. In radiolabeling studies, the highest density of H_3 receptors was found in distinct areas of the CNS [6], and it is suggested that the potential therapeutic role of H_3 receptor antagonists may be the treatment of various neurological and psychiatric diseases, *e.g.* epilepsy, narcolepsy, schizophrenia, or dementia [7]. New pharmacological tools are highly recommended to clarify these therapeutic indications.



Cyclopropylhistamine **Immepip** **Spinacine**

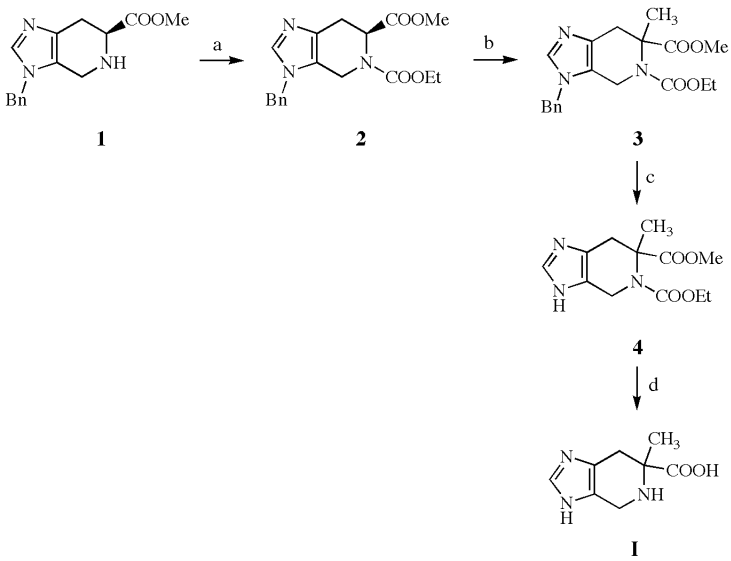
Figure 1



I **IIa** R = Ph **IIb** R =

Figure 2

Scheme 1



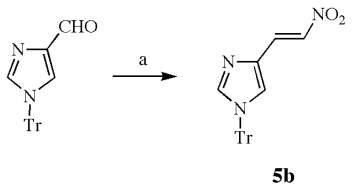
(a) ClCOOEt, K_2CO_3, EtOH; (b) (i) NaHMDS, THF, -78°C; (ii) ICH_3, THF, -78°C; (c) cyclohexene, Pd-C (10%), absolute EtOH, Δ; (d) HCl 6N, Δ.

In this work we describe the synthesis of 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine derivatives as new ligands for the H_3 receptor of histamine. The development of rigid histamine analogues had contributed to the determination of the H_3 receptor pharmacophore, *e.g.* the cyclopropylhistamine [8] or the immepip [9] (Figure 1). Therefore, as part of our medicinal chemistry studies directed towards the preparation of new H_3 receptor ligands, we have selected spinacine [10], as a template for the development of such analogues, as it can be looked at as conformationally restricted analogue of histidine (Figure 1). Several substituents have been introduced at the C6 position in order to determine the influence on the biological activities of these derivatives **I** and **IIa-b** (Figure 2).

The pathway outlined in Scheme 1 yielded the desired histamine analogue **I**. N_{im}-benzyl-spinacine methyl ester **1** was obtained according to literature procedures [11]. Protection of the amino group was achieved by reaction of **1** with ethyl chloroformate (70% yield). The only productive reaction conditions for the alkylation of **2** were determined to be generation of the carbanion of **2** with NaHMDS in THF at –78 °C, followed by reaction with 2 equiv of methyl iodide at –78 °C (97% yield). The hydrogenation of the *N*-benzyl group in the racemic ester **3** [12], followed by acidic hydrolysis of the carbamate moiety and the ester group, furnished **I** (73% two steps yield).

The synthetic route for preparing the target compounds **IIa-b** is portrayed in Scheme 2. The diastereoselective Michael addition of nitrovinyl compounds **5a-b** to the enolate of **2** afforded **6a** (52%) and **6b** (93%). The Michael acceptor **5b** was synthesized by ultrasound promoted Knovenagel condensation of its correspondent aldehyde in moderate yield (52%) [13] (Scheme 3). The relative stereochemistry of the compounds **6a-b** was determined by single–crystal X-rays analysis (Figures 3 and 4) of their cyclic derivatives **9a-b** (Scheme 4). The hydrogenation of **6a-b**, with cyclohexene and the Pd-C (10%) catalyst [12], provided **7a-b** in good yield. Reduction of the amino group under 40 psi of hydrogen in presence of palladium, followed by acidic hydrolysis of the ester group and the carbamate moiety rendered **IIa** (90%) and **IIb** (92%).

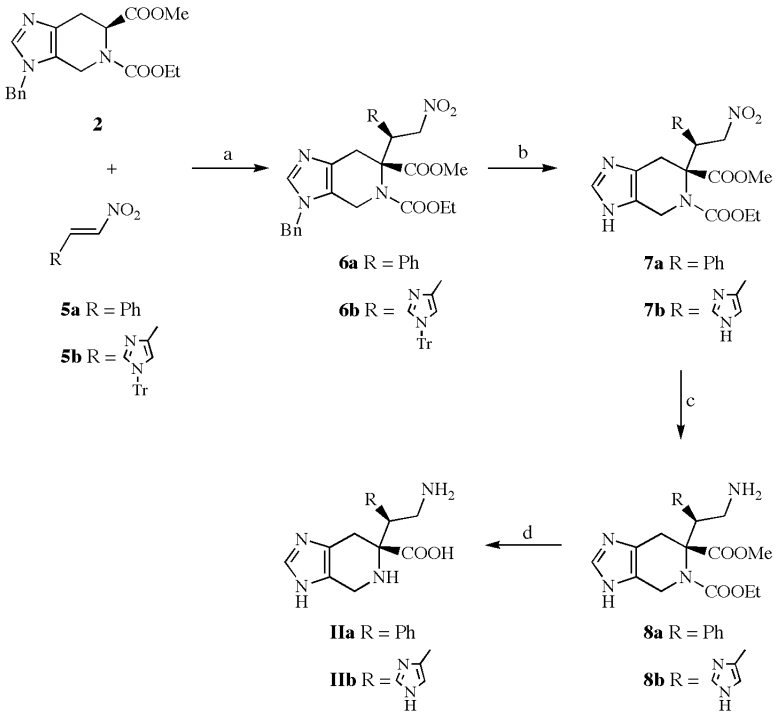
Scheme 3



5b

(a) CH_3NO_2, AcOH, NH_4OAc.

