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Palladium(II)-catalyzed heterocyclisation of 8-arylethynyl-1,2,3,4-tetrahydroquinolines: a facile route to 2-aryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives

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Abstract—Dihydropyrroloquinolines have been synthesized reacting 8-arylethynyl-1,2,3,4-tetrahydroquinolines in the presence of palladium(II) chloride catalyst. Heteroannulation has been achieved in good yields and tolerates substituents on the tetrahydroquinoline, including bromo, cyano, and ester.
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1. Introduction

The 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline ring constitutes the central core of different series of compounds exerting platelet activating factor production inhibition[1] or acting as 5-hydroxytryptamine (5-HT_{2c}) receptor agonists and exerting antiepileptic or anti-obesity activities[2] (Fig. 1).

During our work in the field of peptidomimetic antagonists of G-protein coupled receptors (GPCRs) we were interested in the synthesis of analogues of the nonpeptidyl luteinizing hormone-releasing hormone (LHRH) receptor antagonist **3** (Fig. 2).[3]

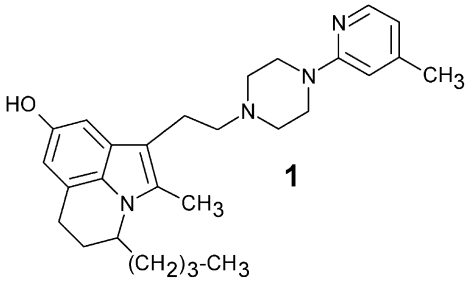
Pharmacomodulation at the level of the central indole core led us to envision the incidence of its replacement by an indole-bridged heterocycle, 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (Fig. 3).

Access to such compounds is regularly described by the well known Fischer indole derivatives synthesis.[1,4]

Herein, we report the strategy for the synthesis of the central scaffold using a palladium(II)-catalyzed intramolecular heterocyclisation.

2. Results and discussion

The 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline is classically



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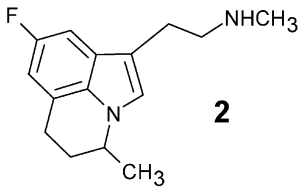

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Figure 1. Structures of a PAF antagonist **1** and a 5HT_{2C} receptor agonist **2**.

Keywords: 5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines; 1,2,3,4-Tetrahydroquinolines; Palladium(II)-catalyzed intramolecular heterocyclisation.
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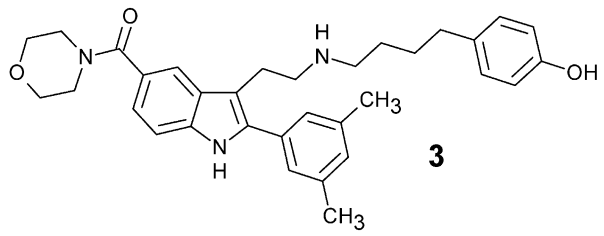


Figure 2. Structure of the nonpeptidyl gonadotropin-releasing hormone (GnRH) receptor antagonist **3**.

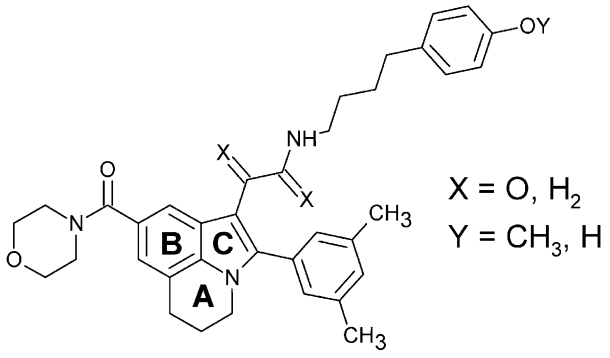
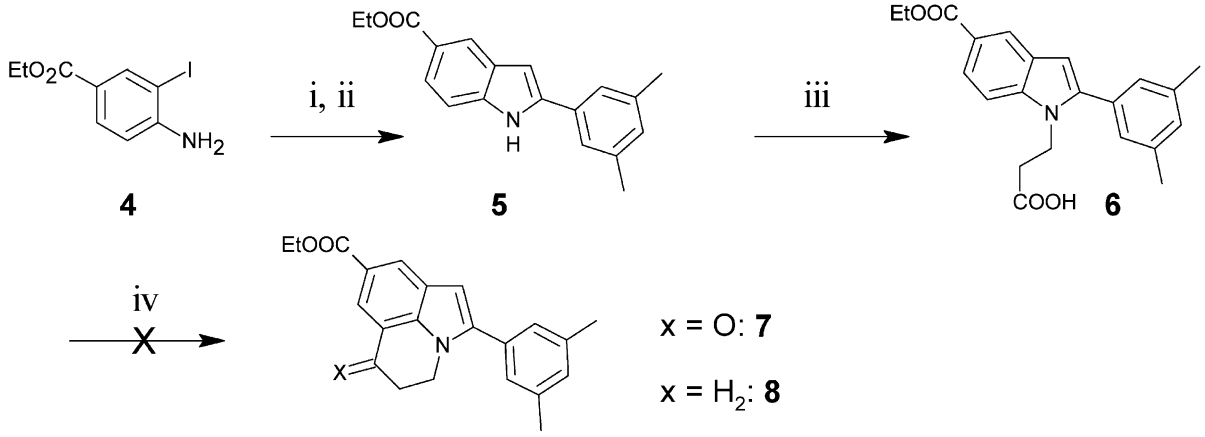


Figure 3. Structure of the novel pyrroloquinolines prepared.

first tried to obtain the tricyclic compound **8** (Scheme 1) by intramolecular acylation of the 1-indolepropionic acid **6** (obtained by reaction of **5** with propiolactone) followed by reduction[5] of the desired 4,5-dihydro-6*H*-pyrroloquinolin-6-one **7**; although the starting 2-xylylindole **5** could be prepared by the Sonogashira[8]/palladium(II)-catalyzed intramolecular cyclisation methods[9] in a 70% overall yield, cyclodehydration of acid **6**, using PPA or $AlCl_3$, failed.

