Supporting Information

Further Studies on Imidazo[4,5-*b*]pyridine AT_1 Angiotensin II Receptor Antagonists. Effects of the Transformation of the 4-Phenylquinoline Backbone into 4-Phenylisoquinolinone or 1-Phenylindene Scaffolds

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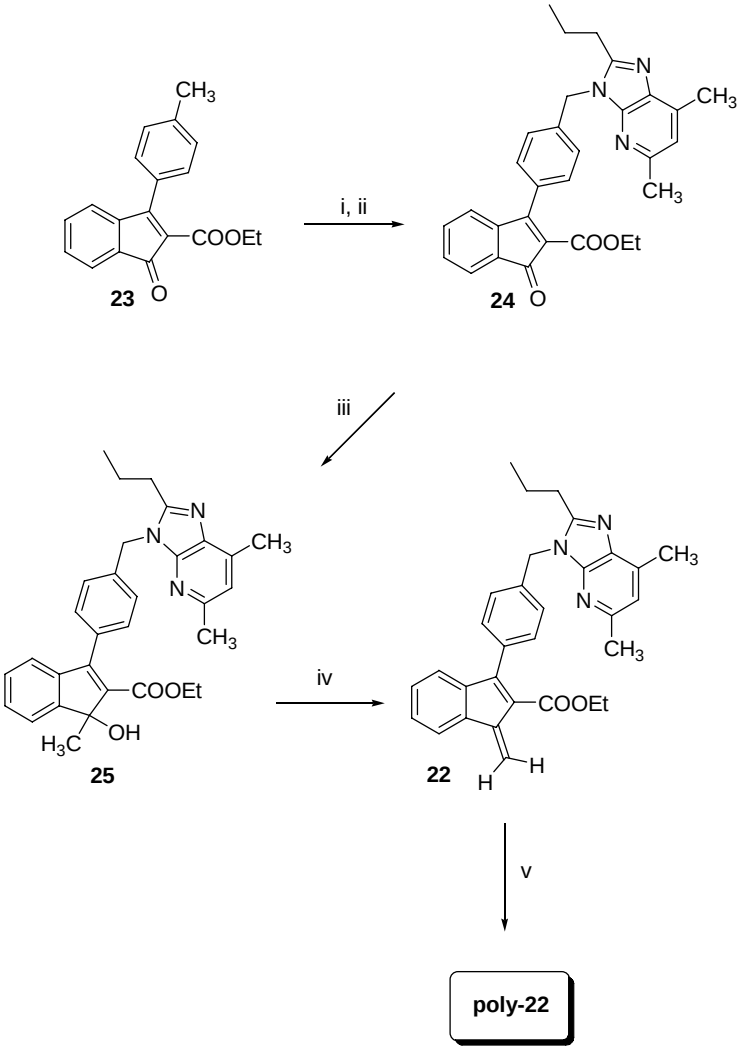
Contents: Synthesis of compound **22** (ethyl ester of acid **6c**).

Experimental details for the synthesis and the characterization of compounds **5**, **6**, **17**, **19**, **20**, **21**, **22**, their intermediates, and poly-**6c** (chemistry, NMR, MS, analytical data).

In order to understand the structural determinants responsible for the behaviour of benzofulvene derivative **6c** (which was stable as a pure crystalline solid, but polymerized spontaneously when the mixture of the dehydration reaction of **6e** was concentrated without the elimination of PTSA), the corresponding ethyl ester **22** was synthesized following the procedure described in Scheme 1SI.

Scheme 1SI



Reagents: (i) NBS, dibenzoyl peroxide, CCl_4; (ii) 5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine, NaH, DMF; (iii) $Al(CH_3)_3$, CH_2Cl_2; (iv) PTSA, $CDCl_3$; (v) solvent removal.

Ethyl ester **22** showed a spontaneous polymerization similar to that shown by **BF1** and this result suggested a key role for the contemporary presence of the 5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine moiety and COOH group in **6c** molecule.

Experimental Section

Chemistry

All chemicals used were of reagent grade. Yields refer to purified products and are not optimized. Melting points were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. Microanalyses were carried out by means of a Perkin-Elmer 240C or a Perkin-Elmer Series II CHNS/O Analyzer 2400. Merck silica gel 60 (230-400 mesh) was used for column chromatography. Merck TLC plates, silica gel 60 F_{254} were used for TLC. ^{1}H-NMR spectra were recorded with a Bruker AC 200 spectrometer in the indicated solvents (TMS as internal standard): the values of the chemical shifts are expressed in ppm and the coupling constants (*J*) in Hz. Mass spectra were recorded on either a Varian Saturn 3 spectrometer or a ThermoFinnigan LCQ-Deca.

General Procedure for the Preparation of Compounds 11a-f, 15a,b and 24 (Radical Bromination-Coupling Procedure).

A mixture of the toluene derivative **10, 13, 14,** and **23** in 40 mL of CCl_4 with *N*-bromosuccinimide (1.02 equivalents) and dibenzoyl peroxide (0.1 equivalents) was refluxed for a suitable time (typically 2-3 h), and the reaction progress was monitored by TLC. The initial solvent volume was reduced by half under reduced pressure, the insoluble succinimide was filtered-off, and the resulting mixture was evaporated under reduced pressure. The residue was dissolved into anhydrous DMF (10 mL) and added to a mixture (aged at 0 °C for 20 min) of the appropriate 2-alkyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine[1] (1.0 equivalent) in anhydrous DMF (10 mL) with NaH (1.0 equivalent). The resulting mixture was stirred at room temperature for 15-18 h under argon and the reaction was quenched with ice-water (5 mL). The bulk of the DMF was evaporated under reduced

pressure, and the residue was diluted with water (20 mL) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography with ethyl acetate-petroleum ether (7:3) (or ethyl acetate) as the eluent gave pure compounds **11a-f, 15a,b**, and **24**.

Ethyl 1,2-Dihydro-4-[4-[(5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-1-oxo-3-isoquinolinecarboxylate (11b).

The title compound was prepared in 36% yield (0.33 g, mp 152-155 °C) starting from **10** (0.60 g, 1.87 mmol) and 5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (0.33 g, 1.9 mmol) according to the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 0.87 (t, *J* = 7.1, 3H), 1.34 (t, *J* = 7.6, 3H), 2.59 (s, 3H), 2.63 (s, 3H), 2.84 (q, *J* = 7.6, 2H), 3.57 (s, 3H), 3.97 (q, *J* = 7.1, 2H), 5.51 (s, 2H), 6.90 (s, 1H), 7.18-7.27 (m, 5H), 7.47-7.56 (m, 2H), 8.45-8.50 (m, 1H). MS(ESI) m/z 495 ($M + H^+$).

Ethyl 1,2-Dihydro-4-[4-[(5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-1-oxo-3-isoquinolinecarboxylate (11d).

The title compound was prepared in 32% yield (0.10 g) starting from **10** (0.20 g, 0.62 mmol) and 5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine (0.12 g, 0.63 mmol) according to the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 0.86 (t, *J* = 7.3, 3H), 0.97 (t, *J* = 7.3, 3H), 1.68-1.85 (m, 2H), 2.57 (s, 3H), 2.61 (s, 3H), 2.79 (t, *J* = 7.6, 2H), 3.56 (s, 3H), 3.96 (q, *J* = 7.3, 2H), 5.50 (s, 2H), 6.88 (s, 1H), 7.17-7.26 (m, 5H), 7.47-7.51 (m, 2H), 8.43-8.48 (m, 1H).

Ethyl 1,2-Dihydro-4-[4-[(2-butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-1-oxo-3-isoquinolinecarboxylate (11f).

The title compound was prepared in 34% yield (0.14 g) starting from **10** (0.25 g, 0.78 mmol) and 2-butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (0.16 g, 0.79 mmol) according to the general

procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 0.86-0.96 (m, 6H), 1.32-1.51 (m, 2H), 1.67-1.82 (m, 2H), 2.60 (s, 3H), 2.64 (s, 3H), 2.81 (t, *J* = 7.9, 2H), 3.59 (s, 3H), 3.99 (q, *J* = 7.2, 2H), 5.52 (s, 2H), 6.91 (s, 1H), 6.90-7.14 (m, 1H), 7.19-7.25 (m, 4H), 7.50-7.54 (m, 2H), 8.47-8.51 (m, 1H). MS(ESI) m/z 523 ($M + H^+$).