Scheme 2



5a R = Ph
5b R =
6a R = Ph
6b R =
7a R = Ph
7b R =
8a R = Ph
8b R =
IIa R = Ph
IIb R =

(a) NaHMDS, THF, -78°C; (b) cyclohexene, Pd-C (10%), absolute EtOH, Δ; (c) Ni-Raney, MeOH, H_2 (40 psi); (d) HCl 6N, Δ.

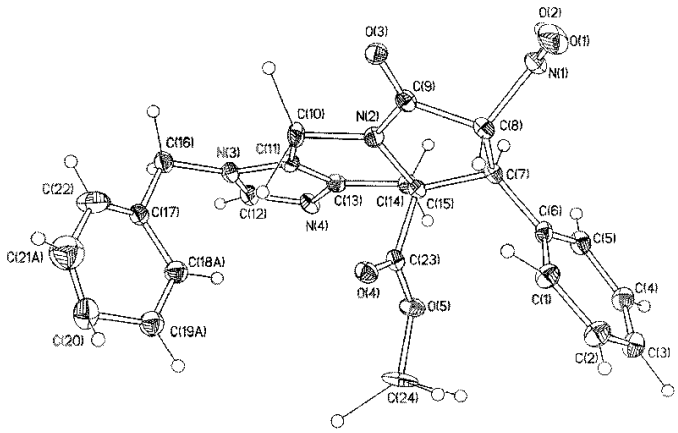


Figure 3. ORTEP drawingo or compound **9a**.

states in this reaction explains the total diastereoselectivity observed.

The affinity of new compounds for the histamine H_3 receptor was assessed by the study of the inhibition of the specific binding of [^{3}H] (R)-α-methylhistamine ([^{3}H] RMHA) in rat brain membranes [14]. All the compounds tested showed less affinity than (R)-α-methylhistamine, used as the reference compound (data not shown).

EXPERIMENTAL

Melting points were determined on a Büchi 530 apparatus and were uncorrected. IR spectra were recorded on a Perkin Elmer 1330 infrared spectrophotometer as potassium bromide pellets. NMR spectra were determined on a Bruker AM-300 instrument. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.43 MHz, respectively. Chemical shifts for hydrogen and carbon were reported in ppm (δ) relative to tetramethylsilane, using DMSO-d_6, D_2O, CD_3OD and $CDCl_3$ as solvents. Merck silica gel (230-400 mesh) was used for flash chromatography. Elemental analyses were performed in the UCM Microanalysis Service (Facultad de Farmacia, Universidad Complutense de Madrid, Spain) and agreed with theoretical values to within ±0.4%. Single crystals of compounds **9a-b** suitable for X-ray diffraction were selected directly from the analytical samples.

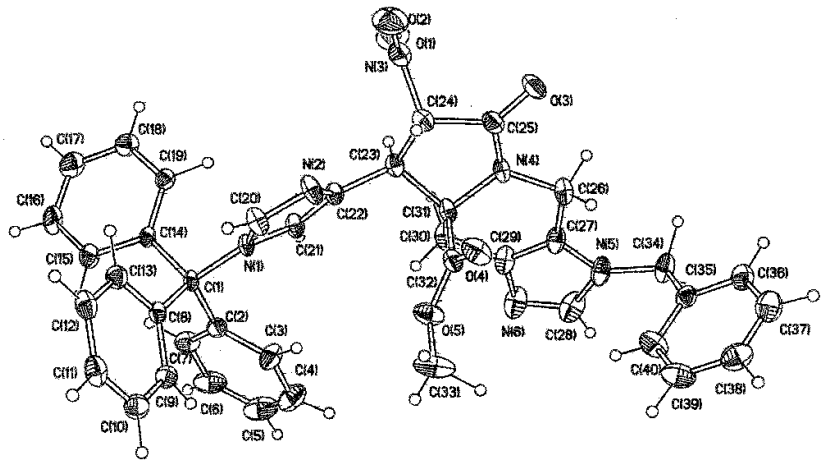
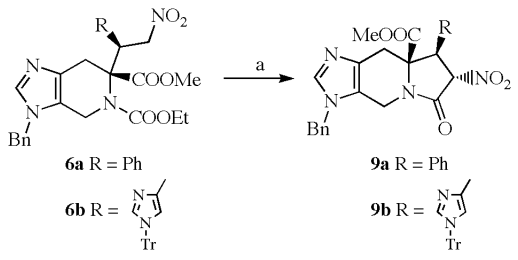


Figure 4. ORTEP drawingo or compound **9b**.

Functionalization of spinacine at C6 position had not been described yet, so we have established the reaction conditions for alkylations and Michael reactions on this structure. Michael reactions are totally diastereoselective for the Michael acceptors we have used. Although a deeper study is required, it seems probable that an important difference in stability between the two possible transition

Scheme 4



(a) NaOH 1N, MeOH, Δ.

Methyl (6*S*)-3-Benzyl-5-ethyloxycarbonyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylate (**2**).

A solution of Na_2CO_3 2 *M* (67.7 ml) and ethyl chloroformate (11.8 ml, 123.18 mmol) were added dropwise to a stirred solution of N_{im}-benzyl-spinacine methyl ester **1** (16.71 g, 61.59 mmol) in absolute EtOH (100 ml) at 0 °C. The mixture was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure, the residual semisolid was purified by column chromatography on silica using $CHCl_3$/MeOH (250:1→50:1) as eluent to give a homogeneous residue, which was crystallized from EtOAc to yield the ester **2** (14.70 g, 70%) as a white solid, m.p.

