Novel fluorescent isoquinoline derivatives obtained *via* Buchwald-Hartwig coupling of isoquinolin-3-amines

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Dedicated to Prof. Ferenc Fülöp on the occasion of his 60th birthday

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Abstract
Isoquinolin-3-amines bearing an alkyl group or hydrogen atom in position 4 easily underwent Buchwald-Hartwig coupling reactions with various substituted aryl halides. Investigation of the selected new derivatives with fluorescent spectroscopy revealed that the reaction products have similar photophysical properties to those of isoquinolin-3-amine except the *N*-(nitrophenyl) derivatives, which emit negligible fluorescence.

Keywords: Isoquinolinamine, pyridinamine, fluorescence, Buchwald-Hartwig amination

Introduction

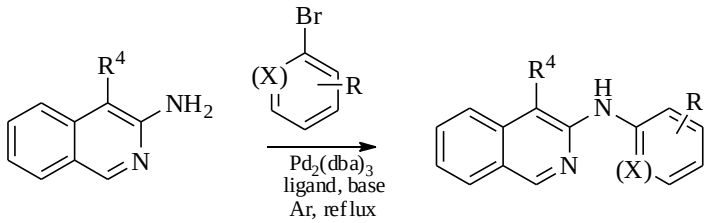
Recently we have published[1] that some isoquinoline derivatives bearing a morpholine group in position 1 or 3 represent a new group of fluorescent compounds. In the course of continuation of our activity in the area of isoquinolinamines, synthesis of variously substituted *N*-arylisoquinolinamines has been decided. Such compounds could serve as valuable starting compounds for subsequent ring closure reactions. To this end, use of the available isoquinolin-3-amine as well its 4-methyl and 4-benzyl derivative in Buchwald-Hartwig amination[2-4] of aryl halides has been envisaged.

Results and Discussion

Inspection of the pertinent literature revealed that very few cases of direct amination with isoquinolinamine have been carried out.[5] Similarly, Buchwald-Hartwig amination with

quinolinamines and pyridinamines and other related *N*-heterocycles have also been published by the same research group.[6]

In the frame of the present study, unsubstituted and 4-alkyl substituted isoquinolin-3-amines (**1**, R^4 = H, CH_3 and $CH_2C_6H_5$, respectively) were treated with various substituted bromobenzene derivatives and 2,3-dibromopyridine as shown in Scheme 1. The substituents of the bromobenzene reagent involved *m*- and *p*-Cl, *o*-, *m*-, and *p*-Br, *o*- and *p*-NO_2, *o*-, *m*-, and *p*-COOEt, *o*-CHO moieties. As a ligand to $Pd_2(dba)_3$ JohnPhos and Xantphos provided the best results. As bases, cesium carbonate and sodium *t*-butoxide were used. The products have been obtained in 46–94% yields. The derivatives and experimental conditions are summarized in Table 1.



1 **2**

Scheme 1

In order to reveal the photophysical properties of the new compounds, some selected derivatives have been studied by absorption and fluorescence spectroscopy. As shown in Figure 1, the nitro-substitution leads to a significant bathochromic shift of the first absorption band, whereas the introduction of the *p*-$COOC_2H_5$ moiety brings about marked blue- and red-shifts for the first and second absorption bands, respectively. The *m*-$COOC_2H_5$ and *p*-Cl substituents have smaller effect. Intramolecular hydrogen bonding between N-H and the oxygen of the *o*-NO_2 may contribute to the considerable diminution of the energy of the lowest singlet-excited state in the case of **2l**. Table 2 summarizes the photophysical parameters of the new compounds and, for the sake of comparison, those of isoquinolin-3-amine (**1**, R^4 = H). The fluorescence maximum (λ_{max}(fl)) exhibits a marked displacement to longer wavelength upon attachment of *N*-phenyl group to **1a**, but λ_{max}(fl) diminishes in the series of **2a** > **2g** > **2s** > **2t** > **1a**. The Stokes-shift of the fluorescence band is larger when a substituted phenyl group is attached to the isoquinolinamine skeleton indicating that more substantial structural alteration occurs upon excitation than in the case of **1a**. The *N*-(nitrophenyl) derivatives (**2o** and **2l**) emit negligible fluorescence due probably to the enhanced charge transfer character of the lowest singlet-excited state. The new compounds have slightly smaller fluorescence quantum yields (Φ_f) and somewhat longer fluorescence lifetimes (τ_f) than **1a,**[1] but neither of these quantities is sensitive to the $COOC_2H_5$ or Cl substitution. The rate constant of fluorescence emission (k_f) and radiationless deactivation (k_{nr}) from the singlet excited state were calculated using $k_f = \Phi_f/\tau_f$ and $k_{nr} = (1- \Phi_f)/\tau_f$ relationships, respectively. As seen in Table 2, practically constant k_{nr} values were