4-[4-[(5,7-Dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-1(2*H*)-isoquinolinone (11a).

The title compound was prepared in 45% yield (0.070 g, mp 174-180 °C) starting from **13** (0.12 g, 0.21 mmol) and 5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (0.040 g, 0.23 mmol) according to the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 1.25 (t, *J* = 7.6, 3H), 2.58 (s, 3H), 2.66 (s, 3H), 2.71 (q, *J* = 7.6, 2H), 3.30 (s, 3H), 5.42 (s, 2H), 6.88-6.93 (m, 7H), 7.04-7.15 (m, 4H), 7.21-7.34 (m, 10H), 7.51-7.56 (m, 2H), 8.49-8.58 (m, 1H). MS(ESI) m/z 733 ($M + H^+$).

4-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-1(2*H*)-isoquinolinone (11c).

The title compound was prepared in 41% yield (0.065 g, mp 170-174 °C) starting from **13** (0.12 g, 0.21 mmol) and 5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine (0.04 g, 0.21 mmol) according to the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 0.90 (t, *J* = 7.3, 3H), 1.57-1.73 (m, 2H), 2.58 (s, 3H), 2.64-2.71 (m, 5H), 3.29 (s, 3H), 5.42 (s, 2H), 6.88-6.91 (m, 7H), 7.04-7.14 (m, 4H), 7.21-7.37 (m, 10H), 7.51-7.55 (m, 2H), 8.50-8.57 (m, 1H). MS(ESI) m/z 747 ($M + H^+$).

4-[4-[(2-Butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-1(2*H*)-isoquinolinone (11e).

The title compound was prepared in 74% yield (0.13 g, mp 160-162 °C) starting from **13** (0.13 g, 0.23 mmol) and 5,7-dimethyl-2-butyl-3*H*-imidazo[4,5-*b*]pyridine (0.050 g, 0.25 mmol) according to

the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 0.86 (t, *J* = 7.1, 3H), 1.21-1.41 (m, 2H), 1.54-1.70 (m, 2H), 2.58 (s, 3H), 2.64 (s, 3H), 2.70 (t, *J* = 7.6, 2H), 3.29 (s, 3H), 5.41 (s, 2H), 6.88-6.91 (m, 7H), 7.04-7.14 (m, 4H), 7.22-7.38 (m, 10H), 7.50-7.57 (m, 2H), 8.50-8.55 (m, 1H). MS(ESI) m/z 761 ($M + H^+$).

***tert*-Butyl 3-[4-[(5,7-Dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxo-1*H*-indene-2-carboxylate (15a).**

The title compound was prepared in 33% yield (0.10 g of yellow solid melting at 119-123 °C) starting from **14** (0.20 g, 0.62 mmol) and 5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (0.11 g, 0.63 mmol) according to the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 1.32 (t, *J* = 7.4, 3H), 1.29 (s, 9H), 2.56 (s, 3H), 2.61 (s, 3H), 2.78 (q, *J* = 7.4, 2H), 5.51 (s, 2H), 6.88 (s, 1H), 7.04 (m, 1H), 7.23 (d, *J* = 8.1, 2H), 7.33 (m, 2H), 7.41 (d, *J* = 8.1, 2H), 7.53 (m, 1H). MS(ESI) m/z 494 ($M + H^+$).

***tert*-Butyl 3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxo-1*H*-indene-2-carboxylate (15b).**

The title compound was prepared in 46% yield (0.80 g of yellow glassy solid) starting from **14** (1.1 g, 3.4 mmol) and 5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine (0.67 g, 3.5 mmol) according to the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 0.97 (t, *J* = 7.4, 3H), 1.31 (s, 9H), 1.69-1.88 (m, 2H), 2.58 (s, 3H), 2.62 (s, 3H), 2.77 (t, *J* = 7.7, 2H), 5.53 (s, 2H), 6.90 (s, 1H), 7.06 (m, 1H), 7.24 (d, *J* = 8.3, 2H), 7.34 (m, 2H), 7.42 (d, *J* = 8.3, 2H), 7.53 (m, 1H). MS(ESI) m/z 508 ($M + H^+$).

Ethyl 3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxo-1*H*-indene-2-carboxylate (24).

The title compound was prepared in 36% yield (0.87 g of yellow glassy solid) starting from **23**[2] (1.5 g, 5.1 mmol) and 5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridine (0.97 g, 5.1 mmol) according to the general procedure for the radical bromination and coupling. ^{1}H-NMR ($CDCl_3$): 0.96 (t, *J* = 7.4, 3H), 1.13 (t, *J* = 7.3, 3H), 1.69-1.88 (m, 2H), 2.57 (s, 3H), 2.62 (s, 3H), 2.77 (t, *J* = 7.6, 2H), 4.12 (q, *J* = 7.6, 2H), 5.52 (s, 2H), 6.89 (s, 1H), 7.07-7.14 (m, 1H), 7.24 (d, *J* = 8.0, 2H), 7.32-7.49 (m, 4H), 7.52-7.58 (m, 1H). MS(ESI): m/z 480 ($M + H^+$)

Preparation of Target Carboxylic Acid Derivatives 5b,d,f (Basic Hydrolysis).

To a solution of the appropriate ester (**11b,d,f**) (0.2-0.6 mmol) in ethanol (20 mL) 2N NaOH (2.0 mL) was added and the resulting mixture was refluxed while the reaction progress was monitored by TLC. When the ester derivative disappeared from the chromatogram, the reaction mixture was evaporated under reduced pressure, diluted with water (20 mL) and the pH was adjusted to 5-6 by addition of 1N HCl. The precipitate was collected by filtration (or extracted with chloroform when necessary), washed with water and dried under reduced pressure. Purification of the solid obtained by washing with ethyl acetate or diethyl ether gave the pure target carboxylic acid derivatives.

1,2-Dihydro-4-[4-[(5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-1-oxo-3-isoquinolinecarboxylic Acid (5b).

This compound was prepared in 83% yield (0.22 g, white solid, mp > 300 °C) starting from the ethyl ester **11b** (0.28 g, 0.57 mmol) according to the general procedure for basic hydrolysis. ^{1}H-NMR ($CDCl_3$): 1.38 (t, *J* = 7.6, 3H), 2.61 (s, 6H), 2.88 (q, *J* = 7.6, 2H), 3.69 (s, 3H), 5.46 (s, 2H), 6.88 (s, 1H), 7.05 (d, *J* = 8.1, 1H), 7.19 (d, *J* = 8.1, 2H), 7.32-7.47 (m, 4H), 8.42-8.45 (m, 1H). MS(ESI negative ions) m/z 465 ($M - H^+$). Anal. ($C_{28}H_{26}N_4O_3 \cdot H_2O$) C,H,N.

1,2-Dihydro-4-[4-[(5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-1-oxo-3-isoquinolinecarboxylic Acid (5d).

This compound was prepared in 83% yield (0.080 g, mp > 300 °C) starting from the ethyl ester **11d** (0.10 g, 0.20 mmol) according to the general procedure for basic hydrolysis. ^{1}H-NMR ($CDCl_3$): 0.91 (t, *J* = 7.5, 3H), 1.74-1.89 (m, 2H), 2.59 (s, 6H), 2.83 (t, *J* = 7.7, 2H), 3.70 (s, 3H), 5.47 (s, 2H), 6.88 (s, 1H), 7.05 (d, *J* = 7.7, 1H), 7.19 (d, *J* = 8.1, 2H), 7.32-7.47 (m, 4H), 8.42-8.45 (m, 1H). MS(ESI negative ions) m/z 479 (M - H^+). Anal. ($C_{29}H_{28}N_4O_3 \cdot 0.5\ H_2O$) C,H,N.

1,2-Dihydro-4-[4-[(2-butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-1-oxo-3-isoquinolinecarboxylic Acid (5f).