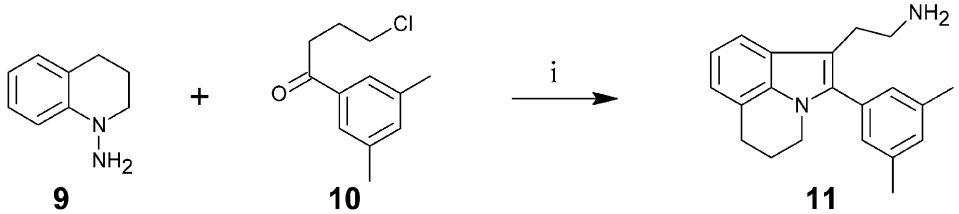
In a second approach, we tried to obtain directly 1-(2-aminoethyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline **11** by the elegant Fischer indole synthesis worked out by Grandberg[10] for tryptamine derivatives. Condensation of 1-amino-1,2,3,4-tetrahydroquinoline[1] **9** with 4-chloro-1-(3,5-dimethylphenyl)butan-1-one **10** afforded the desired azaarylethylamine **11** (Scheme 2), but yield remained poor (15%) and its purification necessitated multiple tedious column chromatography elutions.

We hypothesized that palladium-catalyzed ring closure of alkynylanilines to indoles[11,12] may be directly applicable to the preparation of 2-aryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines (Scheme 3). The synthesis began with the bromination of the commercially available 1,2,3,4-tetrahydroquinoline **12** to give 6-bromo-1,2,3,4-tetrahydroquinoline **13** as major product in 60% yield. The

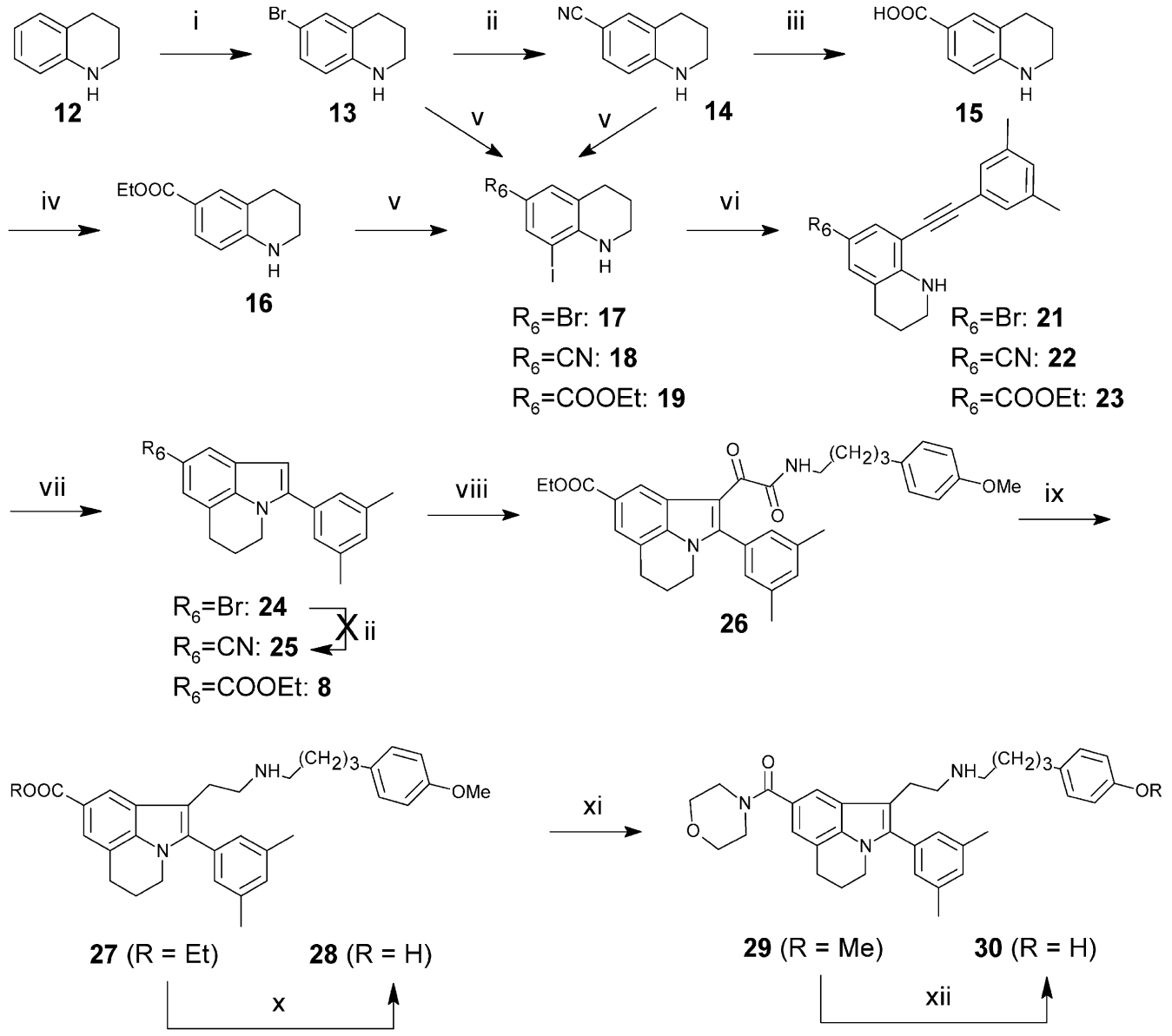


Scheme 1. Synthesis of the 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline **8**: (i) (3,5-dimethylphenyl)acetylene **20**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 10 °C, 89%; (ii) $PdCl_2$, CH_3CN, reflux, 78%; (iii) propiolactone, NaH, DMF, rt, 72%; (iv) PPA or $AlCl_3$, CH_2Cl_2.

