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New approach for the synthesis of 3*H*-pyrrolo[2,3-*c*]isoquinoline derivatives

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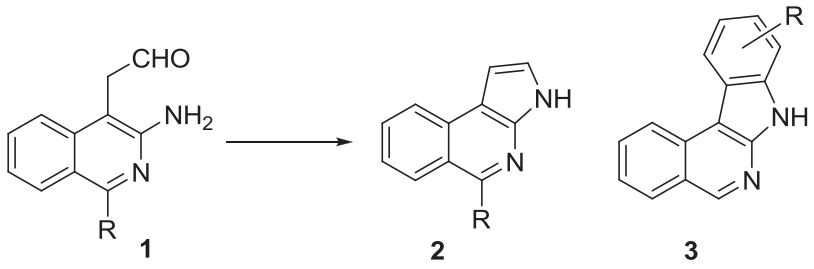
ABSTRACT

Synthesis of new 2,3-diaryl-3*H*-pyrrolo[2,3-*c*]isoquinoline derivatives has been elaborated starting from isoquinoline-3-amine. Buchwald–Hartwig arylation and subsequent iodination in position 4 afforded 3-arylamino-4-iodoisoquinolines. These compounds were subjected to Sonogashira cross-coupling reactions with some selected acetylenes, and the resulting coupled products underwent cyclization in the presence of tetrabutylammonium fluoride to give title derivatives.

1. Introduction

Our previous extended studies[1,2] in the area of isoquinoline chemistry and availability of novel derivatives of this ring system, efforts to synthesize novel isoquinoline-fused ring systems seemed reasonable. In this context, application of the recently established cross-coupling methodologies seemed of particular interest. In the present paper we report on a straightforward new synthetic pathway to the 3*H*-pyrrolo[2,3-*c*]isoquinoline ring system starting from isoquinoline-3-amine. Only one research group: Biehl et al. investigated formation of this particular ring system (**2**) from the 4-formymethylisoquinolineamine (**1**) under acidic conditions.[3,4] Furthermore, the related tetracyclic 7*H*-indolo[2,3-*c*]isoquinoline (**3**)[5] and other *N*-positional isomers[6,7] have been reported (Scheme 1). To the best of our knowledge, no cross-coupling methodology has been applied along the pathways to these heterocycles.



Scheme 1. Earlier known pyrrolo[2,3-*c*]isoquinoline derivatives and related tetracyclic derivatives.

Some of the pyrrole-fused isoquinolines are of biological importance, which provided a further motivation for our research; pyrrolo[2,1-*a*]isoquinoline moieties[8] are present in alkaloid families, such as erythrina[9] and lamellarin[10] and, exhibit diverse biological activities.[7,11]

2. Results and discussion

On the basis of our expertise in the area of aminoisoquinoline chemistry[1,2,12] and cross-coupling methodologies[13] the retrosynthetic analysis for preparation of the title ring system shown in

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Fig. 1 was used. Inspection of this figure reveals that besides the ring-closing step (b)→(a), another predominant structural modification, (c)→(b) has been planned, in which the amino group is substituted by a phenyl ring, whereas the X atom (halogen) is exchanged for an acetylic moiety. Both of these transformations can be carried out by cross-coupling methodologies (Buchwald–Hartwig arylation of the amine and Sonogashira coupling at the X group in position 4, respectively).

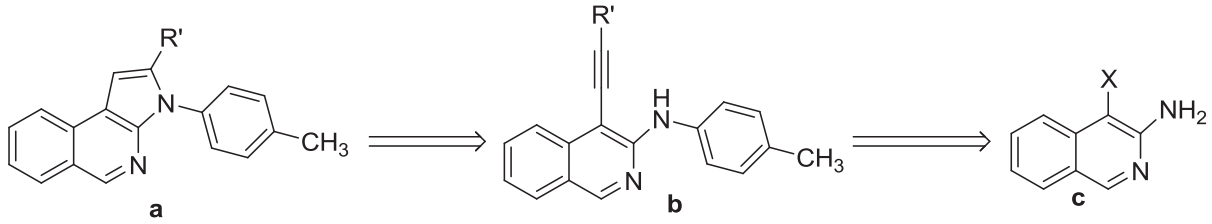


Fig. 1. Retrosynthetic analysis of preparation of the tricyclic pyrrolo[2,3-*c*]isoquinoline ring (a).

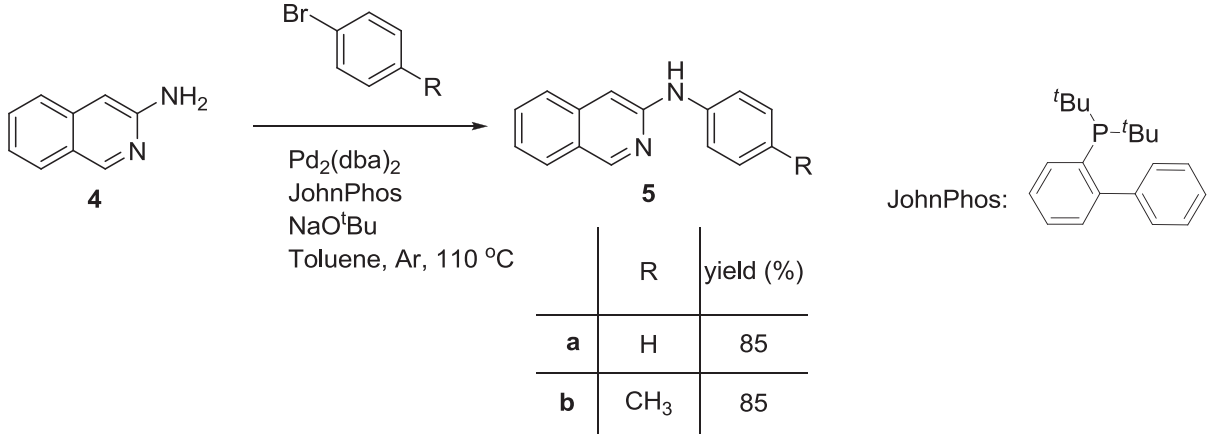
Concerning the ring-closing step (b)→(a) a literature survey of related cyclizations seemed of interest. Molecules having adjacent carbon–carbon multiple bond and nucleophilic amine were often used for the intramolecular cyclization to various indoles,[14–16] benzofurans,[17] isocoumarines,[18] benzopyranes,[19] etc. derivatives using basic conditions,[20] transition metal-catalyzed reactions,[21] gold(III),[22] copper(I),[23] copper(II) salt-catalyzed reactions,[24] and ammonium fluoride-mediated reactions.[25] The most frequently used reagents or catalysts for these ring-closing reactions are the palladium complexes,[26,27] iodine-promoted and many applications together with polymer-supported reactions[28] have also been established.