obtained for all fluorescent derivatives, whereas k_f is slightly larger for **1a** compared to the corresponding values of the phenylamino derivatives.

Table 1. Various derivatives of (**2**) obtained by Buchwald-Hartwig coupling of isoquinolin-3-amines (**1**)

	X	R^4	R	Ligand	Base	Solvent	mp (°C)	colour	yield (%)	time (h)
a	CH	H	H	JohnPhos	NaO^{t}Bu	Toluene	101-102	yellow	87	5
b	CH	Me	H	JohnPhos	NaO^{t}Bu	Toluene	76-78	brownish yellow	77	5
c	CH	Benzyl	H	JohnPhos	NaO^{t}Bu	Toluene	155-157	dark yellow	70	5
d	CH	H	*m*-Cl	JohnPhos	NaO^{t}Bu	Toluene	123-126	yellow	91	6
e	CH	Me	*m*-Cl	JohnPhos	NaO^{t}Bu	Toluene	77-79	pale yellow	75	6
f	CH	Benzyl	*m*-Cl	JohnPhos	NaO^{t}Bu	Toluene	72-74	pale yellow	81	6
g	CH	H	*p*-Cl	XantPhos	Cs_2CO_2	1,4-Dioxane	148-151	yellow	70	6
h	CH	H	*o*-Br	XantPhos	Cs_2CO_3	1,4-Dioxane	100-102	green	47	8
i	CH	H	*m*-Br	JohnPhos	NaO^{t}Bu	Toluene	123-125	greenish yellow	46	1
j	CH	Benzyl	*m*-Br	JohnPhos	NaO^{t}Bu	Toluene	60-62	yellow	49	1
k	CH	H	*p*-Br	XantPhos	Cs_2CO_2	1,4-Dioxane	159-162	yellow	80	8
l	CH	H	*o*-NO_2	XantPhos	Cs_2CO_3	1,4-Dioxane	148-149	dark orange	94	5
m	CH	Me	*o*-NO_2	XantPhos	Cs_2CO_4	1,4-Dioxane	130-133	dark orange	94	5
n	CH	Benzyl	*o*-NO_2	XantPhos	Cs_2CO_3	1,4-Dioxane	143-146	orange	95	5
o	CH	H	*p*-NO_2	XantPhos	Cs_2CO_3	1,4-Dioxane	174-176	brownish yellow	55	4
p	CH	Me	*p*-NO_2	JohnPhos	NaO^{t}Bu	Toluene	196-199	brownish orange	60	2
q	CH	Benzyl	*p*-NO_2	JohnPhos	NaO^{t}Bu	Toluene	120-122	brownish yellow	64	2
r	CH	H	*o*-COOEt	XantPhos	Cs_2CO_2	1,4-Dioxane	44-46	green	43	6
s	CH	H	*m*-COOEt	XantPhos	Cs_2CO_3	1,4-Dioxane	107-109	yellow	84	6
t	CH	H	*p*-COOEt	XantPhos	Cs_2CO_3	1,4-Dioxane	141-144	yellow	83	6
u	CH	H	*o*-CHO	XantPhos	Cs_2CO_3	1,4-Dioxane	92-95	brownish yellow	84	2
v	N	H	-	XantPhos	Cs_2CO_3	1,4-Dioxane	107-110	brownish yellow	80	10
w	N	Benzyl	-	XantPhos	Cs_2CO_3	1,4-Dioxane	116-118	brownish yellow	70	10