elaborated by two strategies (Fig. 3): (i) creation of ring A starting from indole derivative, (ii) creation of ring C using suitably substituted 1,2,3,4-tetrahydroquinoline. In the first case, numerous indole cyclisation reactions have been carried out using N-1 and/or C-7 substituted indoles.[5–7] We temperature must be kept at 0 °C to avoid simultaneous bromination in position 8. Iodination with iodine monochloride gave the 6-bromo-8-iodo-1,2,3,4-tetrahydroquinoline **17**. The Sonogashira palladium-catalyzed cross-coupling reaction[8] of amine **17** with (3,5-



Scheme 2. Grandberg synthesis of azaarylethylamine **11**. (i) EtOH, reflux, 15%.



Scheme 3. Synthesis of 1-aminoethyl-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives. (i) NBS, CCl_4, 0 °C; (ii) CuCN, DMF, reflux; (iii) NaOH, H_2O_2, reflux; (iv) EtOH, HCl, reflux; (v) ICl, $CaCO_3$, MeOH/H_2O, 0 °C; (vi) (3,5-dimethylphenyl)acetylene **20**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 10 °C; (vii) $PdCl_2$, CH_3CN, reflux; (viii) (1) $(COCl)_2$, Et_2O, 0 °C (2) 4-(4-methoxyphenyl)butylamine, THF, rt; (ix) (1) BH_3:THF, reflux (2) *N*,*N*-dimethylethanolamine, MeOH/THF, reflux; (x) NaOH, EtOH, reflux; (xi) morpholine, PyBOP, *N*-methylmorpholine, DMF, rt; (xii) BBr_3, CH_2Cl_2, rt.

dimethylphenyl)acetylene **20**[14] using catalytic amount of the $Pd(PPh_3)_2Cl_2$-CuI system in triethylamine under nitrogen at 0 °C provided access to the key intermediate, the 6-bromo-8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline **21**, in excellent yield.

Palladium dichloride is a well-established catalyst for converting 2-alkynylanilines into 2-substituted indoles through N–C_2 ring closure.[9] We used such reaction conditions with refluxing acetonitrile as solvent to obtain 2-phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline **24** from compound **21**, in 70% yield. The corresponding nitrile **25** could not be obtained by heating the bromo derivative **24** at reflux with copper cyanide in dimethylformamide in a Rosenmund-von Braun reaction.[14] Another attempt using $ZnCN_2$ as cyanation reagent[15] in palladium-catalyzed conditions remained unsuccessful. This problem was solved by carrying out the cyanation with 6-bromo-1,2,3,4-tetrahydroquinoline **13** as starting material in the previous conditions (CuCN/DMF, reflux) to afford 6-cyano-1,2,3,4-tetrahydroquinoline **14** in 60% yield (Scheme 3). Subsequent reactions of iodination (compound **18**), Sonogashira coupling (compound **22**) and palladium-catalyzed cyclisation gave pyrroloquinoline **25** in a 31% overall yield. The cyano derivative **25** was converted to the corresponding carboxylic acid, with aqueous solution of sodium hydroxide in the presence of hydrogen peroxide, only in very poor yield. Since the synthetic route to the ester **8** via the carboxylic acid appeared to be unsuitable, the cyano derivative **14** was first hydrolysed as described above. The synthesis of the 1,2,3,4-tetrahydroquinoline-6-carboxylic acid **15** was achieved easily and in an excellent yield (95%).

Ethyl ester **16** was synthesized by refluxing the compound **15** in an hydrogen chloride ethanolic solution. The ethyl pyrroloquinoline-8-carboxylate **8** was then prepared using a sequence of reactions similar to those described for compounds **24** and **25**, in a satisfactory global yield (39%).

The aminoethyl chain was built in the position 1 of the azaheterocycle **8** via the glyoxamide **26** after reaction with oxalyl chloride and subsequent condensation with 4-(4-methoxyphenyl)butylamine.[1] The glyoxamide **26** was reduced with a borane–THF complex to give ethylamine **27** after treatment with *N*,*N*-dimethylethanolamine to break down the boron–amine complex intermediate. The ester **27** was hydrolyzed under alkaline conditions to afford the corresponding carboxylic acid **28**, which was condensed with morpholine using PyBOP as coupling reagent and *N*-methylmorpholine in dimethylformamide at room temperature to yield the morpholide **29**. Demethylation of **29** with boron tribromide at room temperature gave the corresponding phenol **30** in a 45% yield.

3. Conclusion

Palladium(II)-catalyzed intramolecular heterocyclisation of 8-arylethynyl-1,2,3,4-tetrahydroquinolines provides a simple and high yield method for the preparation of 2-aryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (**8**, **24**, **25**). They can be modified by substitution to compounds (**26**–**30**), which are of interest as potential antagonists of GPCRs as pharmacological targets.

4. Experimental

4.1. General methods

All common chemicals and solvents utilized were reagent grade and purchased from Sigma-Aldrich (Saint Quentin, France). Melting points were determined on a Electrothermal IA9300 melting point digital apparatus and reported uncorrected. Infrared (IR) spectra were obtained in KBr pellets or neat liquid films with a Perkin–Elmer Paragon FTIR 1000 PC spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance 400 apparatus operating at 400 MHz in d_6-DMSO as solvent. Chemical shifts are expressed as δ values (ppm) relative to Me_4Si as internal standard. Electrospray mass spectrometric analysis was performed on a Esquire-LC Ion Trap System mass spectrometer. All reactions were monitored by TLC, using 0.25 mm-thick precoated silica gel plates (E. Merck) eluted with CH_2Cl_2/EtOH gradients. Compounds were purified by column chromatography using silica gel 60 as stationary phase and eluted with CH_2Cl_2 or CH_2Cl_2/hexane gradients.