102-104 °C); IR ν cm^{-1}: 1740, 1720, 1490; ^{1}H-NMR (DMSO-d_6): δ 1.16 (t, 3H, $COOCH_2CH_3$, *J* = 7.3 Hz.), 2.88-2.94 (m, 1H, 1/2 ImCH_2CH), 3.03 (d, 1H, 1/2 ImCH_2CH, *J* = 15.8 Hz.), 3.55 (s, 3H, $COOCH_3$), 3.96 (d, 1H, 1/2 ImCH_2N, *J* = 15.2 Hz.), 4.07 (q, 2H, $COOCH_2CH_3$, *J* = 7.3Hz.), 4.48 (d, 1H, 1/2 ImCH_2N, *J* = 15.2 Hz.), 5.17 (br s, 2H, NCH_2Ph), 5.23 (d, 1H, C*H*$COOCH_3$, *J* = 6.1 Hz.), 7.08 (d, 2H, Ar, *J* = 7.3 Hz.), 7.30-7.39 (m, 3H, Ar), 7.69 (s, 1H, Im-H2); ^{13}C-NMR ($CDCl_3$): δ 14.5 ($COOCH_2CH_3$), 26.5 (ImCH_2CH), 39.0 (ImCH_2N), 48.9 (NCH_2Ph), 52.4 ($COOCH_2CH_3$), 53.2 ($COOCH_3$), 62.1 (*C*H$COOCH_3$), 121.7 (Im-C5), 126.9 (Im-C4), 128.3 (Ar), 129.0 (Ar), 132.5 (Ar), 133.0 (Ar), 135.2 (Ar), 137.0 (Im-C2), 156.4 (N*C*$OOCH_2CH_3$), 171.6 (*C*$OOCH_3$); MS (EI): *m/z* 343 (M^+, 17), 284 (17), 270 (32), 252 (27), 120 (7), 91 (100).

Methyl (±)-3-Benzyl-5-ethyloxycarbonyl-6-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylate (**3**).

To a 1 *M* solution of sodium hexamethyldisilazide in THF (3.2 ml, 3.20 mmol) stirred at –78 °C under argon atmosphere was added a solution of ester **2** (1.00 g, 2.90 mmol) in dry THF (10 ml). The mixture was stirred at –78 °C for 1 h. Methyl iodide (0.4 ml, 5.80 mmol) disolved in dry THF (5 ml) was added at –78 °C, and the mixture was then stirred for 12 h at room temperature. The reaction mixture was quenched with saturated solution of ammonium chloride and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The residual semisolid was purified by column chromatography on silica using $CHCl_3$/MeOH (120:1) as eluent to give a homogeneous residue which was crystallized from $CHCl_3$ to yield the ester **3** (1.01 g, 97%) as a white solid, m.p. 106-108 °C; IR ν cm^{-1}: 1730, 1690. ^{1}H-NMR ($CDCl_3$): δ 1.09 (t, 3H, $COOCH_2CH_3$, *J* = 7.1 Hz.), 1.33 (s, 3H, CCH_3), 2.67 (d, 1H, 1/2 ImCH_2C, *J* = 15.9 Hz.), 3.26 (d, 1H, 1/2 ImCH_2C, *J* = 15.9 Hz.), 3.69 (s, 3H, $COOCH_3$), 3.82 (d, 1H, 1/2 ImCH_2N, *J* = 15.9 Hz.), 3.96-4.00 (m, 2H, $COOCH_2CH_3$), 4.61 (d, 1H, 1/2 ImCH_2N, *J* = 15.9 Hz.), 4.98 (s, 2H, NCH_2Ph), 7.02 (d, 2H, Ar, *J* = 6.6 Hz.), 7.27-7.29 (m, 3H, Ar), 7.43 (s, 1H, Im-H2); ^{13}C-NMR ($CDCl_3$): δ 13.4 ($COOCH_2CH_3$), 20.7 (CCH_3), 31.6 (ImCH_2CH), 38.4 (ImCH_2N), 48.2 (NCH_2Ph), 51.4 ($COOCH_2CH_3$), 59.7 ($COOCH_3$), 61.2 (*C*H$COOCH_3$), 120.8 (Im-C5), 126.0 (Im-C4), 127.4 (Ar), 128.2 (Ar), 133.3 (Ar), 134.9 (Ar), 136.5 (Im-C2), 155.6 (N*C*$OOCH_2CH_3$), 172.9 (*C*$OOCH_3$); MS (ESI): *m/z* 358 $[M+H]^+$.

Methyl (±)-5-Ethyloxycarbonyl-6-methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylate (**4**).

To a stirred suspension of the ester **3** (1.40 g, 3.92 mmol) and 10% Pd-C (700 mg) in absolute EtOH (30 ml), cyclohexene (31.8 ml, 313.60 mmol) was added at reflux temperature. The resulting reaction mixture was stirred for 24 h. The catalyst was removed by filtration through a celite pad and washed with methanol. The filtrate was evaporated under reduced pressure. The residue was purified by recrystallization from EtOAc to give the ester **4** (1.01 g, 96%) as a white solid, m.p. 158-160 °C; IR ν cm^{-1}: 3400, 1740, 1700; ^{1}H-NMR (DMSO-d_6): δ 1.14 (t, 3H, $COOCH_2CH_3$, *J* = 7.1 Hz.), 1.37 (s, 3H, CCH_3), 2.72 (d, 1H, 1/2 ImCH_2C, *J* = 16.0 Hz.), 3.19 (d, 1H, 1/2 ImCH_2C, *J* = 16.0 Hz.), 3.67 (s, 3H, $COOCH_3$), 3.97-4.08 (m, 2H, $COOCH_2CH_3$), 4.26 (d, 1H, 1/2 ImCH_2N, *J* = 16.5 Hz.), 4.85 (d, 1H, 1/2 ImCH_2N, *J* = 16.5 Hz.), 8.60 (s, 1H, Im-H2); ^{13}C-NMR (DMSO-d_6): δ 14.2 ($COOCH_2CH_3$), 21.5 (CCH_3), 28.4 (ImCH_2CH), 39.3 (ImCH_2N), 52.2 ($COOCH_2CH_3$), 59.4 ($COOCH_3$), 62.0 (*C*H$COOCH_3$), 124.4 (Im-C5), 124.8 (Im-C4), 133.9 (Im-C2), 156.0 (N*C*$OOCH_2CH_3$), 172.5 (*C*$OOCH_3$); MS (EI): *m/z* 267 (M^+, 32), 252 (3), 208 (79), 194 (21), 134 (41), 119 (24), 94 (100).