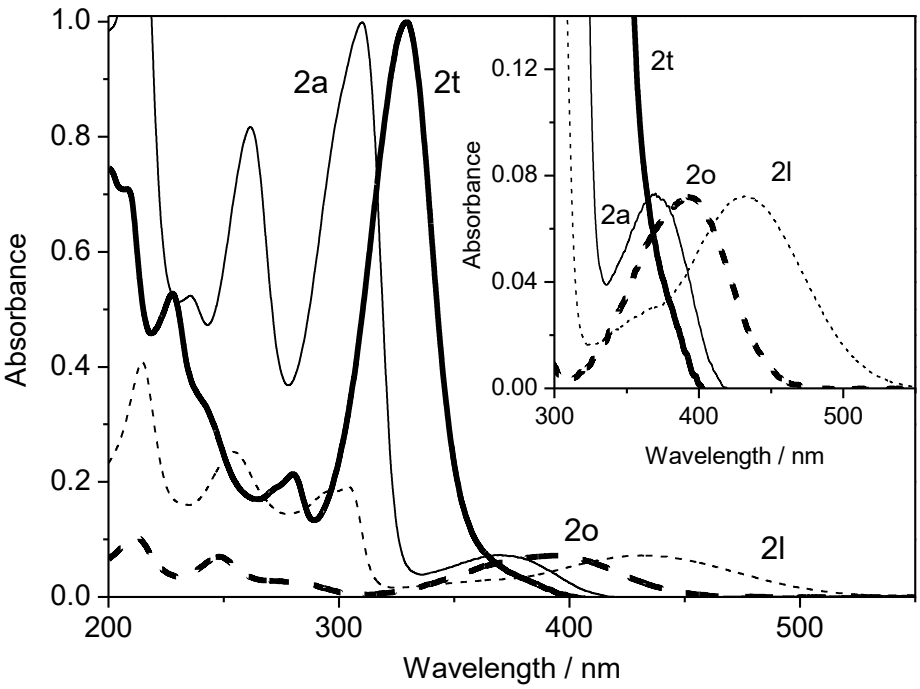


Figure 1. Absorption spectra of **2a** (thin line**), 2t** (thick line), **2o** (thick dash line) and **2l** (thin dash line) in acetonitrile. Inset shows the zoomed view of the long wavelength range.

Table 2. Photophysical properties of the selected isoquinolin-3-amines in acetonitrile

	1a[a]	**2a**	**2t**	**2s**	**2g**	**2o**	**2l**
λ_{max}(abs)/nm[b]	363	371	[c]	363[c]	367	395	433
λ_{max}(fl)/nm	431	464	441	446	457	[d]	[d]
Φ_f	0.28	0.20	0.23	0.23	0.20	$< 10^{-4}$	$< 10^{-4}$
τ_f / ns	12.4	14.2	13.0	13.3	14.2	[d]	[d]
k_f / 10^7 s^{-1}	2.3	1.4	1.7	1.7	1.4	[d]	[d]
k_{nr} / 10^7 s^{-1}	5.8	5.6	5.9	5.8	5.6	[d]	[d]

[a] Reference 1. [b] The location of the maximum of the lowest-energy absorption band, [c] shoulder, [d] fluorescence is too weak to determine precisely.