4.1.1. 6-Bromo-1,2,3,4-tetrahydroquinoline.[16] (13) To a solution of 1,2,3,4-tetrahydroquinoline **12** (5.00 g, 37.5 mmol) in carbon tetrachloride (10 mL) at 0 °C, was added portion wise *N*-bromosuccinimide (6.68 g, 37.5 mmol). The mixture was stirred at room temperature for 3 h. The succinimide which resulted as a precipitate was filtered off and washed with hexane (4×10 mL). The solvents were removed under reduced pressure, the residue was purified by chromatography (CH_2Cl_2) to give **13** as a yellow oil (4.77 g, 60%). IR (neat) cm^{-1}: 3415 (νNH); 3012 (νCH arom.); 2926, 2836 (νCH alkane); 1598, 1495 (νC=C arom.); 544 (νC–Br). ^{1}H NMR δ 6.98 (d, 1H, J=2.3 Hz, H_5), 6.96 (d, 1H, J=9.2 Hz, H_8), 6.40 (dd, 1H, J=9.2 Hz, J=2.3 Hz, H_7), 5.87 (s, 1H, NH), 3.18 (t, 2H, J=5.5 Hz, H_2), 2.66 (t, 2H, J=6.1 Hz, H_4), 1.89–1.71 (m, 2H, H_3). MS-ES$^+$ (MeOH): *m*/*z* 213 (M+H$^+$, 100%).

4.1.2. 6-Cyano-1,2,3,4-tetrahydroquinoline (14). Compound **13** (3.40 g, 16.0 mmol) was stirred with cuprous cyanide (1.72 g, 19.2 mmol) in dimethylformamide (30 mL) and heated to reflux for 16 h. After the mixture had cooled, 10% ammonium hydroxide solution (50 mL) was added and the resultant mixture was extracted with dichloromethane. The aqueous layer was washed with brine (4×50 mL), water and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography (CH_2Cl_2) to give **14** as a white solid (1.52 g, 60%). Mp 77–79 °C (lit.[16] 78–80 °C). IR (KBr) cm^{-1}: 3382 (νNH); 3052 (νCH arom.); 2931, 2853 (νCH alkane); 2210 (νC≡N); 1608, 1522 (νC=C arom.). ^{1}H NMR δ 7.29–7.21 (m, 2H, H_5, H_7), 6.78 (s, 1H, NH), 6.50 (d, 1H, J=8.0 Hz, H_8), 3.26 (t, 2H, J=5.5 Hz, H_2), 2.67 (t, 2H, J=6.1 Hz, H_4), 1.89–1.71 (m, 2H, H_3). MS-ES$^+$ (MeOH): *m*/*z* 159 (M+H$^+$, 100%).

4.1.3. 1,2,3,4-Tetrahydroquinoline-6-carboxylic acid (15). Thirty-five percent aqueous hydrogen peroxide solution (6 mL) was added to a solution of **14** (1.50 g, 9.5 mmol) in aqueous solution of 2 N NaOH (30 mL) at room temperature. The mixture was refluxed for 24 h, cooled to room temperature and acidified with an aqueous solution of 2 N HCl. The precipitate which resulted was collected by filtration, washed by water and dried over P_2O_5 to give **15** as a white solid (1.60 g, 95%). Mp 169–171 °C (lit.[17] 168–170 °C). IR (KBr) cm^{-1}: 3600–2900 (νOH); 3425 (νNH); 2981, 2928 (νCH alkane); 1703 (νC=O); 1613 (νC=C arom.). ^{1}H NMR δ 7.58–7.41 (m, 2H, H_5, H_7), 6.55 (s, 1H, NH), 6.44 (d, 1H, J=9.1 Hz, H_8), 3.26–3.22 (m, 2H, H_2), 2.69 (t, 2H, J=5.8 Hz, H_4), 1.89–1.71 (m, 2H, H_3). MS-ES$^+$ (MeOH): *m*/*z* 178 (M+H$^+$, 100%).

4.1.4. Ethyl 1,2,3,4-tetrahydroquinoline-6-carboxylate (16). Carboxylic acid **15** (1.00 g, 5.6 mmol) in ethanolic solution of 2 N HCl (50 mL) was refluxed for 3 days. The solution was cooled to room temperature and basified with an aqueous solution of 1 N NaOH. The precipitate which resulted was collected by filtration, washed by ethanol and dried over P_2O_5 to give **16** as a white solid (0.69 g, 60%). Mp 80–81 °C (lit.[17] 82–83 °C, hexane). IR (KBr) cm^{-1}: 3388 (νNH); 2935 (νCH alkane); 1677 (νC=O); 1608, 1525 (νC=C arom.). ^{1}H NMR δ 7.58–7.40 (m, 2H, H_5, H_7), 6.62 (s, 1H, NH), 6.44 (d, 1H, J=8.2 Hz, H_8), 4.21 (q, 2H, J=7.0 Hz, CH_2), 3.28–3.24 (m, 2H, H_2), 2.70 (t, 2H, J=6.1 Hz, H_4), 1.89–1.71 (m, 2H, H_3), 1.28 (t, 3H, J=7.0 Hz, CH_3). MS-ES$^+$ (MeOH): *m*/*z* 206 (M+H$^+$, 100%).