In accordance with some literature records[30] we have found that isoquinoline-3-amine (**4**)[12] readily undergoes Buchwald–Hartwig coupling reaction[29] with bromobenzene derivatives to give *N*-aryl-3-isoquinolineamines (**5**, Scheme 2). The best yields have been achieved by using $Pd_2(dba)_2$ catalyst with the JohnPhos ligand, sodium *t*-butoxide as base in boiling toluene under an argon atmosphere.

bromo analogs[31] prompted us to investigate the planned transformation with 4-iodoisoquinoline-3-amine.

Very little precedent can be found for the direct iodination of azines. To the best of our knowledge, there is only one publication for the iodination of an isoquinoline in the position 4, which was carried out with *N*-iodosuccinimide (NIS).[32] When **5a** was subjected to iodination according to this literature reference, i.e., with maintaining the reaction mixture at room temperature for prolonged time (24 h), a mixture of the expected 4-iodoisoquinoline-3-amine (**6**) and an unexpected diiodo product (**7**) was obtained, where the two products were found in a comparable ratio (Scheme 3). When, however, this reaction was repeated at lower temperature (−20 °C), formation of **7** could be excluded, but the desired iodo compound **6** was obtained in very low yield, which was not increased even after long reaction time.

Since separation of these products seemed to be very difficult because of their similar chromatographic behavior, the *para* position of the phenyl ring was blocked by a methyl group and, thus, **5b** was subjected to iodination. Although even in this case the iodination of the phenyl ring (in *ortho* position to the methyl group) as a side reaction was experienced (the diiodo compound **9** was formed), proper work up (column chromatography on silica by hexane/CH_2Cl_2 (2:1) as the eluent) allowed isolation of the desired 4-iodo-3-(4-toluidinyl)isoquinoline (**8**) in acceptable (50%) yield (Scheme 3).



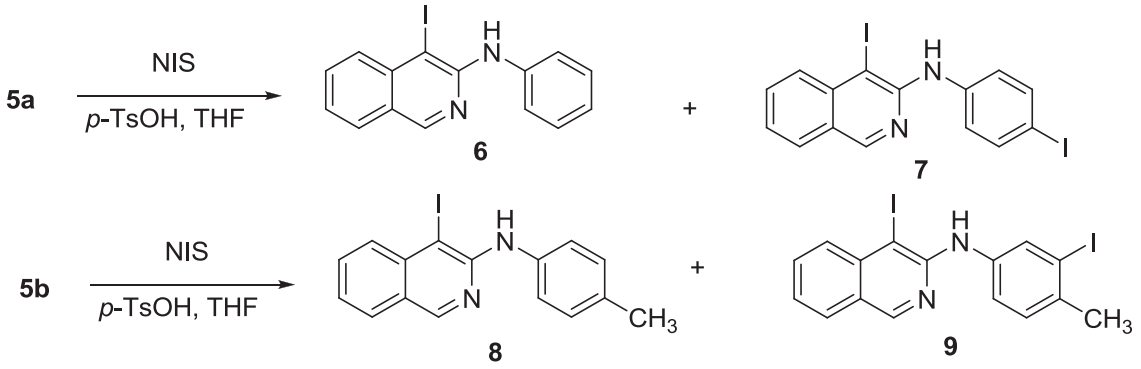
	R	yield (%)
a	H	85
b	CH_3	85

Scheme 2. Buchwald–Hartwig arylation of isoquinoline-3-amine.

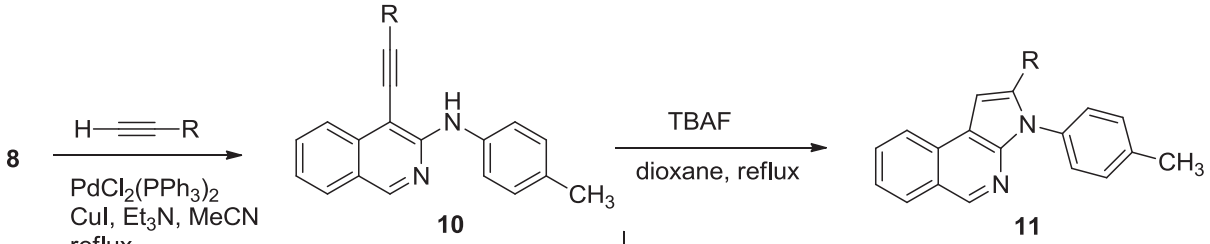
In order to gain an excess to the 4-halogen substituted isoquinolines that could enable the planned Sonogashira coupling to an acetylene, introduction of halogen atom was necessary. Bromination of isoquinoline-3-amine in position 4 is well documented in the literature and, thus, preparation of 4-bromoisoquinoline-3-amine has been described.[30] Unfortunately, however, all of our efforts for Sonogashira coupling of this compound proved to be unsuccessful. The general experience that iodohetaryl compounds more readily participate in cross-coupling reactions than the

Sonogashira coupling[33] of **8** with five various acetylenic compounds was carried out successfully to give 4-ethynyl derivatives **10a**–**e** as stable crystalline substances (Scheme 4). Inclusion of the acetylenic chain was shown by the appearance of the typical IR absorption around 2200 cm^{-1}.