This compound was prepared in 79% yield (0.090 g, mp 292-295 °C) starting from the ethyl ester 11f (0.12 g, 0.23 mmol) according to the general procedure for the basic hydrolysis. ^{1}H-NMR ($CDCl_3$): 0.70 (t, *J* = 7.1, 3H), 1.03-1.14 (m, 2H), 1.32-1.40 (m, 2H), 2.58-2.69 (m, 8H), 3.74 (s, 3H), 5.53 (s, 2H), 7.00 (s, 1H), 7.08-7.12 (m, 1H), 7.22 (d, *J* = 8.0, 2H), 7.41-7.55 (m, 4H), 8.48-8.52 (m, 1H). MS(ESI negative ions) m/z 493 (M - H^+). Anal. ($C_{30}H_{30}N_4O_3 \cdot 0.5\ H_2O$) C,H,N.

Preparation of Target Tetrazole Derivatives 5a,c,e (Deprotection of the Trityl-Protected Tetrazole Derivatives). A mixture of the appropriate trityl-protected tetrazole derivative (0.4-0.6 mmol) with formic acid (15 mL) was stirred at room temperature under argon for a suitable time (18-48 h), and the reaction progress was monitored by TLC. When the trityl-protected tetrazole derivative disappeared from the chromatogram, the reaction mixture was evaporated under reduced pressure. Purification of the residue by washing with diethyl ether or ethyl acetate gave the pure target compounds.

4-[4-[(5,7-Dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-3-(2*H*-tetrazol-5-yl)-1(2*H*)-isoquinolinone (5a).

This compound was prepared in 68% yield (0.020 g of white solid melting at 194-198 °C) starting from the protected tetrazolyl derivate **11a** (0.044 g, 0.060 mmol) according to the general procedure for acid hydrolysis. ^{1}H-NMR ($CDCl_3$): 0.95 (br t, 3H), 2.59 (s, 3H), 2.63 (s, 3H), 2.85 (br q, 2H),

3.30 (s, 3H), 3.98 (br s, H^+ + H_2O), 5.52 (s, 2H), 7.02-7.06 (m, 3H), 7.13-7.20 (m, 3H), 7.53-7.57 (m, 2H), 8.52-8.57 (m, 1H). MS(ESI) m/z 491 (M + H^+). Anal. ($C_{28}H_{26}N_8O$·2 H_2O) C,H,N.

4-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-3-(2*H*-tetrazol-5-yl)-1(2*H*)-isoquinolinone (5c).

This compound was prepared in 73% yield (0.022 g of white solid melting at 174-179 °C) starting from the protected tetrazolyl derivate **11c** (0.045 g, 0.060 mmol) according to the general procedure for acid hydrolysis. ^{1}H-NMR ($CDCl_3$): 0.77 (br t, 3H), 1.40-1.60 (br m, 2H), 2.64 (s, 6H), 2.86 (br t, 2H), 3.29 (s, 3H), 3.50 (br s, H^+ + H_2O), 5.53 (s, 2H), 7.02-7.28 (m, 6H), 7.49-7.75 (m, 2H), 8.49-8.64 (m, 1H). MS(ESI) m/z 505 (M + H^+). Anal. ($C_{29}H_{28}N_8O$·H_2O) C,H,N.

4-[4-[(2-Butyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-2-methyl-3-(2*H*-tetrazol-5-yl)-1(2*H*)-isoquinolinone (5e).

This compound was prepared in 98% yield (0.023 g of white solid melting at 169-173 °C) starting from the protected tetrazolyl derivate **11e** (0.034 g, 0.045 mmol) according to the general procedure for acid hydrolysis. ^{1}H-NMR ($CDCl_3$, TEA): 0.88 (t, *J* = 7.2, 3H), 1.30-1.41 (m, 2H), 1.56-1.71 (m, 2H), 2.55 (s, 3H), 2.59 (s, 3H), 2.75 (t, *J* = 7.3, 2H), 3.28 (s, 3H), 4.30 (br s, H^+ + H_2O), 5.33 (s, 2H), 6.86 (s, 1H), 6.96 (d, *J* = 7.9, 2H), 7.08-7.15 (m, 3H), 7.45-7.49 (m, 2H), 8.49-8.54 (m, 1H). MS(ESI) m/z 519 (M + H^+). Anal. ($C_{30}H_{30}N_8O$·0.5 H_2O) C,H,N.

Preparation of Target Carboxylic Acid Derivatives 6a,b,e,f (Acid Hydrolysis).

A mixture of the suitable ester (0.1-0.39 mmol) with formic acid (15 mL) was stirred at room temperature under argon for a suitable time (typically 18h), and the reaction progress was monitored by TLC. When the ester disappeared from the chromatogram, the reaction mixture was evaporated under reduced pressure. Purification of the residue by washing with diethyl ether gave the pure target compounds.

3-[4-[(5,7-Dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxo-1*H*-indene-2-carboxylic Acid (6a).

This compound was prepared in 80% yield (0.035 g of yellow solid melting at 197-198 °C) starting from the *t*-butyl ester **15a** (0.050 g, 0.10 mmol) according to the general procedure for acid hydrolysis. ^{1}H-NMR ($CDCl_3$): 1.31 (t, *J* = 7.5, 3H), 2.58 (s, 3H), 2.62 (s, 3H), 2.71 (q, *J* = 7.5, 2H), 5.53 (s, 2H), 6.90 (s, 1H), 7.16 (m, 1H), 7.26 (d, *J* = 8.4, 2H), 7.44 (m, 2H), 7.60 (m, 3H). MS(ESI negative ions) m/z 436 (M - H^+). Anal. ($C_{27}H_{23}N_3O_3 \cdot 0.33\ H_2O$) C,H,N.

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxo-1*H*-indene-2-carboxylic Acid (6b).

This compound was prepared in 91% yield (0.16 g of yellow solid melting at 209-213 °C) starting from the *t*-butyl ester **15b** (0.20 g, 0.39 mmol) according to the general procedure for acid hydrolysis. ^{1}H-NMR ($CDCl_3$): 0.94 (t, *J* = 7.3, 3H), 1.66-1.85 (m, 2H), 2.58 (s, 3H), 2.62 (s, 3H), 2.78 (t, *J* = 7.7, 2H), 5.54 (s, 2H), 6.90 (s, 1H), 7.17 (m, 1H), 7.26 (d, *J* = 8.4, 2H), 7.44 (m, 2H), 7.61 (m, 3H). MS(ESI negative ions) m/z 450 (M - H^+). Anal. ($C_{28}H_{25}N_3O_3 \cdot 0.5\ H_2O$) C,H,N.

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-hydroxy-1-methyl-1*H*-indene-2-carboxylic Acid (6e).

This compound was prepared from the *t*-butyl ester **16e** (0.15 g, 0.29 mmol) according to the general procedure for acid hydrolysis (reaction time 45 min) and was purified by washing with ether to give 0.045 g (yield 33%) of **6e** as a white solid (mp 246-247 °C). ^{1}H-NMR (DMSO-d_6): 0.88 (t, *J* = 7.3, 3H), 1.58-1.70 (m, 5H), 2.49 (s, 6H), 2.74 (t, *J* = 7.5, 2H), 5.27 (br s, 1H), 5.50 (s, 2H), 6.96 (m, 2H), 7.13-7.38 (m, 6H), 7.47 (d, *J* = 7.2, 1H), 12.20 (br s, 1H). MS (ESI): *m/z* 468 (M + H^+). Anal. ($C_{29}H_{29}N_3O_3 \cdot 0.33\ H_2O$) C,H,N.

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-ethyl-1-hydroxy -1*H*-indene-2-carboxylic Acid (6f).

This compound was prepared from the *t*-butyl ester **16f** (0.030 g, 0.056 mmol) according to the general procedure for acid hydrolysis (reaction time 45 min) and was purified by washing with

ether to obtain 0.011 g, mp 232-234 °C (yield 41%). ^{1}H-NMR (DMSO-d_6): 0.41 (t, *J* = 7.3, 3H), 0.88 (t, *J* = 7.3, 3H), 1.58-1.77 (m, 2H), 1.98-2.07 (m, 1H), 2.28-2.38 (m, 1H), 2.49 (s, 6H), 2.74 (t, *J* = 7.6, 2H), 5.50 (s, 2H), 6.94 (m, 2H), 7.15-7.43 (m, 7H), 12.10 (br s, 1H). MS (ESI negative ions): *m/z* 480 ($M - H^+$). Anal. ($C_{30}H_{31}N_3O_3 \cdot 1.5\ H_2O$) C,H,N.