4.2. General procedure for the synthesis of 8-iodo-1,2,3,4-tetrahydroquinolines

A solution of iodine monochloride (21 mmol) in methanol

(25 mL) was added dropwise to a stirred suspension of 1,2,3,4-tetrahydroquinolines **13**, **14** or **16** (20 mmol) and calcium carbonate (30 mmol) in methanol/water (4/1) (100 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h before filtering through a pad of Celite. The filtrate was extracted with dicholoromethane and the organic layer was washed with water. The organic layer was dried over Na_2SO_4 and evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2 to give **17**, **18** or **19**.

4.2.1. 6-Bromo-8-iodo-1,2,3,4-tetrahydroquinoline (17). An orange oil was obtained (69%). IR (neat) cm^{-1}: 3399 (νNH); 3020 (νCH arom.); 2928, 2836 (νCH alkane); 1586, 1494 (νC=C arom.); 546 (νC–Br). ^1H NMR δ 7.54 (s, 1H, H_7), 7.09 (s, 1H, H_5), 5.28 (s, 1H, NH), 3.32–3.26 (m, 2H, H_2), 2.70 (t, 2H, $J=6.2$ Hz, H_4), 1.78–1.72 (m, 2H, H_3). ^{13}C NMR δ 20.5, 27.3, 41.8, 82.0, 97.1, 121.1, 133.1, 140.7, 148.6. MS-ES$^+$ (MeOH): *m/z* 339 ($M+H^+$, 100%).

4.2.2. 6-Cyano-8-iodo-1,2,3,4-tetrahydroquinoline (18). A white solid was obtained (62%). Mp 124–126 °C. IR (KBr) cm^{-1}: 3350 (νNH); 3015 (νCH arom.); 2930, 2842 (νCH alkane); 2212 (νC≡N); 1595, 1512 (νC=C arom.). ^1H NMR δ 7.84 (s, 1H, H_7), 7.31 (s, 1H, H_5), 6.13 (s, 1H, NH), 3.39–3.35 (m, 2H, H_2), 2.72–2.68 (m, 2H, H_4), 1.79–1.74 (m, 2H, H_3). ^{13}C NMR δ 20.3, 27.2, 42.0, 81.8, 97.2, 119.3, 121.4, 132.3, 140.2, 148.4. MS-ES$^+$ (MeOH): *m/z* 285 ($M+H^+$, 100%).

4.2.3. Ethyl 8-iodo-1,2,3,4-tetrahydroquinoline-6-carboxylate (19). An orange oil was obtained (60%). IR (neat) cm^{-1}: 3368 (νNH); 2929, 2843 (νCH arom.); 1700 (νC=O); 1598, 1516 (νC=C arom.). ^1H NMR δ 8.00 (s, 1H, H_7), 7.50 (s, 1H, H_5), 5.97 (s, 1H, NH), 4.23 (q, 2H, $J=7.1$ Hz, CH_2), 3.29–3.25 (m, 2H, H_2), 2.73 (t, 2H, $J=6.1$ Hz, H_4), 1.82–1.78 (m, 2H, H_3), 1.28 (t, 3H, $J=7.1$ Hz, CH_3). ^{13}C NMR δ 14.5, 20.1, 27.1, 41.5, 59.6, 82.6, 96.8, 120.9, 131.6, 140.5, 147.9, 168.1. MS-ES$^+$ (MeOH): *m/z* 332 ($M+H^+$, 100%).

4.3. General procedure for the synthesis of 8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinolines

4.3.1. (3,5-Dimethylphenyl)acetylene.[13] (20) To a mixture of trimethylsilylacetylene (2.64 g, 26.9 mmol) and 3,5-dimethyliodobenzene 6.17 g, 26.6 mmol) in triethylamine (30 mL) was added bis(triphenylphosphine)palladium dichloride (360 mg, 0.52 mmol) and copper(I) iodide (49 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 4 h under nitrogen and a crystalline grey-green solid of triethylamine hydroiodide was isolated by filtration and washed with toluene. The filtrate was concentrated under reduced pressure and the crude product was purified by chromatography on neutral alumina using CH_2Cl_2/hexane (1/1) as an eluent to afford the 3,5-dimethyl-1-trimethylsilylethynylbenzene as a yellow oil (5.27 g, 98%). ^1H NMR δ 7.09 (s, 2H, $H_{2,6}$), 7.04 (s, 1H, H_4), 2.54 (s, 6H, CH_3), 0.25 (s, 9H, $Si(CH_3)_3$).

A solution of TBAF 1 M in tetrahydrofuran (12 mL, 12 mmol) was added dropwise to a stirred solution of 3,5-dimethyl-1-trimethylsilylethynylbenzene (2.21 g, 10.9 mmol) in tetrahydrofuran (50 mL) at −15 °C. The mixture was stirred for 30 min and the solvent was evaporated in vacuo. The residue was purified by chromatography on neutral alumina using hexane as an eluent to afford **20** as a light yellow liquid (1.13 g, 80%). IR (neat) cm^{-1}: 3248 (ν≡C–H); 3105, 3002 (νCH arom.); 2100 (νC≡C); 1510, 1482 (νC=C arom.). ^1H NMR δ 7.12 (s, 2H, $H_{2,6}$), 7.07 (s, 1H, H_4), 4.13 (s, 1H, C≡C–H), 2.28 (s, 6H, CH_3).

4.4. Sonogashira coupling

8-Iodo-1,2,3,4-tetrahydroquinolines **17**, **18** or **19** (16.5 mmol), (3,5-dimethylphenyl)acetylene **20** (17.3 mmol), bis(triphenylphosphine)palladium dichloride (0.38 mmol) and copper(I) iodide (0.82 mmol) were dissolved in triethylamine (100 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 h. The precipitate was filtered off and washed with triethylamine. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel, eluting with CH_2Cl_2 to give **21**, **22** or **23**.