Conclusions

The present results reveal that a great number of actively fluorescent phenylamino and pyridyl-aminoisoquinolines can be easily obtained by one single manipulation starting from isoquinolinamines in medium to excellent yields. The quantum yield and lifetime of the fluorescence are insensitive to the substituent of the *N*-phenyl moiety but introduction of nitro group makes the compound practically nonfluorescent.

Experimental Section

General. 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 spectrometer equipped with a 5 mm inverse detection z-gradient probe. ^{1}H and ^{13}C NMR spectra were measured at room temperature (25 °C) in an appropriate solvent. ^{1}H and ^{13}C chemical shifts are expressed in ppm (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 59-67). 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. The UV-visible absorption spectra were recorded on a Unicam UV 500 spectrophotometer. Corrected fluorescence spectra were obtained on a Jobin-Yvon Fluoromax-P photoncounting spectrofluorometer. Fluorescence lifetimes were measured with time-correlated single-photon counting technique as described previously.[7] Fluorescence quantum yield was determined relative to that of quinine sulfate in 1 N H_2SO_4, for which a reference yield of Φ_f = 0.546 was taken.[8]

General procedure for the synthesis of *N*-arylisoquinolin-3-amines

A round-bottomed flask was charged with $Pd_2(dba)_3$ (5 mol %), ligand (10 mol%), aryl halide (1 mmol), appropriate isoquinolinamine (1 mmol), base (1.5 mmol) and dry solvent (5 mL). The flask was flushed with argon for 5 min. The mixture was heated at reflux under magnetic stirring. After cooling down to room temperature, the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel.

***N*-Phenylisoquinolin-3-amine (2a).** Reaction time 5 h. Eluent: Hexane /EtOAc (4:1), yield: 87%; yellow crystals; mp 101-102 °C; 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-Methyl-*N*-phenylisoquinolin-3-amine (2b). Reaction time 5 h. Eluent: Hexane /EtOAc (4:1); yield: 77%; brownish yellow crystals; mp 76-78 °C; ν_{max} (KBr, cm^{-1}): 3253, 1581, 1498, 1247, 746; δ_H (300 MHz, $CDCl_3$): 2.47 (3H, s, CH_3), 6.24 (1H, s, NH), 6.95 (1H. dd, *J* = 7.0, 7.1 Hz, H-4′), 7.21-7.28 (4H, m, H-2′, H-3′, H-5′, H-6′), 7.38 (1H, dd, *J* = 7.4, 7.7 Hz, H-7), 7.62 (1H, dd, *J* = 7.3, 8.13 Hz, H-6), 7.85-7.90 (2H, m, H-5, H-8), 8.93 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 12.6 (CH_3), 111.2 (C-4), 118.3 (C-2′, C-6′), 121.3 (C-5), 122.6 (C-4′), 124.1 (C-7), 125.5 (C-8a), 128.6 (C-8), 129.2 (C-3′, C-5′), 130.4 (C-6), 137.6 (C-4a), 142.9 (C-1′), 148.9 (C-3), 149.6 (C-

1). Anal. Calcd for $C_{16}H_{14}N_2$ (234.29): C, 82.02; H, 6.02; N, 11.96%. Found: C, 81.86; H, 6.14; N, 12.00%.

4-Benzyl-*N*-phenylisoquinolin-3-amine (2c). Reaction time 5 h. Eluent: Hexane /EtOAc (4:1); yield: 70%; dark yellow crystals; mp 155-157 °C; ν_{max} (KBr, cm^{-1}): 3414, 1597, 1494, 1315, 747; δ_H (300 MHz, $CDCl_3$): 4.39 (2H, s, CH_2), 6.17 (1H, s, NH), 6.95 (1H, dd, *J* = 6.3, 6.2 Hz, H-4′), 7.19-7.39 (10H, m, H-5, H2′, H-3′, H-5′, H-6′, H-2″, H-3″, H-4″, H-5″, H-6″), 7.61 (1H, dd, *J* = 7.6, 7.4 Hz, H-6), 7.87-7.91 (2H, m, H-8, H-5), 9.03 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 32.1 (CH_2), 112.0 (C-4), 118.9 (C-2′, C-6′), 121.6 (C-5), 122.4 (C-4′), 123.9 (C-7), 125.4 (C-8a), 127.1 (C-4″), 128.4 (C-2′, C-6″), 128.8 (C-8), 129.2 (C-3″, C-5″), 129.3 (C-3′, C-5′), 130.9 (C-6), 137.7 (C-4a), 138.6 (C-1″), 142.1 (C-1′), 149.8 (C-3), 150.5 (C-1). Anal. Calcd for $C_{22}H_{18}N_2$ (310.39): C, 85.13; H, 5.85; N, 9.03%. Found: C, 85.45; H, 5.90; N, 8.65%.