4-(4-Methylphenyl)-1-oxo-1H-isochromene-3-carboxylic Acid (8).

To a solution of 2-(*p*-toluoyl)benzoic acid **7** (4.0 g, 16.6 mmol) in acetone (100 mL) and DMF (4 mL) diethyl bromomalonate (3.1 mL, 18.3 mmol) and finely grounded potassium carbonate (2.3 g, 16.6 mmol) were added. The resulting mixture was stirred overnight at room temperature under nitrogen. After evaporation of the solvent, the residue was diluted with ethyl acetate, washed with water, dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was diluted with hydrochloric acid (50 mL) and acetic acid (50 mL) and the resulting mixture was heated overnight at 80°C. After the evaporation of the solvent, the residue was partitioned between ethyl acetate and water and the organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a crude product which was recrystallized from diethyl ether to obtain 2.7 g of **8** as white crystals (yield 58%, mp 211-214 °C, literature[3] 210 °C). ^{1}H-NMR ($CDCl_3$): 2.45 (s, 3H), 5.85 (br s, 1H), 7.10-7.19 (m, 3H), 7.28 (d, *J* = 8.0, 2H), 7.61-7.72 (m, 2H), 8.38-8.43 (m, 1H). MS(ESI negative ions) m/z 279 ($M - H^+$).

1,2-Dihydro-4-(4-methylphenyl)-2-methyl-1-oxo-3-isoquinolinecarboxylic Acid (9).

To an ice-cooled mixture of **8** (2.2 g, 7.9 mmol) in ethanol (35 mL) a 33% solution of methylamine (6.8 mL, 55 mmol) in ethanol was added. After stirring at room temperature for 2 h, the solvent was removed under reduced pressure and the residue was diluted with water (5 mL), treated with ethyl acetate and the aqueous layer was then acidified with concentrated hydrochloric acid. The precipitate was collected by filtration, washed with water and dried to obtain a white solid. A suspension of this solid in ethanol (40 mL) and sulfuric acid (1.5 mL) was refluxed for 3 h. The

solvent was then removed under reduced pressure and the residue was diluted with cold water. The solid obtained was collected by filtration, washed with cold water and dried to obtain **9** as a white solid (2.0 g, yield 86%, mp 286-288 °C). ^{1}H-NMR ($CDCl_3$): 2.35 (s, 3H), 3.49 (s, 3H), 7.09 (d, *J* = 7.8, 1H), 7.18 (d, *J* = 7.9, 2H), 7.26 (d, *J* = 7.9, 2H), 7.51-7.68 (m, 2H), 8.29 (d, *J* = 7.8, 1H). MS(ESI negative ions) m/z 292 ($M - H^+$).

Ethyl 1,2-Dihydro-4-(4-methylphenyl)-2-methyl-1-oxo-3-isoquinolinecarboxylate (10).

To an ice-cooled mixture of **9** (1.2 g, 4.1 mmol) in CH_2Cl_2 thionyl chloride (2 mL) was added, the resulting mixture was refluxed for 20 min, cooled to room temperature and concentrated under reduced pressure (thionyl chloride was azeotropically removed with toluene) to give a solid residue. A mixture of the solid in ethanol (25 mL) with triethylamine (1.0 mL) was refluxed for 2 h. After the evaporation of the solvent, the residue was diluted with CH_2Cl_2, washed with water, dried over sodium sulfate and concentrated under reduced pressure to give a pink crude product. Purification of the residue by flash chromatography with *n*-hexane-ethyl acetate (65:35) as the eluent gave 0.51 g of **10** as a white solid (yield 39%, mp 119-121 °C). ^{1}H-NMR ($CDCl_3$): 0.94 (t, *J* = 7.0, 3H), 2.40 (s, 3H), 3.59 (s, 3H), 4.03 (q, *J* = 7.0, 2H), 7.16-7.25 (m, 5H), 7.47-7.57 (m, 2H), 8.46-8.51 (m, 1H). MS(ESI) m/z 322 ($M + H^+$).

2-Methyl-4-(4-methylphenyl)-3-cyano-1(2*H*)-isoquinolinone (12).

A mixture of 2-(*p*-toluoyl)benzoic acid **7** (2.4 g, 10 mmol) in CH_2Cl_2 (50 mL) with thionyl chloride (2.1 mL, 30 mmol) and a catalytic amount of DMF (0.1 mL) was stirred at room temperature for 5 h. After the evaporation of the solvent, the residue was diluted with CH_2Cl_2 (45 mL) and to the resulting mixture triethylamine (3.0 mL, 22 mmol) and (methylamino)acetonitrile hydrochloride (1.2 g, 11.4 mmol) were added. The reaction mixture was stirred overnight at room temperature, the solvent was removed and the residue was partitioned between ethyl acetate and water. The organic layer was washed with 1N HCl, then with water, with a saturated $NaHCO_3$ solution and finally

again with water. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain a yellow oil. A mixture of the oil in toluene (40 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 mL, 10 mmol) was refluxed for 3 h while water was azeotropically removed using a Dean-Stark apparatus. The mixture was cooled to room temperature, the solvent was removed, the residue was diluted with ethyl acetate and washed first with water, than with 1N HCl, water, saturated $NaHCO_3$ solution and finally again with water. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a crude product which was recrystallized from ethyl acetate to give 0.95 g of **12** as a white crystalline solid (yield 35%, mp 260-263 °C). ^{1}H-NMR ($CDCl_3$): 2.46 (s, 3H), 3.83 (s, 3H), 7.27-7.39 (m, 5H), 7.59-7.68 (m, 2H), 8.51-8.55 (m, 1H). MS(ESI) m/z 275 ($M + H^+$).

2-Methyl-4-(4-methylphenyl)-3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-1(2*H*)-isoquinolinone (13).

To a mixture of **12** (0.40 g, 1.46 mmol) in anhydrous xylene (30 mL) azidotrimethyltin (0.60 g, 2.9 mmol) was added. The reaction mixture was heated overnight under reflux, cooled to room temperature and the precipitate was collected by filtration, washed with boiling toluene and dried under reduced pressure. To a mixture of the white solid obtained in THF (30 mL) water (0.5 mL) and sodium hydroxide (64 mg, 1.6 mmol) were added and after stirring for 45 min at room temperature triphenylmethyl chloride (0.60 g, 2.1 mmol) was added. After 10 min the reaction mixture was diluted with water, extracted with dichloromethane and the combined extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography with *n*-hexane-ethyl acetate (3:7) as the eluent to give **13** as a white solid (0.64 g, yield 78%, mp 175-177 °C). ^{1}H-NMR ($CDCl_3$): 2.33 (s, 3H), 3.31 (s, 3H), 6.87-6.90 (m, 6H), 7.06 (s, 4H), 7.20-7.38 (m, 10H), 7.52-7.56 (m, 2H), 8.52-8.59 (m, 1H). MS(ESI) m/z 582 ($M + Na^+$).