(±)-6-Methyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylic Acid (**I**).

A solution of **4** (0.96 g, 3.59 mmol) in HCl 6 *N* (50 ml, 300.00 mmol) was stirred at reflux temperature for 48 h. After removal of the solvent under reduced pressure, the residue was purified by recrystallization from EtOH/Et_2O to give **I** (0.69 g, 76%) as a white solid, m.p. 249-250 °C; IR ν cm^{-1}: 3400, 2900-2700, 1740; ^{1}H-NMR (D_2O): δ 1.45 (s, 3H, CCH_3), 2.94 (d, 1H, 1/2 ImCH_2C, *J* = 17.0 Hz.), 3.23 (d, 1H, 1/2 ImCH_2C, *J* = 17.0 Hz.), 4.23 (d, 1H, 1/2 ImCH_2N, *J* = 15.9 Hz.), 4.40 (d, 1H, 1/2 ImCH_2N, *J* = 15.9 Hz.), 8.51 (s, 1H, Im-H2); ^{13}C-NMR (D_2O): δ 22.8 (CCH_3), 29.9 (ImCH_2CH), 39.1 (ImCH_2N), 63.7 (*C*HCOOH), 121.7 (Im-C5), 126.4 (Im-C4), 137.6 (Im-C2), 175.4 (*C*OOH); MS (ESI): *m/z* 182 $[M+H]^+$.

Anal. Calcd. for $C_8H_{11}N_3O_2$•2HCl•0.25H_2O: C, 37.15; H, 5.22; N, 16.25. Found: C, 37.14; H, 5.02; N, 16.64.

Methyl (6*R**,1'*S**)-3-Benzyl-5-ethyloxycarbonyl-6-(2'-nitroethyl-1'-phenyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]-pyridin-6-carboxylate (**6a**).

To a 1 *M* solution of sodium hexamethyldisilazide in THF (8.0 ml, 8.02 mmol) stirred at –78 °C under argon atmosphere was added a solution of ester **2** (2.50 g, 7.29 mmol) in dry THF (30 ml). The mixture was stirred at –78 °C for 1 h. The *trans*-β-nitrostyrene **5a** (2.17 g, 14.58 mmol) dissolved in dry THF (30 ml) was added at –78 °C, and the mixture was then stirred for 12 h at room temperature. The reaction mixture was quenched with saturated solution of ammonium chloride and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The residual semisolid was purified by column chromatography on silica using $CHCl_3$/MeOH (60:1) as eluent to give a homogeneous residue which was crystallized from $CHCl_3$/MeOH to yield the ester **6a** (1.87 g, 52%) as a white solid, m.p. 68-70 °C; IR ν cm^{-1}: 1730, 1700, 1540; ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H, $COOCH_2CH_3$, *J* = 7.1 Hz.), 2.69 (d, 1H, 1/2 ImCH_2C, *J* = 17.0 Hz.), 3.21 (d, 1H, 1/2 ImCH_2C, *J* = 17.0 Hz.), 3.71 (s, 3H, $COOCH_3$), 3.98-4.07 (m, 4H, 1/2 ImCH_2N and $COOCH_2CH_3$ and C*H*Ph), 4.88 (d, 1H, 1/2 ImCH_2N, *J* = 16.5 Hz.), 4.99-5.08 (m, 3H, NCH_2Ph and 1/2 CH_2NO_2), 5.19 (dd, 1H, 1/2 CH_2NO_2, *J* = 13.7 Hz., *J* = 11.0 Hz.), 6.89-6.92 (m, 2H, Ar), 7.14 (d, 2H, Ar, *J* = 7.1 Hz.), 7.26-7.40 (m, 6H, Ar), 7.58 (s, 1H, Im-H2); ^{13}C-NMR ($CDCl_3$): δ 14.1 ($COOCH_2CH_3$), 27.7 (ImCH_2CH), 39.4 (ImCH_2N), 45.4 (*C*HPh), 49.2 (NCH_2Ph), 52.2 ($COOCH_2CH_3$), 62.7 ($COOCH_3$), 65.5 (*C*H$COOCH_3$), 77.2 (CH_2NO_2), 121.6 (Im-C5), 126.6 (Im-C4), 128.4 (Ar), 128.6 (Ar), 128.8 (Ar), 129.2 (Ar), 133.6 (Ar), 134.4 (Ar), 135.1 (Ar), 137.5 (Ar), 137.6 (Im-C2), 156.8 (N*C*$OOCH_2CH_3$), 170.2 (*C*$OOCH_3$); MS (EI): *m/z* 492 (M^+, 1), 445 (13), 355 (18), 310 (25), 91 (100).

Methyl (6*R**,1'*R**)-3-Benzyl-5-ethyloxycarbonyl-6-[2'-nitro-1'-(1''-trityl-1''*H*-imida-zol-4''-yl)-ethyl]-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylate (**6b**).

To a 1 *M* solution of sodium hexamethyldisilazide in THF (6.5 ml, 6.45 mmol) stirred at –78 °C under argon atmosphere was