When these compounds were subjected to ring closure reactions upon analogy to some related literature data to form a fused pyrrole ring, our initial efforts even by the use of different reaction temperatures, various solvents and palladium catalysts proved to



Scheme 3. Iodination of isoquinoline-3-arylamines.



	R
a	C_6H_5
b	2-NO_2-C_6H_4
c	4-NO_2-C_6H_4
d	CH_2OH
e	CH_2CH_2OH

Scheme 4. Sonogashira coupling at position 4 in isoquinoline-3-amine and TBAF initiated cyclization to fused pyrrole.

be unsuccessful. Inspection of the past literature data on similar ring closure reactions revealed, however, that a quite unique reaction condition, i.e., use of tetrabutylammonium fluoride (TBAF) might be useful in the present case[34] by activation of the acetylenic triple bond and, thereby, promoting the cyclization.

Thus, when **10** was treated with this reagent in a dioxane solution, the cyclization took place smoothly and derivatives of the 3*H*-pyrrolo[2,3-*c*]isoquinoline ring system (**11**) have been obtained in acceptable to excellent (44–85%) yield (Scheme 4). Evidence for the ring closure of the pyrrole moiety was clearly shown by the disappearance of the acetylene function in IR as well as the presence of the new aromatic CH moiety in the five-membered heterocycles was detected by NMR spectroscopy.

As Hiroya et al.[34] suggested, TBAF can strongly polarize the triple bond by forming ion-pairs so that the nucleophilic nitrogen atom can successfully attack one of the carbon atoms to carry out a 5-*endo*-*dig* cyclization process which, in this case, results in formation of a fused pyrrole ring.

3. Conclusions

These studies reveal that a new and convenient approach to pyrrolo[3,4-*c*]isoquinolines has been elaborated by application of Sonogashira coupling of 4-iodo-3-anilinoisoquinolines followed by TBAF assisted ring closure. Continuation of exploration of further ring closure reactions to fused isoquinolines is in progress.

4. Experimental part

4.1. General methods

Melting points were determined on a Büchi apparatus. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. NMR measurements were performed on Varian INOVA-300 and 400 spectrometer equipped with a 5 mm inverse detection z-gradient probe. ^1H and ^{13}C NMR spectra were measured at room temperature (25 °C) in an appropriate solvent. ^1H and ^{13}C chemical shifts are expressed in parts per million (δ) referenced to TMS or residual solvent signals. The elemental analysis has been carried out with an Elementar Vario EL III apparatus (at the Analytical Laboratory for Organic Chemistry, Chemical Research Center, Hungarian Academy of Sciences, H-1025 Budapest, Pusztaszeri út 59). The exact mass measurements were performed using a Q-TOF Premier mass spectrometer (Waters Corporation, 34 Maple St, Milford, MA, USA) in positive electrospray mode. Reactions were monitored with Merck silica gel 60 F_{254} TLC plates (0.25 mm thickness). All the chemicals and solvents were used as supplied.

4.2. *N*-Phenylisoquinoline-3-amine (5a)

A round-bottomed flask was charged with $Pd_2(dba)_3$ (0.233 g, 0.26 mmol, 5 mol %), JohnPhos (0.152 g, 0.51 mmol, 10 mol %),

bromobenzene (0.800 g, 5.10 mmol), isoquinoline-3-amine (0.734 g, 5.10 mmol), and sodium *tert*-butoxide (0.735 g, 7.65 mmol) followed by dry toluene (20 mL). The flask was flushed with argon for 5 min. The resulting mixture was heated under reflux with magnetic stirring for 5 h. After cooling down to room temperature the reaction mixture was evaporated and the residue was purified by flash column chromatography on silica gel using hexane/EtOAc (4:1) as eluent yielding the product (0.940 g, 85%). Yellow crystal; mp 101–102 °C (lit. mp 102–103 °C[30]); ν_{max} (KBr, cm^{-1}): 3239, 3054, 1631, 1453, 741; δ_H (300 MHz, $CDCl_3$): 6.91 (1H, s, NH), 7.08 (1H, dd, *J*=6.6 Hz, 6.4 Hz, H-4′), 7.20 (1H, s, H-4), 7.27–7.41 (5H, m, H-7, H-2′, H-3′, H-5′, H-6′), 7.49–7.58 (2H, m, H-5, H-6), 7.81 (1H, d, *J*=8.2 Hz, H-8), 8.96 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 99.3 (C-4), 120.2 (C-2′, C-6′), 122.9 (C-4′), 123.9 (C-7), 124.8 (C-8a), 125.5 (C-5), 128.0 (C-8), 129.7(C-3′, C-5′), 130.8 (C-6), 138.8 (C-4a), 141.3 (C-1′), 152.3 (C-3, C-1). Anal. Calcd for $C_{15}H_{12}N_2$ (220.26): C, 81.79; H, 5.49; N, 12.72%. Found: C, 81.41; H, 5.56; N, 13.03%.