***tert*-Butyl 3-(4-Methylphenyl)-1-oxo-1*H*-indene-2-carboxylate (14).**

To a mixture of magnesium turnings (0.41 g, 16.8 mmol) in absolute ethanol (0.5 mL) and carbon tetrachloride (0.1 mL) fresh distilled diethyl ether (10 mL) was added and after stirring at room temperature for 10 min, the mixture was heated to reflux. Then, a solution of di-*tert*-butyl malonate (3.7 mL, 16.6. mmol) in freshly distilled diethyl ether (10 mL) and absolute ethanol (2 mL) was added dropwise. After the resulting mixture was stirred under reflux for 3 h, a mixture of the 2-(*p*-toluoyl)benzoic acid chloride (4.3 g, 16.6 mmol) in freshly distilled diethyl ether (10 mL) was added; the resulting mixture was refluxed for 1 h and cooled to room temperature. [The 2-(*p*-toluoyl)benzoic acid chloride was prepared from a mixture of 2-(*p*-toluoyl)benzoic acid **7** (4.0 g, 16.6 mmol) in CH_2Cl_2 (15 mL) with thionyl chloride (6 mL, 82 mmol) and DMF (0.13 mL, 1.7 mmol) stirred at room temperature for 5 h and concentrated under reduced pressure (thionyl chloride was azeotropically removed with toluene). The reaction mixture was then cooled to 0-5 °C and cold 30% H_2SO_4 was added. The organic layer was separated, washed with water, dried over sodium sulfate, and evaporated under reduced pressure to obtain an oil residue. To a solution of the oil in ethanol (80 mL) anhydrous sodium carbonate (4.0 g, 38 mmol) and water (30 mL) were added and the resulting mixture was refluxed for 30 min. The solvent was removed under reduced pressure, the residue was diluted with water and acidified with 1N HCl. The precipitate was extracted with dichloromethane and the combined extracts were dried over sodium sulfate and concentrated under reduced pressure. The orange oil obtained was purified by recrystallization from diethyl ether at – 18 °C to give **14**[4] as yellow crystals (2.9 g, yield 54%, mp 104-107 °C). ^{1}H-NMR ($CDCl_3$): 1.37 (s, 9H), 2.43 (s, 3H), 7.17 (m, 1H), 7.29 (d, J = 8.2, 2H), 7.36 (m, 2H), 7.41 (d, J = 8.2, 2H), 7.55 (m, 1H). MS(ESI) m/z 343 ($M + Na^+$).

General Procedure for the Preparation of Indenol Derivatives 16e,f and 25.

To a solution of the suitable indenone derivative (**15a,b** and **24**) in dichloromethane a 2M trimethylaluminum solution in THF (2.5 equivalent) was added and the resulting mixture was

stirred at room temperature under argon for 1 h. The trimethylaluminum excess was cautiously (at 0-5 °C) decomposed with a 7.5 N NaOH solution and the hydroxide precipitated was removed by filtration. The filtrate was dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by flash chromatography with n-hexane-ethyl acetate (4:6) (or ethyl acetate in the case of **25**) as the eluent gave the expected indenol derivative (**16e,f, 25**).

***tert*-Butyl 3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-hydroxy-1-methyl-1*H*-indene-2-carboxylate (16e).**

The title compound was prepared in 59% yield (0.34 g of white solid melting at 131-132 °C) starting from **15b** (0.56 g, 1.1 mmol) according to the general procedure for the synthesis of indenol derivatives. ^{1}H-NMR ($CDCl_3$): 0.98 (t, *J* = 7.3, 3H), 1.24 (s, 9H), 1.65-1.88 (m, 5H), 2.58 (s, 3H), 2.62 (s, 3H), 2.76 (t, *J* = 7.8, 2H), 3.76 (s, 1H), 5.51 (s, 2H), 6.89 (s, 1H), 7.01 (d, *J* = 7.4, 1H), 7.16-7.39 (m, 6H), 7.53 (d, *J* = 7.2, 1H). MS(ESI) m/z 524 ($M + H^+$).

***tert*-Butyl 3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-ethyl-1-hydroxy-1*H*-indene-2-carboxylate (16f).**

The title compound was prepared in 26% yield (0.040 g of colourless oil) starting from **15b** (0.15 g, 0.29 mmol) according to the general procedure for the synthesis of indenol derivatives. ^{1}H-NMR ($CDCl_3$): 0.62 (t, *J* = 7.4, 3H), 0.99 (t, *J* = 7.3, 3H), 1.22 (s, 9H), 1.81 (m, 2H), 2.20 (q, *J* = 7.4, 2H), 2.58 (s, 3H), 2.63 (s, 3H), 2.76 (t, *J* = 7.8, 2H), 3.79 (s, 1H), 5.51 (s, 2H), 6.88 (s, 1H), 7.00 (d, *J* = 7.3, 1H), 7.15-7.38 (m, 6H), 7.49 (d, *J* = 7.3, 1H).

Ethyl 3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-hydroxy-1-methyl-1*H*-indene-2-carboxylate (25).

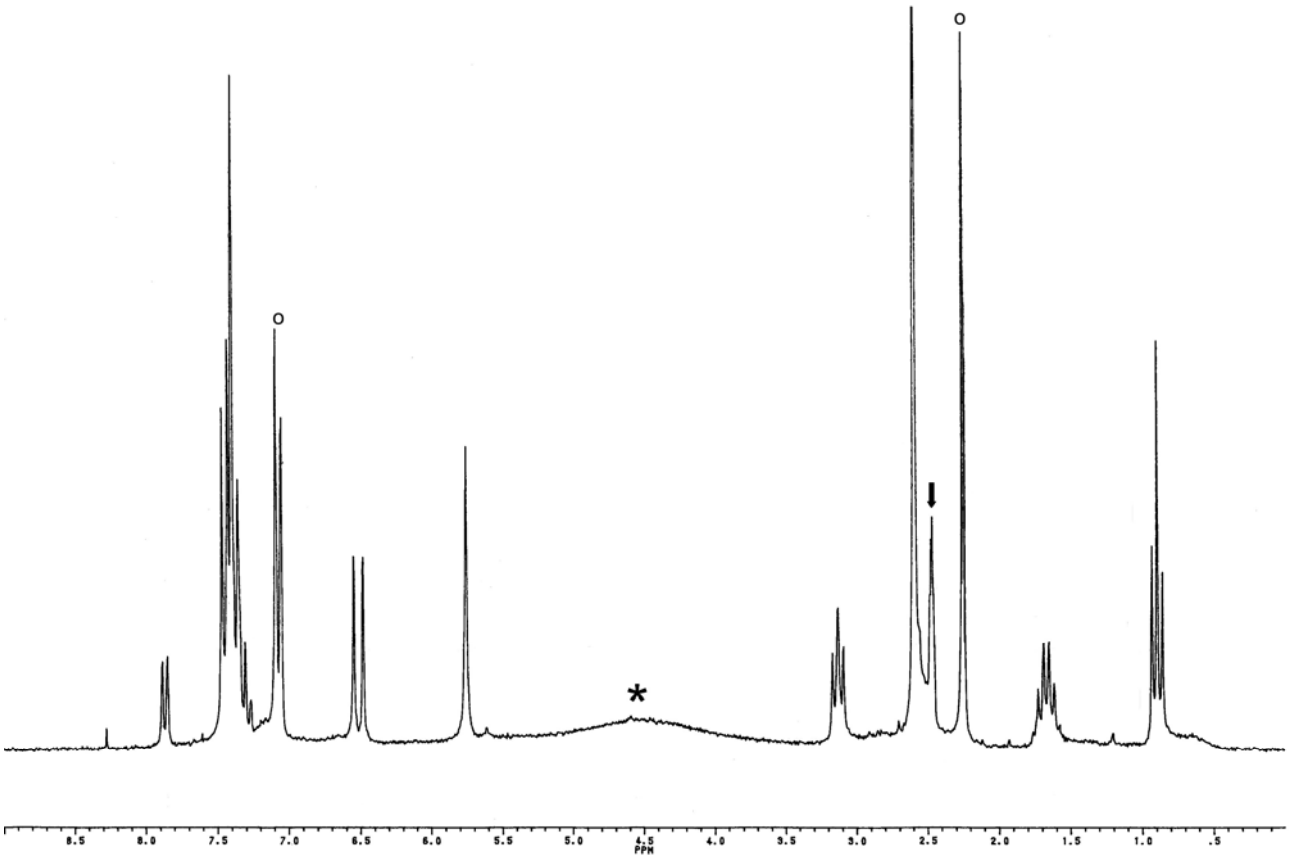
Title compound was prepared in 22% yield (0.20 g of white solid melting at 152-153 °C) starting from **24** (0.87 g, 1.8 mmol) according to the general procedure for the synthesis of indenol derivatives. ^{1}H-NMR ($CDCl_3$): 1.00 (m, 6H), 1.69-1.88 (m, 5H), 2.60 (s, 3H), 2.64 (s, 3H), 2.78 (t, J = 7.6, 2H), 3.58 (s, 1H), 4.13 (m, 2H), 5.53 (s, 2H), 6.91 (s, 1H), 7.07 (d, J = 7.3, 1H), 7.18-7.42 (m, 6H), 7.56 (d, J = 7.2, 1H). MS (ESI): m/z 496 ($M + H^+$).