added a solution of ester **2** (1.70 g, 4.96 mmol) in dry THF (30 ml). The mixture was stirred at –78 °C for 1 h. The 4-(2'-nitrovinyl)-1-trityl-1*H*-imidazole **5b** (2.46 g, 6.45 mmol) dissolved in dry THF (60 ml) was added at –78 °C and the mixture was then stirred for 12 h at room temperature. The reaction mixture was quenched with saturated solution of ammonium chloride and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The residual semisolid was purified by column chromatography on silica using $CHCl_3$/MeOH (250:1) as eluent to give a homogeneous residue which was crystallized from cyclohexane to yield the ester **6b** (3.35 g, 93%) as a pale yellow solid, m.p. 122-123°C; IR ν cm^{-1}: 1730, 1700, 1540; ^{1}H-NMR ($CDCl_3$): δ 1.09 (t, 3H, $COOCH_2CH_3$, *J* = 6.6 Hz.), 2.97 (d, 1H, 1/2 ImCH_2C, *J* = 16.5 Hz.), 3.28 (d, 1H, 1/2 ImCH_2C, *J* = 17.0 Hz.), 3.62 (s, 3H, $COOCH_3$), 3.89-4.10 (m, 4H, 1/2 ImCH_2N and $COOCH_2CH_3$ and C*H*Im'), 4.85-5.10 (m, 4H, NCH_2Ph and 1/2 CH_2NO_2 and ImCH_2N), 5.26 (dd, 1H, 1/2 CH_2NO_2, *J* = 11.9 Hz., *J* = 10.5 Hz.), 6.57 (s, 1H, Im'-H5), 7.05-7.13 (m, 8H, Ar), 7.31-7.34 (m, 12H, Ar), 7.36 (s, 1H, Im'-H2), 7.44 (s, 1H, Im-H2); ^{13}C-NMR ($CDCl_3$): δ 14.0 ($COOCH_2CH_3$), 27.9 (ImCH_2CH), 39.2 (ImCH_2N), 40.1 (*C*HIm'), 49.2 (NCH_2Ph), 52.2 ($COOCH_2CH_3$), 62.5 ($COOCH_3$), 65.2 (*C*HCOOCH$_3$), 75.3 (N*C*Ph$_3$), 77.2 (CH_2NO_2), 121.3 (Im-C5), 121.5 (Im'-C5), 126.8 (Im-C4 and Im'-C4)), 128.0 (Ar), 129.1 (Ar), 129.6 (Ar), 134.5 (Ar), 134.7 (Ar), 135.1 (Ar), 137.4 (Ar), 138.9 (Im-C2), 142.0 (Im'-C2), 156.8 (N*C*OOCH$_2$CH$_3$), 169.9 (*C*OOCH$_3$); MS (ESI): *m/z* 725 $[M+H]^+$.

Methyl (6*R**,1'*S**)-5-Ethyloxycarbonyl-6-(1'-phenyl-2'-nitroethyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylate (**7a**).

To a stirred suspension of the ester **6a** (0.83 g, 1.68 mmol) and 10% Pd-C (300 mg) in absolute EtOH (20 ml), cyclohexene (20.4 ml, 201.60 mmol) was added at reflux temperature. The resulting reaction mixture was stirred for 24 h. The catalyst was removed by filtration through a celite pad and washed with methanol. The filtrate was evaporated under reduced pressure. The residual semisolid was purified by column chromatography on silica using $CHCl_3$/MeOH (20:1) as eluent to give a homogeneous residue which was crystallized from EtOAc to yield the ester **7a** (0.54 g, 80%) as a white solid, m.p. 151-152 °C; IR ν cm^{-1}: 3350, 1730, 1700, 1550; ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 3H, $COOCH_2CH_3$, *J* = 7.1 Hz.), 2.59 (d, 1H, 1/2 ImCH_2C, *J* = 16.5 Hz.), 3.24 (d, 1H, 1/2 ImCH_2C, *J* = 16.5 Hz.), 3.78 (s, 3H, $COOCH_3$), 4.04-4.16 (m, 3H, C*H*Ph and $COOCH_2CH_3$), 4.41 (d, 1H, 1/2 ImCH_2N, *J* = 17.0 Hz.), 5.16-5.27 (m, 3H, 1/2 ImCH_2N and CH_2NO_2), 6.87-6.70 (m, 2H, Ar), 7.25-7.28 (m, 3H, Ar), 7.63 (s, 1H, Im-H2); ^{13}C-NMR ($CDCl_3$): δ 14.2 ($COOCH_2CH_3$), 25.7 (ImCH_2CH), 42.0 (ImCH_2N), 45.6 (*C*HPh), 52.4 ($COOCH_2CH_3$), 62.9 ($COOCH_3$), 65.3 (*C*HCOOCH$_3$), 77.5 (CH_2NO_2), 121.3 (Im-C5), 126.5 (Im-C4), 128.8 (Ar), 128.9 (Ar), 129.0 (Ar), 129.7 (Ar), 133.9 (Ar), 134.8 (Im-C2), 157.5 (N*C*OOCH$_2$CH$_3$), 169.9 (*C*OOCH$_3$); MS (EI): *m/z* 402 (M^+, 3), 355 (7), 343 (4), 252 (100), 220 (42), 180 (99), 120 (84), 94 (87).

Methyl (6*R**,1'*R**)-5-Ethyloxycarbonyl-6-[1'-(1''*H*-imidazol-4''-yl)-2'-nitro-ethyl]-4,5, 6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylate (**7b**).

To a stirred suspension of the ester **6b** (1.00 g, 1.38 mmol) and 10% Pd-C (600 mg) in absolute EtOH (50 ml), cyclohexene (27.9 ml, 276.00 mmol) was added at reflux temperature. The resulting reaction mixture was stirred for 48 h. The catalyst was removed by filtration through a celite pad and washed with methanol. The filtrate was evaporated under reduced pressure. The residue was purified by recrystallization from Et_2O to give the ester **7b** (0.33 g, 61%) as a white solid, m.p. 205-206 °C; IR ν cm^{-1} 3400, 1740, 1700, 1550; ^{1}H-NMR (DMSO-d_6): δ 1.13 (t, 3H, $COOCH_2CH_3$, *J* = 7.3 Hz.), 2.90 (d, 1H, 1/2 ImCH_2C, *J* = 16.5 Hz.), 3.00 (d, 1H, 1/2 ImCH_2C, *J* = 16.5 Hz.), 3.60 (s, 3H, $COOCH_3$), 3.89 (t, 1H, C*H*Im', *J* = 6.1 Hz.), 3.98-4.06 (m, 2H, $COOCH_2CH_3$), 4.27 (d, 1H, 1/2 ImCH_2N, *J* = 17.1 Hz.), 4.97 (d, 1H, 1/2 ImCH_2N, *J* = 17.1 Hz.), 5.19 (d, 2H, CH_2NO_2, *J* = 6.1 Hz.), 6.85 (s, 1H, Im'-H5), 7.56 (s, 1H, Im'-H2), 7.72 (s, 1H, Im-H2); ^{13}C-NMR (DMSO-d_6): δ 13.6 ($COOCH_2CH_3$), 24.7 (ImCH_2CH), 41.0 (*C*HIm'), 51.4 (ImCH_2N), 60.1 ($COOCH_2CH_3$), 61.6 ($COOCH_3$), 64.1 (*C*HCOOCH$_3$), 76.6 (CH_2NO_2), 124.7 (Im-C5), 124.9 (Im'-C5), 133.3 (Im-C4 and Im'-C4), 134.3 (Im-C2), 134.9 (Im'-C2), 156.3 (N*C*OOCH$_2$CH$_3$), 168.7 (*C*OOCH$_3$); MS (ESI): *m/z* 393 $[M+H]^+$.