4.3. *N*-*p*-Tolylisoquinolin-3-amine (5b)

$Pd_2(dba)_3$ (0.254 g, 0.277 mmol, 5 mol %), JohnPhos (0.166 g, 0.56 mmol, 10 mol %), 4-bromotoluene (0.951 g, 5.56 mmol), isoquinoline-3-amine (0.800 g, 5.56 mmol), sodium *tert*-butoxide (0.800 g, 8.33 mmol), and dry toluene (20 mL). Reaction time (5 h) using the same procedure described for the synthesis of **5a**. Eluent: hexane/EtOAc (4:1); yield: 1.106 g, 85%. Yellow crystals; mp 134–136 °C; ν_{max} (KBr, cm^{-1}): 3248, 3054, 1629, 1363, 820; δ_H (300 MHz, DMSO-d_6): 2.23 (3H, s, C*H*$_3$), 7.06–7.09 (3H, m, H-4, H-3′, H-5′), 7.24 (1H, dd, *J*=7.5, 7.5 Hz, H-7), 7.38 (2H, m, H-2′, H-6′), 7.50 (1H, dd, *J*=7.8, 7.5 Hz, H-6), 7.63 (1H, d, *J*=7.8 Hz, H-5), 7.86 (1H, d, *J*=7.5 Hz, H-8), 8.83 (1H, s, NH), 8.98 (1H, s, H-1); δ_C (75 MHz, DMSO-d_6): 20.3 (*C*H$_3$), 99.1 (C-4), 118.6 (C-2′, C-6′), 122.9 (C-7), 123.4 (C-8a), 124.8 (C-5), 127.5 (C-8), 129.2 (C-3′, C-5′), 129.4 (C-4′), 130.3 (C-6), 138.0 (C-4a), 139.2 (C-1′), 151.2 (C-1), 152.5 (C-3). Anal. Calcd for $C_{16}H_{14}N_2$ (234.29): C, 82.02; H, 6.02; N, 11.96%. Found: C, 82.31; H, 5.95; N, 11.74%.

4.4. Iodination of *N*-phenylisoquinolin-3-amine (5a)

A solution of *N*-phenylisoquinoline-3-amine (**5a**, 0.200 g, 0.91 mmol) in THF (10 mL) at −20 °C was treated with *N*-iodosuccinimide (0.225 g, 1.0 mmol) and *p*-TsOH·H_2O (0.064 g, 0.34 mmol). The mixture was stirred at −20 °C for 1 h and, then maintained at 25 °C for 24 h. The mixture was diluted with EtOAc (30 mL) and treated with aqueous saturated Na_2SO_3 (30 mL). The aqueous layer was extracted with EtOAc (3×30 mL), dried (Na_2SO_4), and concentrated in vacuo to give a mixture of **6** and **7**. The residue was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (2:1) as the eluent. Evaporation of the first fraction yielded 4-iodo-*N*-(4-iodophenyl)isoquinolin-3-amine (**7**) as yellow crystals (0.129 g, 30%; mp 188–189 °C); ν_{max} (KBr, cm^{-1}): 3392, 2361, 1588, 1235, 749; δ_H (300 MHz, $CDCl_3$): 7.10 (1H, s, NH), 7.33–7.40 (3H, m, H-7, H-2″, H-6″), 7.61–7.64 (3H, m, H-6, H-3″, H-5″), 7.77–7.86 (2H, m, H-8, H-5), 8.83 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 79.8 (C-4), 85.1 (C-4″), 122.0 (C-2′, C-6′), 124.6 (C-7), 125.7 (C-8a), 128.3 (C-8), 129.6 (C-5), 132.3 (C-6), 137.8 (C-3″, C-5″), 139.8 (C-4a), 140.7 (C-1′), 150.9 (C-3), 151.4 (C-1). Anal. Calcd for $C_{15}H_{10}I_2N_2$ (472.06): C, 38.16; H, 2.14; N, 5.93%. Found: C, 38.01; H, 2.29; N, 5.81%. Work up of the second fraction (of smaller R_f value) afforded 4-iodo-*N*-(phenyl) isoquinolin-3-amine (**6**) as yellow crystals (0.107 g, 34%, mp 113–115 °C); ν_{max}(KBr, cm^{-1}): 3376, 1572, 1414, 1231, 752; δ_H (300 MHz, $CDCl_3$): 7.04–7.13 (2H, m, NH, H-4′), 7.33–7.40 (3H, H-7, H-3′, H-5′), 7.53–7.66 (3H, m, H-6, H-2′, H-6′), 7.76–7.85 (2H, m, H-8, H-5), 8.83 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 79.4 (C-4), 120.4 (C-2′, C-6′), 122.8 (C-4′), 124.3 (C-7), 125.6 (C-8a), 128.4 (C-8), 129.1 (C-3′, C-5′), 129.5 (C-5), 132.2 (C-6), 140.0 (C-4a), 140.9 (C-1′), 151.5 (C-1), 162.8 (C-3). Anal. Calcd for $C_{15}H_{11}IN_2$ (346.16): C, 52.04; H, 3.20; N, 8.09%. Found: C, 51.95; H, 3.34; N, 7.89%.

4.5. 4-Iodo-*N*-*p*-tolylisoquinolin-3-amine (8)

A solution of *N*-*p*-tolylisoquinolin-3-amine (0.400 g, 1.71 mmol) in THF (20 mL) at −20 °C was treated with *N*-iodosuccinimide (0.423 g, 1.88 mmol) and *p*-TsOH·H_2O (0.120 g, 0.64 mmol). The mixture was stirred at −20 °C for 1 h and, then, maintained at 25 °C for 24 h. The mixture was diluted with EtOAc (30 mL) and treated with aqueous saturated Na_2SO_3 (30 mL). The aqueous layer was extracted with EtOAc (3×30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (2:1) as the eluent. Evaporation of the second fraction afforded 4-iodo-*N*-*p*-tolylisoquinolin-3-amine (**8**) as the main product, yellow crystals (0.332 g, 54%; mp 97–100 °C). ν_{max} (KBr, cm^{-1}): 3414, 3395, 2914, 1617, 1235; δ_H (300 MHz, $CDCl_3$): 2.35 (3H, s, C*H*$_3$), 7.05 (1H, s, NH), 7.16 (2H, m, H-3′, H-5′), 7.33 (1H, dd, *J*=7.7, 7.4 Hz, H-7), 7.40 (2H, m, H-2′, H-6′), 7.62 (1H, dd, *J*=7.5, 7.5 Hz, H-6), 7.75 (1H, d, *J*=8.1 Hz, H-5), 7.82 (1H, d, *J*=8.7 Hz, H-8), 8.81 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 21.1 (*C*H$_3$), 78.9 (C-4), 121.3 (C-2′, C-6′), 124.1 (C-7), 125.5 (C-8a), 128.5 (C-8), 129.5 (C-5), 129.7 (C-3′, C-5′), 132.3 (C-6), 132.8 (C-1′), 138.3 (C-4′), 140.1 (C-4a), 151.7 (C-1), 152.0 (C-3). Anal. Calcd for $C_{16}H_{13}IN_2$ (360.19): C, 53.35; H, 3.64; N, 7.78%. Found: C, 53.61; H, 3.48; N, 7.72%.