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-methylene-1*H*-indene-2-carboxylic Acid (6c).

From 16e. A mixture of **16e** (0.25 g, 0.48 mmol) in chloroform (10 mL) with *p*-toluenesulfonic acid monohydrate (PTSA, 0.18 g, 0.95 mmol) was refluxed for 1 h (the reaction was monitored by means of TLC). The resulting mixture was then washed with water, dried over sodium sulfate and concentrated under reduced pressure and the crude product was purified by flash chromatography with ethyl acetate as the eluent to give 97 mg of **6c** as pale yellow crystalline solid (yield 45%). ^{1}H-NMR ($CDCl_3$): 0.71 (t, *J* = 7.3, 3H), 1.51 (m, 2H), 2.57 (s, 3H), 2.58 (s, 3H), 2.67 (t, *J* = 7.7, 2H), 5.48 (s, 2H), 6.37 (s, 1H), 6.67 (s, 1H), 6.88 (s, 1H), 7.13-7.36 (m, 5H), 7.39 (d, *J* = 7.8, 2H), 7.69 (d, *J* = 7.1, 1H). Anal. ($C_{29}H_{27}N_3O_2 \cdot CH_3COOCH_2CH_3$) C,H,N.

From 6e. To a solution of acid **6e** (0.050 g, 0.107 mmol) in $CDCl_3$ (8.0 mL) PTSA (0.040 g, 0.21 mmol) was added and the resulting mixture was refluxed for 4 h. The reaction was monitored by means of ^{1}H-NMR spectroscopy in order to ascertain the complete transformation of **6e** into the *trans*-diene derivate **6c**. The reaction mixture was then washed with water, dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow oil which crystallized by treatment with diethyl ether (0.030 g of **6c** as a yellow solid, yield 62%, mp 218-224 °C). MS(ESI negative ions): m/z 448 ($M\text{-}H^+$).

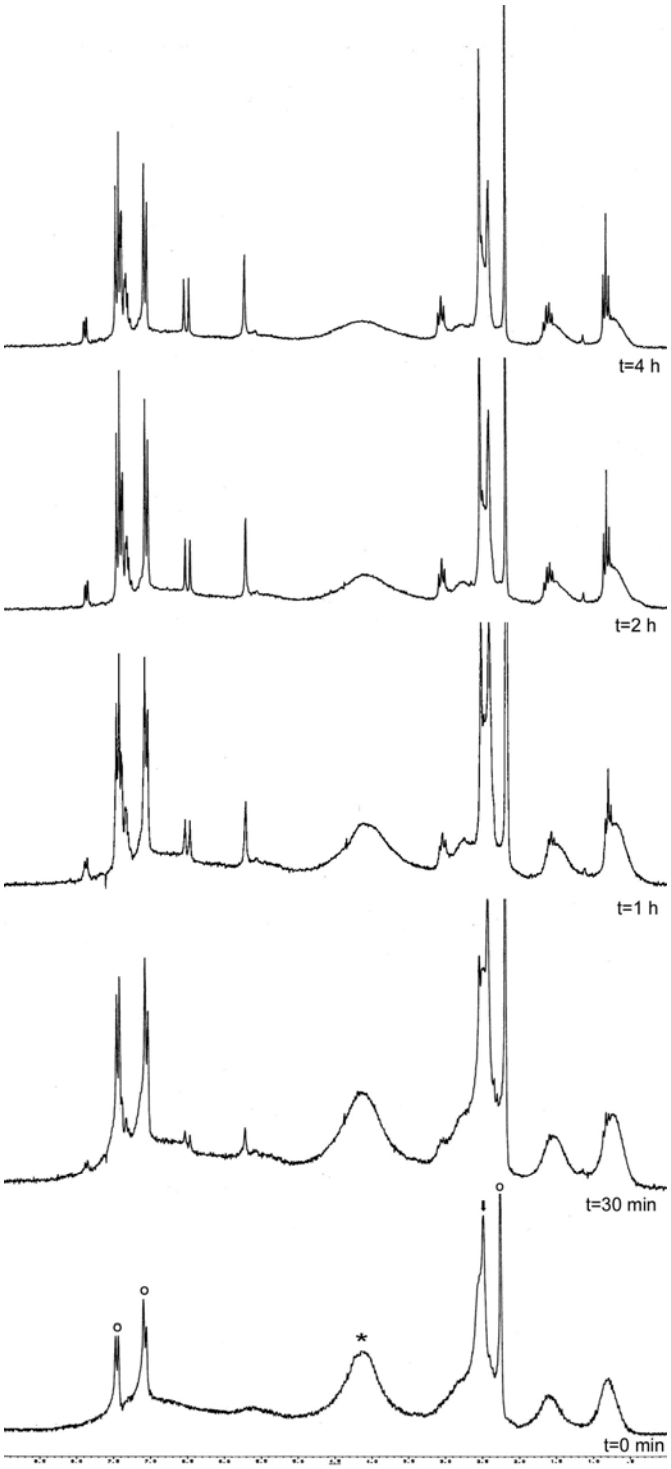
Figure 1SI. ^{1}H NMR spectrum (200 MHz) of **6c**•2 PTSA in DMSO. The arrow indicates the solvent peak, the asterisk the water peak, and the empty circles the signals attributable to PTSA.



Poly[3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-methylene-1*H*-indene-2-carboxylic Acid] (Poly-6c).

To a solution of acid **6c** (0.040 g, 0.089 mmol) in $CHCl_3$ (5.0 mL) PTSA (0.034 g, 0.18 mmol) was added and the resulting mixture was stirred at room temperature for 10 min and then evaporated under reduced pressure. The residue was slurried in $CHCl_3$ (5.0 mL) and evaporated again (this procedure was repeated 4 times). The final residue was washed in sequence with $CHCl_3$ and water and dried under reduced pressure to afford poly-**6c**•PTSA (the amount of PTSA is difficult to determine with precision) as off-white solid (0.055 g). ^{1}H NMR (DMSO-d_6): bottom trace of Figure 2SI.

Figure 2SI. Thermo-induced depolymerization of poly-**6c**, followed by ^{1}H NMR (200 MHz). A solution of 2.5 mg of poly-**6c**•PTSA in 0.5 mL of (DMSO-d_6) was heated at 120 °C and ^{1}H NMR spectra were recorded at regular time intervals. The arrow indicates the solvent peak, the asterisk the water peak, and the empty circles the signals attributable to PTSA.