4.4.1. 6-Bromo-8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline (21). A white solid was obtained (97%). Mp 145–147 °C. IR (KBr) cm^{-1}: 3410 (νNH); 3008 (νCH arom.); 2945, 2912 (νCH alkane); 1596, 1494 (νC=C arom.); 548 (νC–Br). ^1H NMR δ 7.28 (s, 2H, H_{ar}), 7.22 (d, 1H, $J=2.4$ Hz, H_7), 7.07 (d, 1H, $J=2.4$ Hz, H_5), 7.05 (s, 1H, H_{ar}), 6.49 (s, 1H, NH), 3.37–3.33 (m, 2H, H_2), 2.74–2.70 (m, 2H, H_4), 2.31 (s, 6H, CH_3), 1.82–1.78 (m, 2H, H_3). ^{13}C NMR δ 20.3, 20.6, 26.4, 41.2, 84.5, 95.3, 95.7, 105.4, 121.7, 122.4, 129.3, 130.5, 132.4, 134.3, 137.4, 148.5. MS-ES$^+$ (MeOH): *m/z* 341 ($M+H^+$, 100%).

4.4.2. 6-Cyano-8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline (22). A white solid was obtained (96%). Mp 131–133 °C. IR (KBr) cm^{-1}: 3375 (νNH); 3002 (νCH arom.); 2932, 2847 (νCH alkane); 2213 (νC≡N); 1599, 1524 (νC=C arom.). ^1H NMR δ 7.51 (s, 1H, H_7), 7.41–7.38 (m, 3H, $2H_{ar}$, H_5), 7.07 (s, 1H, H_{ar}), 6.64 (s, 1H, NH), 3.37–3.33 (m, 2H, H_2), 2.74–2.70 (m, 2H, H_4), 2.32 (s, 6H, CH_3), 1.82–1.78 (m, 2H, H_3). ^{13}C NMR δ 20.1, 20.8, 26.7, 41.3, 84.1, 95.2, 95.5, 105.3, 120.1, 121.2, 122.3, 129.2, 130.4, 132.2, 134.1, 137.8, 149.0. MS-ES$^+$ (MeOH): *m/z* 287 ($M+H^+$, 100%).

4.4.3. Ethyl 8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (23). An orange solid was obtained (92%). Mp 84–86 °C. IR (KBr) cm^{-1}: 3403 (νNH); 2926, 2843 (νCH arom.); 1694 (νC=O); 1598, 1514 (νC=C arom.). ^1H NMR δ 7.71 (s, 1H, H_7), 7.50 (s, 1H, H_5), 7.32 (s, 2H, H_{ar}), 7.06 (s, 1H, H_{ar}), 6.49 (s, 1H, NH), 4.24 (q, 2H, $J=7.1$ Hz, CH_2), 3.44–3.40 (m, 2H, H_2), 2.78–2.74 (m, 2H, H_4), 2.31 (s, 6H, CH_3), 1.78–1.88 (m, 2H, H_3), 1.31 (t, 3H, $J=7.1$ Hz, CH_3). ^{13}C NMR δ 14.5, 20.5, 20.8, 27.0, 41.4, 59.9, 85.1, 94.8, 104.4, 115.4, 119.9, 122.6, 129.2, 130.2, 130.4, 131.9, 137.7, 149.5, 165.5. MS-ES$^+$ (MeOH): *m/z* 334 ($M+H^+$, 100%).

4.5. General procedure for the synthesis of 2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines

8-(3,5-Dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinolines **21**, **22** or **23** (5 mmol) and palladium dichloride (0.5 mmol) were dissolved in acetonitrile (35 mL) and the reaction mixture was refluxed for 16 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel, eluting with CH_2Cl_2 to give **24**, **25** or **8**.

4.5.1. 8-Bromo-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (24). A white solid was obtained (70%). Mp 136–138 °C. IR (KBr) cm^{-1}: 2971 (νCH alkane); 1582, 1464 (νC=C arom.); 545 (νC–Br). ^{1}H NMR δ 7.56 (s, 1H, H_9), 7.26 (s, 2H, H_{ar}), 7.09 (s, 1H, H_{ar}), 7.04 (s, 1H, H_7), 6.52 (s, 1H, H_1), 4.24–4.20 (m, 2H, H_4), 2.99–2.95 (m, 2H, H_6), 2.37 (s, 6H, CH_3), 2.14–2.10 (m, 2H, H_5). ^{13}C NMR δ 21.1, 22.6, 24.2, 43.6, 99.6, 112.3, 119.7, 120.9, 124.8, 126.3, 127.2, 129.7, 131.5, 133.7, 138.1, 141.1. MS-ES$^+$ (MeOH): *m/z* 341 (M+H$^+$, 100%).

4.5.2. 8-Cyano-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (25). A white solid was obtained (87%). Mp 124–126 °C. IR (KBr) cm^{-1}: 2951 (νCH alkane); 2211 (νC≡N); 1596, 1486 (νC=C arom.). ^{1}H NMR δ 7.92 (s, 1H, H_9), 7.29 (s, 2H, H_{ar}), 7.26 (s, 1H, H_7), 7.12 (s, 1H, H_{ar}), 6.69 (s, 1H, H_1), 4.28–4.24 (m, 2H, H_4), 3.03–2.98 (m, 2H, H), 2.39 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5). ^{13}C NMR δ 21.1, 22.4, 24.4, 43.7, 100.8, 101.6, 120.7, 121.2, 123.5, 123.9, 125.2, 126.4, 130.0, 131.1, 136.7, 138.1, 142.4. MS-ES$^+$ (MeOH): *m/z* 287 (M+H$^+$, 100%).