4.6. 4-Iodo-*N*-(3-iodo-4-methylphenyl)isoquinolin-3-amine (9)

This compound was obtained by work up of the first (more apolar) chromatographic fraction. Yield: 0.233 g, 28%; yellow crystals; mp 161–163 °C; ν_{max} (KBr, cm^{-1}): 3327, 2917, 1589, 1480, 747; δ_H (300 MHz, $CDCl_3$): 2.31 (C*H*$_3$), 7.17 (1H, d, *J*=8.4 Hz, H-6′), 7.34–7.39 (2H, m, NH, H-7), 7.62–7.69 (2H, m, H-6, H-2′), 7.77 (1H, d, *J*=8.1 Hz, H-8), 7.89 (2H, m, H-5, H-5′), 8.81 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 20.5 (CH_3) 80.1 (C-4), 92.1 (C-3′), 121.6 (C-5′), 124.5 (C-7), 125.8 (C-8a), 128.5 (C-8), 129.7 (C-5), 129.8 (C-6′), 132.4 (C-6), 134.5 (C-1′), 139.4 (C-4′), 139.5 (C-2′), 140.1 (C-4a), 151.5 (C-1), 151.6 (C-3). Anal. Calcd for $C_{16}H_{12}I_2N_2$ (486.08): C, 39.53; H, 2.49; N: 5.76%. Found: C, 39.31; H, 2.60; N, 5.59%.

4.7. 4-(Phenylethynyl)-*N*-*p*-tolylisoquinolin-3-amine (10a)

A round-bottomed flask was charged with 4-iodo-*N*-*p*-tolylisoquinolin-3-amine (0.300 g, 0.83 mmol), $PdCl_2(PPh_3)_2$ [dichlorobis(triphenylphosphine)palladium(II)] (0.023 g, 0.033 mmol, 4 mol %), CuI (0.013 g, 0.07 mmol, 8 mol %), and Et_3N (0.167 g, 1.66 mmol, 0.230 mL) followed by dry acetonitrile (2 mL). The mixture was flushed with argon for 5 min. Then phenylacetylene (0.127 g, 1.25 mmol, 0.137 mL) was added and the mixture was heated under reflux for 12 h with magnetic stirring. After cooling down to room temperature the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (30 mL) and the mixture was washed with H_2O (30 mL). The aqueous phase was extracted with EtOAc (2×30 mL) and the collected organic phase dried over anhydrous Na_2SO_4. The residue was purified by column chromatography on silica gel using hexane/EtOAc (25:1) as the eluent yielding yellow crystals (0.181 g, 65%, mp 144–146 °C). ν_{max} (KBr, cm^{-1}): 3402, 2190, 1607, 1240, 753; δ_H (300 MHz, $CDCl_3$): 2.27 (3H, s, C*H*$_3$), 7.09 (2H, m, H-3″, H-5″), 7.25–7.45 (7H, m, H-7, NH, H-5′, H-6′, H-7′, H-2″, H-6″), 7.52–7.60 (3H, m, H-6, H-4′, H-8′), 7.75 (1H, d, *J*=7.8 Hz, H-8), 8.01 (1H, d, *J*=8.4 Hz, H-5), 8.84 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 20.8 (*C*H$_3$), 83.1 (C-1′), 94.2 (C-4), 101.5 (C-2′), 120.5 (C-2″, C-6″), 123.0 (C-8a), 123.4 (C-3′), 123.7 (C-5), 123.8 (C-7), 128.3 (C-8), 128.6 (C-5′, C-7′), 128.6 (C-6′), 129.5 (C-3″, C-5″), 131.2 (C-6), 131.5 (C-4′, C-8′), 132.2 (C-4″), 137.7 (C-1″), 137.9 (C-4a), 151.2

(C-1), 153.5 (C-3); HRMS (ES) for $C_{24}H_{19}N_2$ $[M+H]^+$: calcd 335.1548, found 335.1552.

4.8. 4-((2-Nitrophenyl)ethynyl)-*N*-*p*-tolylisoquinolin-3-amine (10b)

4-Iodo-*N*-*p*-tolylisoquinolin-3-amine (0.240 g, 0.667 mmol), $PdCl_2(PPh_3)_2$ (0.024 g, 0.03 mmol, 5 mol %), CuI (0.006 g, 0.03 mmol, 5 mol %), Et_3N (2.178 g, 21.56 mmol, 3 mL), 1-ethynyl-2-nitrobenzene (0.124 g, 0.84 mmol), and dry acetonitrile (2 mL). Reaction time 3 h. Eluent: hexane/EtOAc (4:1); yield: 0.210 g, 83%; deep purple solid; mp 170–173 °C; ν_{max} (KBr, cm^{-1}): 3384, 2182, 1569, 1240, 741; δ_H (300 MHz, $CDCl_3$): 2.35 (3H, s, C*H*$_3$), 7.20 (2H, m, H-3″, H-5″), 7.32 (1H, dd, *J*=7.8, 7.8 Hz, H-7), 7.48 (1H, dd, *J*=8.0, 8.0 Hz, H-6′), 7.63–7.73 (4H, m, H-6, H-7′, H-2″, H-6″), 7.81–7.87 (2H, m, H-8, H-8′), 8.05–8.11 (2H, m, H-5, NH), 8.24 (1H, d, *J*=8.4 Hz, H-5′), 8.96 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 21.1 (CH_3), 92.9 (C-1′), 93.2 (C-4), 98.2 (C-2′), 119.5 (C-3′), 120.9 (C-2″, C-6″), 123.4 (C-8a), 123.7 (C-5), 123.9 (C-5′), 125.6 (C-7), 128.5 (C-6′), 128.8 (C-8), 129.7 (C-3″, C-5″), 131.9 (C-6), 132.5 (C-4″), 133.6 (C-7′), 134.6 (C-8′), 137.9 (C-1″), 138.5 (C-4a), 148.0 (C-4′), 153.0 (C-1), 155.3 (C-3); HRMS (ES) for $C_{24}H_{18}N_3O_2$ $[M+H]^+$: calcd 380.1399, found 380.1396.