Methyl (6*R**,1'*R**)-5-Ethyloxycarbonyl-6-[2'-amino-1'-(1''*H*-imidazol-4''-yl)-ethyl]-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]piridin-6-carboxylate (**8a**).

A solution of the ester **7a** (0.44 g, 1.09 mmol) in MeOH (35 ml) was hydrogenated over 500 mg of Raney-Ni at 40 psi on a shaker at room temperature for 6 h. The catalyst was removed by filtration through a celite pad and washed with methanol. The filtrate was evaporated under reduced pressure. The residual semisolid was purified by column chromatography on silica using EtOAc/MeOH (3:1) as eluent to give a homogeneous residue which was crystallized from EtOAc to yield the ester **8a** (0.32 g, 79%) as a white solid, m.p. 203-204 °C; IR ν cm^{-1}: 3400, 3100, 1740, 1710; ^{1}H-NMR (CD_3OD): δ 1.24 (t, 3H, $COOCH_2CH_3$, *J* = 6.7 Hz.), 2.62 (d, 1H, 1/2 ImCH_2C, *J* = 16.5 Hz.), 3.14 (d, 1H, 1/2 ImCH_2C, *J* = 16.5 Hz.), 3.54-3.70 (m, 3H, C*H*Ph and CH_2NH_2), 3.75 (s, 3H, $COOCH_3$), 4.08-4.18 (m, 3H, $COOCH_2CH_3$ and 1/2 ImCH_2N), 5.07 (d, 1H, 1/2 ImCH_2N, *J* = 16.5 Hz.), 6.93 (br s, 2H, Ar), 7.37 (br s, 3H, Ar), 7.67 (s, 1H, Im-H2); ^{13}C-NMR (DMSO-d_6): δ 14.1 ($COOCH_2CH_3$), 25.5 (ImCH_2CH), 40.8 (CH_2NH_2), 47.6 (ImCH_2N), 51.7 (*C*HPh), 61.1 ($COOCH_2CH_3$), 61.9 ($COOCH_3$), 65.2 (*C*HCOOCH$_3$), 121.3 (Im-C5), 126.5 (Im-C4), 127.6 (Ar), 127.8 (Ar), 127.9 (Ar), 128.4 (Ar), 129.5 (Ar), 134.7 (Ar), 136.0 (Im-C2), 157.1 (N*C*OOCH$_2$CH$_3$), 169.7 (*C*OOCH$_3$); MS (EI): *m/z* 372 (M^+, 1), 356 (18), 342 (92), 252 (100), 180 (69), 120 (85), 94 (97).

Methyl (6*R**,1'*R**)-5-Ethyloxycarbonyl-6-[2'-amino-1'-(1''*H*-imidazol-4''-yl)-ethyl]-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylate (**8b**).

A solution of the ester **7b** (1.00 g, 2.55 mmol) in MeOH (50 ml) was hydrogenated over 900 mg of Raney-Ni at 40 psi on a shaker at room temperature for 3 h. The catalyst was removed by filtration through a celite pad and washed with methanol. The filtrate was evaporated under reduced pressure. The residue was purified by recrystallization from EtOH/Et_2O to give the ester **8b** (0.82 g, 89%) as a white solid, m.p. 201-202 °C; IR ν cm^{-1}: 3400, 1740, 1700; ^{1}H-NMR (CD_3OD): δ 1.23 (t, 3H, $COOCH_2CH_3$, *J* = 6.7 Hz.), 2.87 (d, 1H, 1/2 ImCH_2C, *J* = 15.8 Hz.), 3.18 (d, 1H, 1/2 ImCH_2C, *J* = 15.8 Hz.), 3.58 (d, 2H, CH_2NH_2, *J* = 11.0 Hz.), 3.72 (s, 3H, $COOCH_3$), 3.77 (t, 1H, C*H*Im', *J* = 11.0 Hz.), 4.11 (q, 2H, $COOCH_2CH_3$, *J* = 6.7 Hz.), 4.27 (d, 1H, 1/2 ImCH_2N, *J* = 16.5 Hz.), 5.09 (d, 1H, 1/2 ImCH_2N, *J* = 16.5 Hz.), 6.91 (s, 1H, Im'-H5), 7.67 (s, 1H, Im'-H2),

7.91 (s, 1H, Im-H2); ^{13}C-NMR (CD_3OD): δ 14.6 ($COOCH_2CH_3$), 26.9 ($ImCH_2CH$), 40.6 (CH_2NH_2), 41.4 (*C*HIm'), 42.8 ($ImCH_2N$), 52.9 ($COOCH_2CH_3$), 63.9 ($COOCH_3$), 66.7 (*C*HCOOCH$_3$), 125.6 (Im-C5), 129.1 (Im'-C5), 134.4 (Im-C4 and Im'-C4), 136.2 (Im-C2), 137.5 (Im'-C2), 159.0 (N*C*OOCH$_2$CH$_3$), 171.1 (*C*OOCH$_3$); MS (ESI): *m/z* 363 $[M+H]^+$.

(6*R**,1'*S**)-6-(2'-Amino-1'-phenyl-ethyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylic Acid (**IIa**).