4.5.3. Ethyl 2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-8-carboxylate (8). A white solid was obtained (70%). Mp 87–88 °C. IR (KBr) cm^{-1}: 2939 (νCH alkane); 1701 (νC=O); 1594 (νC=C arom.). ^{1}H NMR δ 8.14 (s, 1H, H_9), 7.56 (s, 1H, H_7), 7.28 (s, 2H, H_{ar}), 7.10 (s, 1H, H_{ar}), 6.70 (s, 1H, H_1), 4.37 (q, 2H, J=7.1 Hz, CH_2), 4.25 (t, 2H, J=5.5 Hz, H_4), 3.02 (t, 2H, J=5.8 Hz, H_6), 2.38 (s, 6H, CH_3), 2.28–2.15 (m, 2H, H_5), 1.37 (t, 3H, J=7.1 Hz, CH_3). ^{13}C NMR δ 14.5, 21.1, 22.7, 24.3, 43.7, 60.2, 101,4, 119.1, 120.5, 121.5, 122.3, 125.0, 126.3, 129.7, 131.5, 137.6, 138.1, 141.6, 167.2. MS-ES$^+$ (MeOH): *m/z* 334 (M+H$^+$, 100%).

4.6. Procedure for the synthesis of 2-[2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]-2-oxoacetamide (26) and ethylamines (27–30)

4.6.1. *N*-[4-(4-Methoxyphenyl)but-1-yl]-2-[8-ethoxycarbonyl-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]-2-oxoacetamide (26). A solution of ethyl 2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-8-carboxylate **8** (0.80 g, 2.3 mmol) in diethyl ether (10 mL) was added dropwise to a solution of oxalyl chloride (0.62 mL, 7.0 mmol) in diethyl ether (5 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and the solvent was removed with nitrogen flow. The residue was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C. 4-(4-Methoxyphenyl)butylamine (1.26 g, 7.1 mmol) was added portionwise and the mixture was stirred at room temperature overnight. The precipitate which resulted was filtered off and the filtrate was concentrated in vacuo. The crude mixture was purified by silica gel column chromatography eluting with hexane/ethyl acetate (1/1) to give oxoacetamide **26** as a white solid (1.24 g, 95%). Mp 128–130 °C. IR (KBr) cm^{-1}: 3303 (νNH); 2928, 2857 (νCH); 1705, 1651 (νC=O); 1511 (νC=C arom.). ^{1}H NMR δ 8.60 (s, 1H, H_9), 8.49–8.45 (m, 1H, NH), 7.72 (s, 1H, H_7), 7.19–7.02 (m, 5H, 2H'$_{ar}$, 3H$_{ar}$), 6.86 (d, 2H, J=8.5 Hz, 2H'$_{ar}$), 4.37 (q, 2H, J=7.0 Hz, CH_2), 4.04–3.98 (m, 2H, H_4), 3.74 (s, 3H, OCH_3), 3.06–3.02 (m, 2H, H_6), 2.76–2.72 (m, 2H, CH_2), 2.52–2.48 (m, 2H, CH_2), 2.38 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.59–1.21 (m, 4H, CH_2), 1.38 (t, 3H, J=7.0 Hz, CH_3). ^{13}C NMR δ 14.5, 21.0, 22.2, 24.1, 28.1, 28.8, 34.0, 38.3, 43.3, 55.1, 60.6, 110.8, 113.8, 121.1, 121.5, 123.3, 124.4, 128.3, 128.8, 129.3, 129.4, 131.1, 134.0, 136.4, 137.2, 148.9, 157.5, 166.5, 166.8, 187.8. MS-ES$^+$ (MeOH): *m/z* 568 (M+H$^+$, 100%).

4.6.2. Ethyl 1-{*N*-[4-(4-methoxyphenyl)but-1-yl]aminoethyl}-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo-[3,2,1-*ij*]quinoline-8-carboxylate (27). Borane–tetrahydrofuran complex (4.4 mL, 4.4 mmol) was added to a solution of *N*-[4-(4-methoxyphenyl)but-1-yl]-2-[8-ethoxycarbonyl-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]-2-oxoacetamide **26** (0.50 g, 0.87 mmol) in dry tetrahydrofuran (20 mL) under nitrogen at room temperature. The reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in methanol (30 mL). *N*,*N*-Dimethylethanolamine (5 mL) was added and the solution was refluxed for 3 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (1/1), to afford ester **27** as a white solid (197 mg, 42%). Mp 87–89 °C. IR (KBr) cm^{-1}: 3449 (νNH); 2928 (νCH); 1703 (νC=O); 1607, 1512 (νC=C arom.). ^{1}H NMR δ 8.15 (s, 1H, H_9), 7.55 (s, 1H, H_7), 7.16–7.12 (m, 5H, 2H'$_{ar}$, 3H$_{ar}$), 6.87 (d, 2H, J=8.3 Hz, 2H'$_{ar}$), 4.34 (q, 2H, J=8.3 Hz, CH_2), 4.01–3.97 (m, 2H, H_4), 3.74 (s, 3H, OCH_3), 3.02–2.98 (m, 2H, H_6), 2.91–2.72 (m, 4H, CH_2), 2.57–2.53 (m, 2H, CH_2), 2.47–2.43 (m, 2H, CH_2), 2.38 (s, 6H, CH_3), 2.14–2.10 (m, 2H, H_5), 1.59–1.21 (m, 4H, CH_2), 1.37 (t, 3H, J=8.3 Hz, CH_3). ^{13}C NMR δ 14.6, 21.1, 21.4, 22.3, 24.2, 25.4, 28.4, 33.7, 42.8, 46.1, 47.3, 55.1, 60.1, 108.3, 113.6, 119.1, 119.4, 121.4, 122.9, 123.4, 127.9, 128.5, 129.0, 129.3, 130.9, 134.4, 136.3, 137.1, 157.2, 185.3. MS-ES$^+$ (MeOH): *m/z* 540 (M+H$^+$, 100%).