4.9. 4-((4-Nitrophenyl)ethynyl)-*N*-*p*-tolylisoquinolin-3-amine (10c)

4-Iodo-*N*-*p*-tolylisoquinolin-3-amine (0.300 g, 0.833 mmol), $PdCl_2(PPh_3)_2$ (0.029 g, 0.04 mmol, 5 mol %), CuI (0.008 g, 0.04 mmol, 5 mol %), Et_3N (2.178 g, 21.56 mmol, 3 mL), 1-ethynyl-4-nitrobenzene (0.153 g, 1.041 mmol), and dry acetonitrile (2 mL). Reaction time 2 h. Eluent: hexane/EtOAc (6:1); yield: 0.291 g, 92%; deep maroon solid; mp 181–184 °C; ν_{max} (KBr, cm^{-1}): 3402, 2918, 2182, 1568, 1341; δ_H (300 MHz, $CDCl_3$): 2.35 (3H, s, C*H*$_3$), 7.17–7.25 (3H, m, NH, H-3″, H-5″), 7.35 (1H, dd, *J*=7.2, 7.5 Hz, H-7), 7.49 (2H, m, H-2″, H-6″), 7.64–7.73 (3H, m, H-6, H-4′, H-8′), 7.84 (1H, d, *J*=8.4 Hz, H-8), 8.03 (1H, d, *J*=8.7 Hz, H-5), 8.26 (2H, m, H-5′, H-7′), 8.95 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 21.1 (CH_3), 89.3 (C-1′), 93.4 (C-4), 100.0 (C-2′), 121.1 (C-2″, C-6″), 123.6 (C-8a), 123.7 (C-7), 124.1 (C-5′, C-7′), 124.3 (C-5), 128.8 (C-8), 129.8 (C-3″, C-5″), 130.1 (C-3′), 131.9 (C-6), 132.1 (C-4′, C-8′), 133.1 (C-4″), 137.5 (C-1″), 138.2 (C-4a), 147.2 (C-6′), 152.8 (C-1), 154.2 (C-3); HRMS (ES) for $C_{24}H_{18}N_3O_2$ $[M+H]^+$: calcd 380.1399, found 380.1403.

4.10. 3-(3-(*p*-Tolylamino)isoquinolin-4-yl)prop-2-yn-1-ol (10d)

4-Iodo-*N*-*p*-tolylisoquinolin-3-amine (0.300 g, 0.83 mmol), $PdCl_2(PPh_3)_2$ (0.023 g, 0.03 mmol, 4 mol %), CuI (0.013 g, 0.07 mmol, 8 mol %), Et_3N (2.178 g, 21.56 mmol, 3 mL), propargyl alcohol (0.083 g, 1.48 mmol, 0.085 mL), and dry acetonitrile (2 mL). Reaction time 2 h. Eluent: hexane/EtOAc (3:1); yield: (0.176 g, 73%); yellow solid; mp 120–122 °C; ν_{max} (KBr, cm^{-1}): 3361, 2918, 2210, 1573, 1427, 1013; δ_H (300 MHz, $CDCl_3$): 2.20 (1H, s, OH), 2.34 (3H, s, C*H*$_3$), 4.68 (2H, s, H3′x, H3′y), 7.14–7.31 (4H, m, H-3″, H-5″, NH, H-7), 7.46 (2H, m, H-2″, H-6″), 7.57 (1H, t, *J*=8.1, 7.7 Hz, H-6), 7.77 (1H, d, *J*=8.2 Hz, H-8), 7.95 (1H, d, *J*=8.5 Hz, H-5), 8.89 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 21.1 (CH_3), 52.1 (C-3′), 79.8 (C-1′), 93.9 (C-4), 99.7 (C-2′), 121.0 (C-2″, C-6″), 123.5 (C-8a), 123.8 (C-5), 123.9 (C-7), 128.5 (C-8), 129.7 (C-3″, C-5″), 131.5 (C-6), 132.6 (C-4″), 137.8 (C-1″), 138.4 (C-4a), 151.6 (C-1), 154.1 (C-3); HRMS (ES) for $C_{19}H_{17}N_2O$ $[M+H]^+$: calcd 289.1341, found 289.1342.

4.11. 4-(3-(*p*-Tolylamino)isoquinolin-4-yl)but-3-yn-1-ol (10e)