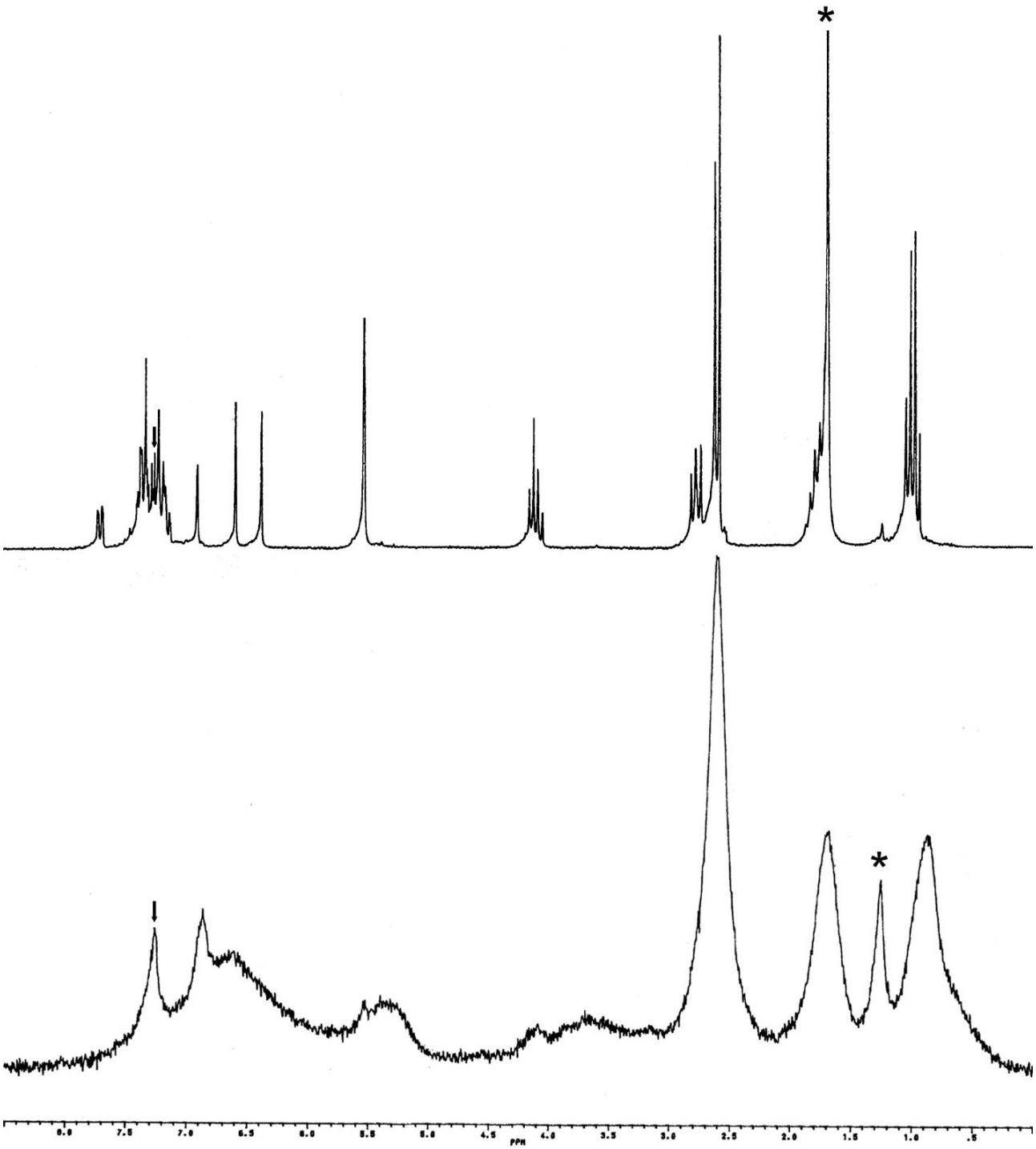
Ethyl 3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-methylene-1*H*-indene-2-carboxylate (22).

A mixture of indenol derivative **25** (0.080 g, 0.16 mmol) in $CDCl_3$ (4 mL) with PTSA (0.060 g, 0.32 mmol) was refluxed for 3.5 h and the reaction progress was monitored by ^{1}H NMR spectroscopy. The resulting solution was washed with a saturated $NaHCO_3$ solution and dried over sodium sulfate to obtain a solution (ca. 0.04M) of **22**. ^{1}H-NMR ($CDCl_3$): 0.94-1.06 (m, 6H), 1.78 (m, 2H), 2.59 (s, 3H), 2.63 (s. 3H), 2.78 (t, *J* = 8.0, 2H), 4.10 (q, *J* = 7.2, 2H), 5.53 (s, 2H), 6.37 (s, 1H), 6.59 (s, 1H), 6.90 (s, 1H), 7.13-7.45 (m, 7H), 7.70 (d, *J* = 7.3, 1H). MS(ESI): m/z 478 ($M+H^+$).

Poly[Ethyl 3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-methylene-1*H*-indene-2-carboxylate] (Poly-22).

A solution (ca. 0.04M) of **22** in $CDCl_3$ (4 mL) was concentrated under reduced pressure to give a viscous oil, which was dissolved into $CHCl_3$ and evaporated again (this procedure was repeated 4 times) to give 0.072 g of poly-**22** as a pale yellow glassy solid. ^{1}H NMR (200 MHz, $CDCl_3$): bottom trace of Figure 3SI.

Figure 3SI. ^{1}H NMR spectra (200 MHz, $CDCl_3$) of **22** (top) and poly-**22** (bottom). The arrow indicates the solvent peak and the asterisk the water peak.



3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-methyl-1*H*-indene-2-carboxylic Acid (6d).

A mixture of **16e** (0.12 g, 0.23 mmol) in toluene (15 mL) with *p*-toluenesulfonic acid monohydrate (0.080 g, 0.42 mmol) and a catalytic amount (20 mg) of Pd/C 10% was hydrogenated at atmospheric pressure and at reflux for 3 days. The catalyst was filtered-off and the reaction mixture was evaporated under reduced pressure. Purification of the residue by flash chromatography with ethyl acetate-methanol (9:1) as the eluent gave 20 mg of **6d** (yield 19%, mp 242-245 °C) as the slower eluting isomer. ^{1}H-NMR ($CDCl_3$): 0.75 (t, *J* = 7.3, 3H), 1.46-1.68 (m, 5H), 2.58 (s, 3H), 2.59 (s, 3H), 2.68 (t, *J* = 7.8, 2H), 3.93 (q, *J* = 7.5, 1H), 5.50 (s, 2H), 6.89 (s, 1H), 7.12-7.38 (m, 7H), 7.49 (d, *J* = 7.2, 1H). MS(ESI negative ions): m/z 450 ($M-H^+$). Anal. ($C_{29}H_{29}N_3O_2$) C,H,N.

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-methyl-3*H*-indene-2-carboxylic Acid (17).

Compound **17** was obtained as the faster eluting isomer (*n*-hexane-ethyl acetate, 3:7) from the above described hydrogenation reaction (8 mg, yield 8%, mp 244-247 °C). ^{1}H-NMR ($CDCl_3$): 0.69 (t, *J* = 7.3, 3H), 1.28-1.56 (m, 2H), 2.54-2.66 (m, 11H), 4.81 (q, *J* = 1.8, 1H), 5.35 (s, 2H), 6.84 (s, 1H), 6.95 (d, *J* = 8.5, 2H), 7.00 (d, *J* = 8.5, 2H), 7.11 (d, *J* = 7.2, 1H), 7.20-7.35 (m, 2H), 7.47 (d, *J* = 7.0, 1H). MS(ESI negative ions): m/z 450 ($M-H^+$). Anal. ($C_{29}H_{29}N_3O_2 \cdot H_2O$) C,H,N.

Di(*tert*-butyl) 2-(*tert*-Butoxycarbonyl)-3-[4-[(5,7-dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-hydroxy-3*H*-indene-3-malonate (18).

To an ice-cooled mixture of NaH (22 mg, 0.92 mmol) in freshly distilled THF (10 mL) under an argon atmosphere a solution of di-*tert*-butyl malonate (0.20 mL, 0.89 mmol) in freshly distilled THF (5 mL) was added dropwise. After the resulting mixture was stirred at room temperature for 1h, a solution of **15b** (0.22 g, 0.43 mmol) in freshly distilled THF (5mL) was added dropwise and the reaction mixture was stirred at room temperature for 3h. After the evaporation of the solvent, the residue was diluted with ethyl acetate, washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography *n*-hexane-

ethyl acetate (6:4) to give **18** as a colourless oil (0.23 g, yield 74 %). ^{1}H-NMR ($CDCl_3$): 0.92 (t, *J* = 7.4, 3H), 1.03 (s, 9H), 1.38 (s, 9H), 1.44 (s, 9H), 1.62-1.78 (m, 2H), 2.52 (s, 3H), 2.58 (s, 3H), 2.68 (t, *J* = 7.8, 2H), 5.01 (s, 1H), 5.36 (s, 2H), 6.83 (s, 1H), 6.87 (s, 4H), 7.39 (m, 2H), 7.58 (m, 1H), 7.98 (m, 1H), 10.90 (br s, 1H).

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxoindane-3-acetic Acid (19).