***N*-(3-Chlorophenyl)isoquinolin-3-amine (2d).** Reaction time 6 h. Eluent: Hexane /EtOAc (3:1); yield: 91%; yellow crystals; mp 123-126 °C; ν_{max} (KBr, cm^{-1}): 3259, 3057, 1630, 1589, 750; δ_H (300 MHz, $CDCl_3$): 6.84 (1H, s, NH), 7.00 (1H, d, *J* = 7.7 Hz, H-4′), 7.18-7.40 (5H, m, H-4, H-7, H-2′, H-5′, H-6′), 7.53-7.63 (2H, m, H-6, H-8), 7.83 (1H, d, *J* = 8.2 Hz, H-5), 8.97 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 100.5 (C-4), 117.5 (C-6′), 119.2 (C-2′), 122.4 (C-4′), 124.4 (C-7), 125.1 (C-5), 125.6 (C-8a), 127.9 (C-8), 130.6 (C-5′), 130.9 (C-6), 135.2 (C-3′), 138.7 (C-4a), 142.7 (C-1′), 151.2 (C-3), 152.3 (C-1). Anal. Calcd for $C_{15}H_{11}ClN_2$ (245.71): C, 70.73; H, 4.35; N, 11.00%. Found: C, 70.45; H, 4.51; N, 11.15%.

***N*-(3-Chlorophenyl)-4-methylisoquinolin-3-amine (2e).** Reaction time 6 h. Eluent: Hexane /EtOAc (3:1); yield: 75%; pale yellow crystals; mp 77-79 °C; ν_{max} (KBr, cm^{-1}): 3215, 2992, 1572, 1475, 683; δ_H (300 MHz, $CDCl_3$): 2.48 (3H, s, CH_3): 6.26 (1H, s, NH), 6.89 (1H, d, *J* = 7.9 Hz, H-4′), 7.06 (1H, d, *J* = 8.1 Hz, H-6′), 7.18 (1H, dd, *J* = 8.0, 8.0 Hz, H-5′), 7.27 (1H, s, H-2′), 7.42 (1H, dd, *J* = 7.6, 7.7 Hz, H-7), 7.65 (1H, dd, *J* = 7.1, 8.2 Hz, H-6), 7.89 (2H, m, H-5, H-8), 8.95 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 12.6 (CH_3), 112.1 (C-4), 116.1 (C-6′), 117.7 (C-2′), 121.0 (C-4′), 122.7 (C-5), 124.6 (C-7), 125.8 (C-8a), 128.6 (C-8), 130.2 (C-5′), 130.6 (C-6), 134.9 (C-3′), 137.5 (C-4a), 144.3 (C-1′), 148.1 (C-3), 149.7 (C-1). Anal. Calcd for $C_{16}H_{13}ClN_2$ (268.74): C, 71.51; H, 4.88; N, 10.42%. Found: C,71.26; H, 4.67; N, 10.65%.