4-Iodo-*N*-*p*-tolylisoquinolin-3-amine (0.300 g, 0.83 mmol), $PdCl_2(PPh_3)_2$ (0.029 g, 0.04 mmol, 5 mol %), CuI (0.008 g, 0.04 mmol, 5 mol %), Et_3N (2.178 g, 21.56 mmol, 3 mL), but-3-yn-1-ol (0.088 g, 1.25 mmol, 0.095 mL), and dry acetonitrile (2 mL). Reaction time 2 h. Eluent: hexane/EtOAc (2:1); yield: 0.215 g, 85%; brownish yellow crystals; mp 100–103 °C; ν_{max} (KBr, cm^{-1}): 3312, 2923, 2210, 1572, 1056, 754; δ_H (400 MHz, $CDCl_3$): 2.0 (1H, br s, OH), 2.31 (3H, s, C*H*$_3$), 2.90 (2H, t, *J*=6.7 Hz, H3′x, H3′y), 3.91 (2H, t, *J*=6.7 Hz, H4′x, H4′y), 7.13 (2H, m, H3″, H5″), 7.26 (1H, dd, *J*=8.2, 7.8 Hz, H7), 7.36 (1H, br s, NH), 7.47 (2H, m, H2″, H6″), 7.57 (1H, dd, *J*=8.5, 7.8 Hz, H6), 7.77 (1H, d, *J*=8.2 Hz, H8), 7.95 (1H, d, *J*=8.5 Hz, H5), 8.86 (1H, s, H1); δ_C (100 MHz, $CDCl_3$): 20.8 (CH_3), 24.3 (C3′), 61.3 (C4′), 76.2 (C1′), 94.8 (C4), 99.1 (C2′), 120.3 (C2″, C6″), 123.2 (C8a), 123.5 (C5), 123.6 (C7), 128.2 (C8), 129.4 (C3″, C5″), 131.0 (C6), 131.9 (C4″), 137.9 (C1″), 138.0 (C4a), 150.5 (C1), 153.7 (C3); HRMS (ES) for $C_{20}H_{19}N_2O$ $[M+H]^+$: calcd 303.1497, found 303.1504.

4.12. 2-Phenyl-3-*p*-tolyl-3*H*-pyrrolo[2,3-*c*]isoquinoline (11a)

A mixture of 4-(phenylethynyl)-*N*-*p*-tolylisoquinolin-3-amine (**10a**, 0.100 g, 0.30 mmol) and tetrabutylammonium fluoride hydrate (TBAF) (0.167 g, 0.60 mmol) in dioxane (10 mL) was degassed with argon and refluxed for 24 h at 110 °C. The solvent was then removed under reduced pressure. The residue was dissolved in EtOAc (25 mL) and the mixture was washed with H_2O (25 mL). The aqueous phase was extracted with EtOAc (2×25 mL) and the collected organic phase dried over anhydrous Na_2SO_4. The residue was purified by column chromatography on silica gel using hexane/EtOAc (3:1) as the eluent yielding the product (0.067 g, 67%), white crystals; mp 198–200 °C; ν_{max} (KBr, cm^{-1}): 3037, 1626, 1516, 1395, 753; δ_H (300 MHz, $CDCl_3$): 2.32 (3H, s, C*H*$_3$), 7.14–7.29 (10H, m, H-1, H-2″, H-3″, H-5″, H-6″, H-2′, H-3′, H-4′, H-5′, H-6′), 7.42 (1H, dd, *J*=7.2, 7.8 Hz, H-7), 7.66 (1H, dd, *J*=7.5, 7.5 Hz, H-8), 7.95 (1H, d, *J*=8.1 Hz, H-6), 8.17 (1H, d, *J*=8.4 Hz, H-9), 8.82 (1H, s, H-5); δ_C (75 MHz, $CDCl_3$): 21.4 (CH_3), 100.6 (C-1), 114.4 (C-1a), 122.7 (C-9), 124.4 (C-7), 125.6 (C-5a), 127.6 (C-4′), 128.5 (C-2″, C-6″), 128.5 (C-2′, C-6′), 128.9 (C-6), 129.1 (C-3′, C-5′), 129.9 (C-3″, C-5″), 130.1 (C-8), 131.2 (C-9a), 132.8 (C-1″), 134.8 (C-2), 137.6 (C-1′), 138.8 (C-4″), 145.6 (C-3a), 147.2 (C-5); HRMS (ES) for $C_{24}H_{19}N_2$ $[M+H]^+$: calcd 335.1548, found 335.1549.

4.13. 2-(2-Nitrophenyl)-3-*p*-tolyl-3*H*-pyrrolo[2,3-*c*] isoquinoline (11b)

This compound was prepared—similar to **11a**—from 4-((2-nitrophenyl)ethynyl)-*N*-*p*-tolylisoquinolin-3-amine (**10b**, 0.130 g, 0.34 mmol) and TBAF (0.334 g, 1.28 mmol) in dioxane (10 mL). Reaction time 6 h. Eluent: hexane/EtOAc (6:1); yield: (0.057 g, 44%); pale yellow crystals; mp 206–209 °C; ν_{max} (KBr, cm^{-1}): 3381, 2923, 1611, 1527, 755; δ_H (300 MHz, $CDCl_3$): 2.35 (3H, s, C*H*$_3$), 7.15–7.23 (5H, m, H-1, H-2″, H-3″, H-5″, H-6″), 7.43–7.61 (4H, m, H-7, H-4′, H-5′, H-6′), 7.75 (1H, dd, *J*=7.7, 7.5 Hz, H-8), 7.84 (1H, d, *J*=8.1 Hz, H-6), 8.04 (1H, d, *J*=8.1 Hz, H-3′), 8.22 (1H, d, *J*=8.1 Hz, H-9), 8.94 (1H, s, H-5); δ_C (75 MHz, $CDCl_3$): 21.4 (CH_3), 101.5 (C-1), 114.2 (1a), 122.8 (C-9), 124.5 (C-3′), 124.7 (C-7), 125.7 (C-5a), 128.0 (C-1′), 128.2 (C-2″, C-6″), 129.0 (C-6), 129.2 (C-4′), 130.0 (C-3″, C-5″), 130.3 (C-8), 131.4 (C-9a), 132.7 (C-6′), 133.5 (C-1″), 133.6 (C-2), 133.7 (C-5′), 137.8 (C-4″), 145.1 (C-3a), 148.1 (C-5), 149.5 (C-2′); HRMS (ES) for $C_{24}H_{18}N_3O_2$ $[M+H]^+$: calcd 380.1399, found 380.1400.