A mixture of **18** (0.20 g, 28 mmol) in hydrochloric acid (10 mL) and acetic acid (10 mL) was heated at 80°C for 5h. After evaporation of the solvent, the residue was partitioned between chloroform and water; the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography with ethyl acetate-methanol (9:1) and recrystallized from ethyl acetate to obtain **19** as pale yellow crystals (0.040 g, yield 31%, mp 130-133 °C). ^{1}H-NMR: ($CDCl_3$): 0.77 (t, *J* = 7.3, 3H), 1.43-1.61 (m, 2H), 2.44 (s, 3H), 2.50 (s, 3H), 2.65 (t, *J* = 7.6, 2H), 3.00 (m, 2H), 3.40 (m, 2H), 5.29 (d, *J* = 15.9, 1H), 5.40 (d, *J* = 15.9, 1H), 6.83 (s, 1H), 6.98 (d, *J* = 8.2, 2H), 7.08 (d, *J* = 8.2, 2H), 7.32 (m, 2H), 7.52 (m, 1H), 7.70 (d, *J* = 7.5, 1H), 9.07 (brs, 1H). MS(ESI negative ions): m/z 466 ($M\text{-}H^+$). Anal. ($C_{29}H_{29}N_3O_3 \cdot 0.5\ CH_3COOCH_2CH_3$) C,H,N.

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxoindane-3-malonic Acid (20).

This compound was prepared from **18** (0.065 g, 0.090 mmol) according to the general procedure for acid hydrolysis and was purified by recrystallization from ethyl acetate to obtain **20** as an off-white solid (0.027 g, yield 59%, mp 140-144 °C). ^{1}H-NMR (DMSO-d_6): 0.82 (t, *J* = 7.3, 3H), 1.51-1.69 (m, 2H), 2.45 (s, 6H), 2.65 (t, *J* = 7.4, 2H), 3.11 (d, *J* = 19.6, 1H), 3.70 (d, *J* = 19.6, 1H), 4.82 (s, 1H), 5.35 (s, 2H), 6.90 (s, 1H), 6.99 (d, *J* = 8.1, 2H), 7.26 (d, *J* = 8.1, 2H), 7.37 (m, 1H), 7.53 (m, 3H), 12.58 (brs, 2H). MS(ESI negative ions): m/z 510 ($M\text{-}H^+$). Anal. ($C_{30}H_{29}N_3O_5 \cdot 1.5\ H_2O$) C,H,N.

2-[1-(4-Methylphenyl)-3-oxo-2,3-dihydro-1*H*-1-indenyl]malonic Acid (21).

The title compound was prepared from compound **14** following the same procedure used for the synthesis of **20** and was recrystallized from chloroform to obtain crystals suitable for X-ray diffraction analysis. ^{1}H-NMR (DMSO-d_6): 2.18 (s, 3H), 3.10 (d, J = 19.6, 1H), 3.74 (d, J = 19.6, 1H), 4.81 (s, 1H), 7.04 (d, J = 8.3, 2H), 7.17 (d, J = 8.3, 2H), 7.36 (m, 1H), 7.60 (m, 3H). MS(ESI negative ions): m/z 323 (M-H$^+$).

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxo-N-phenylsulfonyl-1*H*-indene-2-carboxamide (6h).

A mixture of **6b** (29 mg, 0.064 mmol) in CH_2Cl_2 (10 mL) with 4-dimethylaminopyridine (DMAP) (8.6 mg, 0.070 mmol), benzenesulfonamide (11 mg, 0.070 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (13.5 mg, 0.070 mmol) was stirred at room temperature for 1h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate-methanol, 9:1) to give 15 mg of **6h** as an orange oil (yield 40 %). ^{1}H-NMR: (DMSO-d_6): 0.91 (t, *J* = 7.3, 3H), 1.72 (m, 2H), 2.47 (s, 6H), 2.73 (t, *J* = 7.5, 2H), 5.48 (s, 2H), 6.93-7.56 (m, 14H). MS(ESI negative ions) m/z 589 (M - H$^+$). Anal. ($C_{34}H_{30}N_4O_4S$) C,H,N.

3-[4-[(5,7-Dimethyl-2-propyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]phenyl]-1-oxo-N-methylsulfonyl-1*H*-indene-2-carboxamide (6g).

A mixture of **6b** (100 mg, 0.22 mmol) in CH_2Cl_2 (15 mL) with DMAP (30 mg, 0.25 mmol), methanesulfonamide (23 mg, 0.24 mmol), and EDCI (46 mg, 0.24 mmol) was stirred at room temperature for 1h. The solvent was removed and the crude product was purified by flash chromatography (ethyl acetate-methanol, 7:3) to give an orange oil which was recrystallized from diethyl ether to give 13 mg of **6g** as an orange solid (yield 11 %, mp 191-194 °C). ^{1}H-NMR:

(DMSO-d_6): 0.90 (t, *J* = 7.4, 3H), 1.70 (m, 2H), 2.48 (s, 6H), 2.69-2.78 (m, 5H), 5.50 (s, 2H), 6.92 (s, 1H), 7.14-7.41 (m, 6H), 7.69 (d, *J* = 7.9, 2H). MS(ESI) m/z 529 ($M + H^+$). Anal. ($C_{29}H_{28}N_4O_4S$) C,H,N.

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4. Indenone derivative **14** was described in a patent application, which was published while this work was in progress. See Ueno, K.; Machii, D.; Takai, H.; Nosaka, K.; Kase, H.; Ono, S.; Yamada, K. Pharmaceuticals Containing Indenones for Treatment of Circulatory Disorders. Jpn. Kokai Tokkyo Koho JP 2004-155731, **2004**. CA **141**:17612.

Analytical Data

Compd	formula	C Calcd Found	H	N
5a	$C_{28}H_{26}N_8O \cdot 2\ H_2O$	63.86	5.74	21.28
		63.65	5.46	21.18
5b	$C_{28}H_{26}N_4O_3 \cdot H_2O$	69.41	5.82	11.56
		69.26	5.55	11.91
5c	$C_{29}H_{28}N_8O \cdot H_2O$	66.65	5.79	21.44
		66.53	6.02	21.31
5d	$C_{29}H_{28}N_4O_3 \cdot 0.5\ H_2O$	71.15	5.97	11.44
		71.04	5.93	11.21
5e	$C_{30}H_{30}N_8O \cdot 0.5\ H_2O$	68.29	5.92	21.24
		68.10	5.71	20.93
5f	$C_{30}H_{30}N_4O_3 \cdot 0.5\ H_2O$	71.55	6.20	11.13
		71.43	6.45	10.95
6a	$C_{27}H_{23}N_3O_3 \cdot 0.33\ H_2O$	73.12	5.38	9.47
		73.36	5.44	9.32
6b	$C_{28}H_{25}N_3O_3 \cdot 0.5\ H_2O$	73.03	5.69	9.12
		72.81	5.49	9.41
6c	$C_{29}H_{27}N_3O_2 \cdot CH_3COOCH_2CH_3$	73.72	6.56	7.82
		73.51	6.40	8.13
6d	$C_{29}H_{29}N_3O_2$	77.13	6.47	9.31
		77.02	6.22	9.18
6e	$C_{29}H_{29}N_3O_3 \cdot 0.33\ H_2O$	73.55	6.31	8.87
		73.25	6.65	8.53
6f	$C_{30}H_{31}N_3O_3 \cdot 1.5\ H_2O$	70.84	6.74	8.26
		70.92	6.47	7.92
6g	$C_{29}H_{28}N_4O_4S$	65.89	5.34	10.60
		65.98	5.36	10.54
6h	$C_{34}H_{30}N_4O_4S$	69.13	5.12	9.48
		69.45	5.03	9.51
17	$C_{29}H_{29}N_3O_2 \cdot H_2O$	74.18	6.65	8.95
		74.16	6.36	8.97
19	$C_{29}H_{29}N_3O_3 \cdot 0.5\ CH_3COOCH_2CH_3$	72.78	6.50	8.21
		72.59	6.37	8.30

20	$C_{30}H_{29}N_3O_5 \cdot 1.5\ H_2O$	66.90	5.99	7.80
		67.23	6.26	7.79