4-Benzyl-*N*-(3-chlorophenyl)isoquinolin-3-amine (2f). Reaction time 6 h. Eluent: Hexane /EtOAc (5:1); yield:81%; pale yellow crystals; mp 71-74 °C; ν_{max} (KBr, cm^{-1}): 3224, 1591, 1488, 1308, 752; δ_H (300 MHz, $CDCl_3$): 4.39 (2H, s, CH_2), 6.19 (1H, s, NH), 6.89 (1H, d, *J* = 7.8 Hz, H-4′), 7.04 (1H, d, *J* = 8.2 Hz, H-6′), 7.13-7.34 (7H, m, H-2′, H-5′, H-2″, H-3″, H-4″, H-5″, H-6″), 7.42 (1H, dd, *J* = 7.6, 7.6 Hz, H-7), 7.63 (1H, dd, *J* = 8.4, 7.1 Hz, H-6), 7.91-7.95 (2H, m, H-5, H-8), 9.04 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 32.1 (CH_2), 112.9 (C-4), 116.6 (C-6′), 118.4 (C-2′), 121.3 (C-4′), 122.5 (C-5), 124.4 (C-7), 125.7 (C-8a), 127.2 (C-4″), 128.3 (C-2″, C-6″), 128.8 (C-8), 129.4 (C-3″, C-5″), 130.0 (C-5′), 131.1 (C-6), 134.8 (C-3′), 137.7 (C-4a), 138.4 (C-1″), 143.5 (C-1′), 149.1 (C-3), 150.5 (C-1). Anal. Calcd for $C_{22}H_{17}ClN_2$ (344.83): C, 76.63; H, 4.97; N, 8.12%. Found: C, 76. 52; H, 5.21; N: 8.01%.

***N*-(4-Chlorophenyl)isoquinolin-3-amine (2g).** Reaction time 6 h. Eluent: Hexane /EtOAc (4:1); yield: 70%, yellow crystals, mp 148-151 °C; ν_{max} (KBr, cm^{-1}): 3269, 3052, 1589, 1362, 823; δ_H

(300 MHz, $CDCl_3$): 6.79 (1H, s, NH), 7.12 (1H, m, H-7), 7.22-7.36 (5H, m, H-2′,H-3′, H-5′, H-6′, H-4), 7.53-7.60 (2H, m, H-6, H-5), 7.82 (1H, d, *J* = 7.0 Hz, H-8), 8.95 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 99.8 (C-4), 121.2 (C-2′, C-6′), 124.2 (C-7), 124.9 (C-8a), 125.4(C-5), 127.5 (C-4′), 127.9 (C-8), 129.6 (C-3′,C-5′), 130.9 (C-6), 138.7 (C-1′), 139.9 (C-4a), 151.8 (C-3), 152.3 (C-1). Anal. Calcd for $C_{15}H_{11}ClN_2$ (245.71): C, 70.73; H, 4.35; N, 11.00%. Found: C, 70.63; H, 4.54; N, 10.71%.

***N*-(2-Bromophenyl)isoquinolin-3-amine (2h).** Reaction time 8 h. Eluent: CH_2Cl_2; yield: 47%; green crystals; mp 100-102 °C; ν_{max} (KBr, cm^{-1}): 3390, 1588, 1484, 1304, 754; δ_H (300 MHz, $CDCl_3$): 6.84-6.96 (2H, m, NH, H-5′), 7.20-7.38 (3H, m, H-4, H-4′, H-7), 7.52-7.65 (3H, m, H-6, H-3′, H-6′), 7.76-7.88 (2H, m, H-5, H-8), 9.00 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 101.5 (C-4), 114.6 (C-2′), 119.3 (C-4′), 123.1 (C-5), 124.5 (C-7), 125.3 (C-8a), 125.6 (C-6′), 128.0 (C-8), 128.4 (C-5′), 130.9 (C-6), 133.3 (C-3′), 138.6 (C-4a), 139.4 (C-1′), 151.0 (C-3), 152.3 (C-1). Anal. Calcd for $C_{15}H_{11}BrN_2$ (299.16): C, 60.22; H, 3.71; N, 9.36%. Found: C, 60.49; H, 3.79; N, 9.07%.