4.6.3. 1-[*N*-[4-(4-Methoxyphenyl)but-1-yl]aminoethyl]-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-8-carboxylic acid 28. An aqueous solution of 2 N NaOH (10 mL) was added to ester **27** (180 mg, 0.33 mmol) in ethanol (20 mL) at room temperature. The reaction mixture was refluxed for 2 h, cooled to room temperature and neutralised with a 6 N solution of HCl. The precipitate which resulted was collected by filtration, washed by water and dried over P_2O_5 to give carboxylic acid **28** as a white solid (102 mg, 72%). Mp 315 °C (degradation). IR (KBr) cm^{-1}: 3600–2400 (νOH); 3425 (νNH); 2927, 2856 (νCH); 1701 (νC=O); 1600, 1512 (νC=C arom.). ^{1}H NMR δ 8.25 (s, 1H, H_9), 7.58 (s, 1H, H_7), 7.16–7.12 (m, 5H, 2H'$_{ar}$, 3H$_{ar}$), 6.87 (d, 2H, J=8.3 Hz, 2H'$_{ar}$), 4.01–3.97 (m, 2H, H_4), 3.74 (s, 3H, OCH_3),

3.02–2.98 (m, 2H, H_6), 2.97–2.91 (m, 4H, CH_2), 2.74–2.70 (m, 2H, CH_2), 2.50–2.46 (m, 2H, CH_2), 2.40 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.56–1.52 (m, 4H, CH_2), 12.46 (s, 1H, OH). ^{13}C NMR δ 21.2, 21.6, 22.5, 24.4, 25.4, 28.3, 33.8, 42.9, 46.5, 47.4, 55.1, 108.3, 113.9, 119.4, 119.9, 121.8, 122.4, 124.5, 127.8, 129.4, 130.1, 133.7, 136.3, 137.8, 138.1, 138.5, 157.6, 169.0. MS-ES$^+$ (MeOH): *m/z* 512 ($M+H^+$, 100%).

4.6.4. 4-{1-[*N*-[4-(4-Methoxyphenyl)but-1-yl]aminoethyl]-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-8-oyl}morpholine 29. Morpholine (0.17 mL, 0.58 mmol) and PyBOP (0.56 g, 0.32 mmol) were added to the solution of *N*-methylmorpholine (0.22 mL, 0.58 mmol) and carboxylic acid **28** (0.50 g, 0.29 mmol) in dimethylformamide (5 mL). The mixture was stirred at room temperature for 3 days. The mixture was quenched with water and the aqueous solution was extracted with dichloromethane. The organic layer was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography eluting with dichloromethane/ethanol (9/1) to give morpholide **29** as a white solid (109 mg, 65%). Mp 92–94 °C. IR (KBr) cm^{-1}: 3448 (νNH); 2926, 2855 (νCH); 1604 (νC=O); 1512, 1435 (νC=C arom.). ^{1}H NMR δ 7.56 (s, 1H, H_9), 6.99 (s, 1H, H_7), 7.16–7.12 (m, 3H, $3H_{ar}$), 7.11 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 6.87 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 4.01–3.97 (m, 2H, H_4), 3.74 (s, 3H, OCH_3), 3.65–3.61 (m, 2H, CH_2 morph.), 3.60–3.57 (m, 2H, CH_2 morph.), 3.00–2.96 (m, 2H, H_6), 2.88–2.84 (m, 4H, CH_2), 2.68–2.66 (m, 2H, CH_2), 2.50–2.46 (m, 2H, CH_2), 2.39 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.52–1.48 (m, 4H, CH_2). ^{13}C NMR δ 21.2, 21.9, 22.6, 24.4, 25.5, 28.2, 33.8, 42.8, 46.7, 47.1, 48.3, 55.2, 66.4, 108.1, 113.9, 118.1, 122.1, 124.3, 126.8, 127.7, 129.4, 130.1, 130.3, 133.6, 134.4, 136.6, 138.1, 138.2, 157.6, 173.4. MS-ES$^+$ (MeOH): *m/z* 581 ($M+H^+$, 100%).

4.6.5. 4-{1-[*N*-[4-(4-Hydroxyphenyl)but-1-yl]aminoethyl]-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-8-oyl}morpholine 30. A solution of amide **29** (0.28 g, 0.48 mmol) in dry dichloromethane was stirred at room temperature during dropwise addition of boron tribromide (1 mL, 1 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 2 h. Saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted by dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the waited phenol **30** as a white solid (122 mg, 45%). Mp 120–122 °C. IR (KBr) cm^{-1}: 3600–2400 (νOH); 3426 (νNH); 2926, 2856 (νCH); 1600 (νC=O); 1514, 1438 (νC=C arom.). ^{1}H NMR δ 7.56 (s, 1H, H_9), 6.99 (s, 1H, H_7), 7.14–7.10 (m, 3H, $3H_{ar}$), 7.11 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 6.86 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 4.01–3.97 (m, 2H, H_4), 3.65–3.61 (m, 2H, CH_2 morph.), 3.60–3.57 (m, 2H, CH_2 morph.), 3.00–2.96 (m, 2H, H_6), 2.88–2.84 (m, 4H, CH_2), 2.62–2.58 (m, 2H, CH_2), 2.50–2.46 (m, 2H, CH_2), 2.39 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.52–1.48 (m, 4H, CH_2). ^{13}C NMR δ 21.1, 21.7, 22.6, 24.4, 25.1, 28.6, 34.0, 42.4, 46.1, 47.3, 48.6, 66.4, 115.2, 116.2, 118.0, 122.0, 124.4, 126.1, 127.7, 129.2, 130.4, 131.9, 133.1, 134.4, 135.9, 138.0, 138.1, 155.6, 171.1. MS-ES$^+$ (MeOH): *m/z* 567 ($M+H^+$, 100%).

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