4.14. 2-(4-Nitrophenyl)-3-*p*-tolyl-3*H*-pyrrolo[2,3-*c*] isoquinoline (11c)

This compound was prepared, similar to **11a** from 4-((4-nitrophenyl)ethynyl)-*N*-*p*-tolylisoquinolin-3-amine (**10c**, 0.160 g, 0.42 mmol) and TBAF (0.228 g, 0.87 mmol) in dioxane (10 mL). Reaction time 3 h. Eluent: hexane/EtOAc (4:1); yield: (0.125 g, 78%); yellow crystals; mp 242–245 °C; ν_{max} (KBr, cm^{-1}): 3419, 2922, 1519,

1338, 755; δ_H (300 MHz, $CDCl_3$): 2.43 (3H, s, CH_3), 7.25–7.32 (4H, m, H-2″, H-3″, H-5″, H-6″), 7.38 (1H, s, H-1), 7.47–7.57 (3H, m, H-2′, H-6′, H-7), 7.79 (1H, dd, J=7.7, 7.4 Hz, H-8), 8.05 (1H, d, J=8.1 Hz, H-6), 8.13 (2H, m, H-3′, H-5′), 8.26 (1H, d, J=8.1 Hz, H-9), 8.94 (1H, s, H-5); δ_C (75 MHz, $CDCl_3$): 21.4 (*C*H_3), 103.0 (C-1), 114.3 (C-1a), 122.6 (C-9), 123.9 (C-3′, C-5′), 125.0 (C-7), 125.8 (C-5a), 128.4 (C-2″, C-6″), 129.0 (C-2′, C-6′), 129.1 (C-6), 130.4 (C-3″, C-5″), 130.6 (C-8), 131.2 (C-9a), 134.3 (C-1″), 135.9 (C-2), 138.4 (C-4″), 139.1 (C-1′), 146.4 (C-3a), 146.6 (C-4′), 148.9 (C-5); HRMS (ES) for $C_{24}H_{18}N_3O_2$ $[M+H]^+$: calcd 380.1399, found 380.1398.

4.15. (3-*p*-Tolyl-3*H*-pyrrolo[2,3-*c*]isoquinolin-2-yl)methanol (11d)

This compound was prepared, similar to **11a**, from 3-(3-(*p*-tolylamino)isoquinolin-4-yl)prop-2-yn-1-ol (**10d**, 0.139 g, 0.48 mmol) and TBAF (0.156 g, 0.60 mmol) in dioxane (10 mL) . Reaction time 5 h. Eluent: hexane/EtOAc (3:1); yield: (0.109 g, 78%); pale brown crystals; mp 133–136 °C; ν_{max} (KBr, cm^{-1}): 3383, 2919, 1625, 1517, 759; δ_H (300 MHz, $CDCl_3$): 1.78 (1H, s, OH), 2.45 (3H, s, CH_3), 4.73 (2H, s, H1′x, H1′y), 7.07 (1H, s, H-1), 7.34–7.42 (4H, m, H-2″, H-3″, H-5″, H-6″), 7.49 (1H, dd, J=8.1, 8.1 Hz, H-7), 7.73 (1H, dd, J=8.1, 8.1 Hz, H-8), 8.00 (1H, d, J=8.4 Hz, H-6), 8.18 (1H, d, J=8.1 Hz, H-9), 8.86 (1H, s, H-5); δ_C (75 MHz, $CDCl_3$): 21.5 (*C*H_3), 57.6 (C-1′), 100.0 (C-1), 113.5 (C-1a), 122.6 (C-9), 124.4 (C-7), 125.5 (C-5a), 128.2 (C-2″, C-6″), 129.0 (C-6), 130.2 (C-8), 130.3 (C-3″, C-5″), 131.4 (C-9a), 133.9 (C-1″), 137.8 (C-2), 138.6 (C-4″), 145.2 (C-3a), 147.6 (C-5); HRMS (ES) for $C_{19}H_{17}N_2O$ $[M+H]^+$: calcd 289.1341, found 289.1342.

4.16. 2-(3-*p*-Tolyl-3*H*-pyrrolo[2,3-*c*]isoquinolin-2-yl)ethanol (11e)

This compound was prepared, similar to **11a**, from 4-(3-(*p*-tolylamino)isoquinolin-4-yl)but-3-yn-1-ol (**10e**, 0.120 g, 0.40 mmol) and TBAF (0.152 g, 0.58 mmol) in dioxane (10 mL). Reaction time 3 h. Eluent: hexane/EtOAc (2:1); yield: (0.102 g, 85%); brownish white crystals; mp 122–125 °C; ν_{max} (KBr, cm^{-1}): 3318, 2961, 1531, 1403, 766; δ_H (400 MHz, $CDCl_3$): 2.43 (3H, s, CH_3), 3.00 (2H, t, J=6.6 Hz, H1′x, H1′y), 3.80 (2H, t, J=6.6 Hz, H2′x, H2′y), 6.92 (1H, s, H1), 7.29 (2H, m, H2″, H6″), 7.34 (2H, m, H3″, H5″), 7.45 (1H, dd, J=8.2, 7.5 Hz, H7), 7.70 (1H, dd, J=8.5, 7.5Hz, H8), 7.97 (1H, d, J=8.2 Hz, H6), 8.17 (1H, d, J=8.5 Hz, H9), 8.80 (1H, s, H5); δ_C (100 MHz, $CDCl_3$): 21.2 (*C*H_3), 30.7 (C1′), 61.3 (C2′), 98.4 (C1), 113.6 (C1a), 122.4 (C9), 123.9 (C7), 125.1 (C5a), 128.3 (C2″, C6″), 128.6 (C6), 129.7 (C8), 130.1 (C3″, C5″), 130.6 (C9a), 133.8 (C1″), 135.6 (C2), 138.3 (C4″), 144.8 (C3a), 146.2 (C5); HRMS (ES) for $C_{20}H_{19}N_2O$ $[M+H]^+$: calcd 303.1497, found 33.1500.

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