A solution of **8a** (0.94 g, 2.53 mmol) in HCl 6 *N* (40 ml, 240.00 mmol) was stirred at reflux temperature for 96 h. After removal of the solvent under reduced pressure, the residue was purified by recrystallization from EtOH/Et_2O to give **IIa** (0.82 g, 90%) as a white solid, m.p. 249-250 °C; IR ν cm^{-1}: 3500, 3440, 3150-2450, 1710, 1640; ^{1}H-NMR (D_2O): δ 2.90-2.99 (m, 1H, 1/2 ImC*H*$_2$C), 3.12-3.27 (m, 1H, 1/2 ImC*H*$_2$C), 3.37-3.53 (m, 1H, 1/2 C*H*$_2$NH$_2$), 3.59-3.71 (m, 1H, 1/2 C*H*$_2$NH$_2$), 3.81-3.84 (m, 1H, C*H*Ph), 4.11-4.43 (m, 2H, ImC*H*$_2$N), 7.03-7.15 (m, 2H, Ar), 7.32 (br s, 3H, Ar), 8.16 (s, 1H, Im-H2); ^{13}C-NMR (D_2O): δ 23.1 ($ImCH_2CH$), 27.0 (CH_2NH_2), 37.5 ($ImCH_2N$), 45.2 (*C*HPh), 63.3 (*C*HCOOH), 121.0 (Im-C5), 123.1 (Im-C4), 124.4 (Ar), 127.9 (Ar), 128.3 (Ar), 128.4 (Ar), 128.6 (Ar), 134.0 (Ar), 136.4 (Im-C2), 171.0 (*C*OOH). MS (ESI): *m/z* 287 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{18}N_4O_2$•2HCl•0.75H_2O: C, 48.33; H, 5.81; N, 15.03. Found: C, 48.58; H, 5.63; N, 14.73.

(6*R**,1'*R**)-6-[2'-Amino-1'-(1"*H*-imidazol-4"-yl)-ethyl]-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridin-6-carboxylic Acid (**IIb**).

A solution of **8b** (0.61 g, 1.68 mmol) in HCl 6 *N* (30 ml, 180.00 mmol) was stirred at reflux temperature for 168 h. After removal of the solvent under reduced pressure, the residue was purified by recrystallization from EtOH/Et_2O to give **IIb** (0.65 g, 92%) as a white solid, m.p. 206-207 °C; IR ν cm^{-1} 3400, 3120, 1720, 1620; ^{1}H-NMR (D_2O): δ 2.78 (d, 1H, 1/2 ImC*H*$_2$C, *J* = 17.0 Hz.), 2.87 (d, 1H, 1/2 ImC*H*$_2$C, *J* = 17.0 Hz.), 3.47 (dd, 1H, 1/2 C*H*$_2$NH$_2$, *J* = 11.0 Hz., *J* = 7.7 Hz.), 3.76 (t, 1H, 1/2 C*H*$_2$NH$_2$, *J* = 9.6 Hz.), 3.95 (t, 1H, C*H*Im', *J* = 7.7 Hz.), 4.11 (d, 1H, 1/2 ImC*H*$_2$N, *J* = 16.5 Hz.), 4.28 (d, 1H, 1/2 ImC*H*$_2$N, *J* = 16.5 Hz.), 7.42 (s, 1H, Im'-H5), 8.41 (s, 1H, Im'-H2), 8.50 (s, 1H, Im-H2); ^{13}C-NMR (D_2O): δ 26.0 ($ImCH_2CH$), 39.5 (CH_2NH_2), 42.4 (*C*HIm'), 46.4 ($ImCH_2N$), 64.2 (*C*HCOOH), 120.7 (Im-C5 and Im-C5), 131.0 (Im-C4), 131.1 (Im'-C4), 136.5 (Im-C2), 137.0 (Im'-C2), 184.1 (*C*OOH); MS (ESI): *m/z* 277 $[M+H]^+$.

Anal. Calcd. for $C_{12}H_{16}N_6{\cdot}O_2$•4HCl•2$H_2O$: C, 31.45; H, 5.24; N, 18.34. Found: C, 31.08; H, 5.23; N, 18.01.

Methyl (7*S**,8*S**,8a*R**)-3-Benzyl-8-phenyl-7-nitro-6-oxo-3,4,6,7,8,9-hexahydroimidazo[4,5-*f*]indolizin-8a-carboxylate (**9a**).

To a solution of the ester **6a** (0.24 g, 0.49 mmol) in MeOH (30 ml) was added a solution 1 *N* NaOH (0.5 ml). The reaction mixture was heated at reflux for 24 h. The residue was taken up in water and neutralizated with 3 *N* HCl. MeOH was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc. The organic layer was washed with saturated aqueous sodium chloride, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by recrystallization from EtOAc/hexane to give **9a** (0.21 g, 96%) as a white solid, m.p. 204-205 °C; IR ν cm^{-1}: 1730, 1710, 1560; ^{1}H-NMR ($CDCl_3$): δ 3.10 (d, 1H, 1/2 ImC*H*$_2$C, *J* = 15.3 Hz.), 3.25 (s, 3H, $COOCH_3$), 3.82 (d, 1H, 1/2 ImC*H*$_2$C, *J* = 15.3 Hz.), 3.99 (d, 1H, 1/2 ImC*H*$_2$N, *J* = 15.9 Hz), 4.42 (d, 1H, C*H*Ph, *J* = 11.0 Hz.), 4.64 (d, 1H, 1/2 ImC*H*$_2$N, *J* = 15.9 Hz.), 4.98 (d, 1H, 1/2 NC*H*$_2$Ph, *J* = 15.9 Hz.), 5.06 (d, 1H, 1/2 NC*H*$_2$Ph, *J* = 15.9 Hz.), 5.91 (d, 1H, $CHNO_2$, *J* = 11.0 Hz.), 7.03-7.05 (m, 2H, Ar), 7.22-7.24 (m, 3H, Ar), 7.34-7.41 (m, 5H, Ar), 7.50 (s, 1H, Im-H2); ^{13}C-NMR ($CDCl_3$): δ 33.0 ($ImCH_2CH$), 37.7 ($ImCH_2N$), 49.2 (NCH_2Ph), 52.9 (*C*HPh), 54.2 ($COOCH_3$), 69.8 (*C*HCOOCH$_3$), 87.5 ($CHNO_2$), 119.8 (Im-C5), 126.7 (Im-C4), 127.5 (Ar), 128.5 (Ar), 128.9 (Ar), 129.2 (Ar), 129.3 (Ar), 129.4 (Ar), 130.8 (Ar), 133.1 (Ar), 134.6 (Ar), 138.3 (Im-C2), 164.4 (N*C*OCH), 169.7 (*C*OOCH$_3$); MS (EI): *m/z* 446 (M^+, 1), 414 (14), 400 (21), 355 (51), 91 (100).

Crystal Data of Compound **9a**.

$C_{40}H_{34}N_6O_5$, M = 678.73, monoclinic, space group $P2_1/n$. a = 13.131(3) Å, b = 12.130(2) Å, c = 22.230(4) Å, α = δ = 90°, β = 102.26(3)°. V = 3460.1(12) Å^3, Z = 4, D_c = 1.303 Mg/m^3, m = (Cu-K$_\alpha$) = 0.088, F(000) = 1424. Data collection (4440 collected reflections and 2767 observed reflections [I > 2 σ (I)]) were measured on a Seifert 3003 SC rotating anode diffractometer with (Cu-Kα) radiation (graphite monochromator) using 2θ–ω scans at 293(2) K. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F^2 to give the agreement factors R_1 = 0.0370, wR_2 = 0.0743.

Methyl (7*S**,8*R**,8a*R**)-3-Benzyl-8-(1'-trityl-1'*H*-imidazol-4'-yl)-7-nitro-6-oxo-3,4,6,7, 8,9-hexahydroimidazo[4,5-*f*]indolizin-8a-carboxilate (**9b**).

To a solution of the ester **6b** (0.27 g, 0.37 mmol) in MeOH (20 ml) was added a solution 1 *N* NaOH (0.4 ml). The reaction mixture was heated at reflux for 24 h. The residue was taken up in water and neutralized with 3 *N* HCl. MeOH was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc. The organic layer was washed with saturated aqueous sodium chloride, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residual semisolid was purified by column chromatography on silica using $CHCl_3$/MeOH (20:1) as eluent to give a homogeneous residue which was crystallized from EtOAc to yield **9b** (0.22 g, 88%) as a pale yellow solid, m.p. 201-202 °C; IR ν cm^{-1}: 1740, 1730, 1550; ^{1}H-NMR ($CDCl_3$): δ 2.88 (d, 1H, 1/2 ImC*H*$_2$C, *J* = 15.0 Hz.), 3.44 (s, 3H, $COOCH_3$), 3.75 (d, 1H, 1/2 ImC*H*$_2$C, *J* = 15.0 Hz.), 3.97 (d, 1H, 1/2 ImC*H*$_2$N, *J* = 15.4 Hz.), 4.31 (d, 1H, C*H*Im', *J* = 10.4 Hz.), 4.59 (d, 1H, 1/2 ImC*H*$_2$N, *J* = 15.4 Hz.), 4.97 (d, 1H, 1/2 NC*H*$_2$Ph, *J* = 15.9 Hz.), 5.04 (d, 1H, 1/2 NC*H*$_2$Ph, *J* = 16.5 Hz.), 6.15 (d, 1H, $CHNO_2$, *J* = 10.4 Hz.), 6.85 (s, 1H, Im'-H5), 7.02-7.10 (m, 7H, Ar and Im'-H2), 7.35 (br s, 14H, Ar), 7.51 (s, 1H, Im-H2); ^{13}C-NMR ($CDCl_3$): δ 29.6 ($ImCH_2CH$), 32.8 ($ImCH_2N$), 37.6 (*C*HIm'), 48.9 (NCH_2Ph), 53.3 ($COOCH_3$), 68.4 (*C*HCOOCH$_3$), 75.6 ($NCPh_3$), 87.4 (CH_2NO_2), 119.9 (Im-C5), 120.9 (Im'-C5), 126.7 (Im-C4 and Im'-C4)), 128.2 (Ar), 128.5 (Ar), 129.2 (Ar), 129.6 (Ar), 131.1 (Ar), 133.1 (Ar), 134.6 (Ar), 138.1 (Im-C2), 139.4 (Im'-C2), 165.0 (N*C*OCH), 169.2 (*C*OOCH$_3$); MS (EI): *m/z* 435 (1%), 345 (11), 243 (100), 165 (72), 91 (40).

Crystal Data of Compound **9b**.

$C_{24}H_{22}N_4O_5$, M = 446.46, triclinic, space group P-1. a = 9.068(2) Å, b = 11.615(2) Å, c = 11.774(2) Å, α = 107.36(3)°, β = 100.35(3)°, δ = 106.63(3)°. V = 1085.4(4) Å^3, Z = 2, D_c = 1.366 Mg/m^3, m = (Cu-K$_\alpha$) = 0.098, F(000) = 468. (3579 col-

lected reflections and 1019 observed reflections [I > 2 σ (I)]). Final values were R_1 = 0.1099, wR_2 = 0.2444.

4-(2'-Nitrovinyl)-1-trityl-1*H*-imidazol (**5b**).

A mixture of 1-trityl-1*H*-imidazol-4-carboxaldehyde [15] (12.01 g, 35.48 mmol), nitromethane (35.5 ml, 656.82 mmol), glacial acetic acid (10.6 ml) and ammonium acetate (5.41 g) was sonicated at 22 °C for 6 h. After removal of the solvent, the residue was dissolved into CH_2Cl_2 and washed with saturated aqueous sodium chloride. The organic layer was dried over Na_2SO_4, filtered and evaporated until dryness. The residue was purified by recrystallization from THF to give **5b** (7.07 g, 52%) as a pale yellow solid, m.p. 228-229 °C; IR ν cm^{-1}: 1640, 1490; ^{1}H-NMR ($CDCl_3$): δ 7.10-7.14 (m, 6H, Ar), 7.26 (s, 1H, Im-H5), 7.38 (sa, 9H, Ar), 7.52 (s, 1H, Im-H2), 7.75 (d, 1H, *J* 12.1, C*H*=CHNO$_2$), 7.83 (s, 1H, CH=C*H*NO$_2$, *J* = 12.1 Hz.); ^{13}C-NMR ($CDCl_3$) δ 75.4 (N*C*Ph$_3$), 126.6 (Im-C5), 127.5 (Im-C4), 127.7 (Ar), 128.2 (Ar), 128.5 (Ar), 129.1 (Ar), 132.5 (Ar), 132.6 (Ar), 134.5 (Im-C2), 141.1 (*C*H=CHNO$_2$), 141.6 (CH=*C*HNO$_2$).

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