***N*-(3-Bromophenyl)isoquinolin-3-amine (2i).** Reaction time 1 h. Eluent: Hexane /EtOAc (4:1); yield: 46%; greenish yellow crystals; mp 122-125 °C; ν_{max} (KBr, cm^{-1}): 2925, 2853, 1589, 1361, 747; δ_H (300 MHz, $CDCl_3$): 6.78 (1H, s, NH), 7.14-7.25 (4H, m, NH, H-2′, H-4′, H-5′), 7.34 (1H, dd, *J* = 7.4 Hz, 7.4 Hz, H-7), 7.53-7.63 (3H, m, H-6′, H-6, H-8), 7.84 (1H, d, *J* = 8.1 Hz, H-5), 8.97 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 100.5 (C-4), 118.0 (C-2′), 122.1 (C-6′), 123.3 (C-3′), 124.4 (C-4′), 125.1 (C-8a), 125.3 (C-7), 125.6 (C-5), 127.9 (C-8), 130.9 (C-6), 131.0 (C-5′), 138.7 (C-4a), 142.8 (C-1′), 151.2 (C-3), 152.3 (C-1). Anal. Calcd for $C_{15}H_{11}BrN_2$ (299.16): C, 60.22; H, 3.71; N, 9.36%. Found: C, 60.31; H, 3.82; N, 9.45%.

4-Benzyl-*N*-(3-bromophenyl)isoquinolin-3-amine (2j). Reaction time 1 h. Eluent: Hexane /EtOAc (3:1); yield: 49%; yellow crystals; mp 60-62 °C; ν_{max} (KBr, cm^{-1}): 1591, 1572, 1489, 994, 751; δ_H (300 MHz, $CDCl_3$): 4.39 (2H, s, CH_2), 6.17 (1H, s, NH), 7.04-7.33 (8H, m, H-2′, H-4′, H-5′, H-2″, H-3″, H-4″, H-5″, H-6″), 7.40-7.47 (2H, m, H-7, H-6′), 7.64 (1H, dd, *J* = 7.9, 7.6 Hz, H-6), 7.91-7.95 (2H, m, H-5, H-8), 9.05 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 32.1 (CH_2), 112.7 (C-4), 117.1 (C-2′), 121.2 (C-6′), 122.5 (C-4′), 122.9 (C-3′), 124.2 (C-5), 124.4 (C-7), 125.7 (C-8a), 127.2 (C-4″), 128.3 (C-2″, C-6″), 128.8 (C-8), 129.4 (C-3″, C-5″), 130.3 (C-6), 131.1 (C-5′), 137.7 (C-4a), 138.4 (C-1′), 143.6 (C-1′), 149.0 (C-3), 150.6 (C-1). Anal. Calcd for $C_{22}H_{17}BrN_2$ (389.28): C, 67.88; H, 4.40; N, 7.20%. Found: C, 67.65; H, 4.53; N, 7.31%.

***N*-(4-Bromophenyl)isoquinolin-3-amine (2k).** Reaction time 8 h. Eluent: CH_2Cl_2; yield: 80%, yellow crystals; mp 159-162 °C; ν_{max} (KBr, cm^{-1}): 3269, 3050, 1631, 1580, 749; δ_H (300 MHz, $CDCl_3$): 6.90 (1H, s, H-4), 7.05-7.19 (5H, m, H-2′, H-3′, H-5′, H-6′, H-7), 7.29-7.37 (2H, m, H-6, H-5), 7.58 (1H, d, *J* = 8.1 Hz, H-8), 7.69 (1H, s, NH), 8.72 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 100.6 (C-4), 113.2 (C-4′), 120.6 (C-2′, C-6′), 123.8 (C-5), 124.6 (C-8a), 125.3 (C-7), 127.7 (C-8), 130.6 (C-6), 131.9 (C-3′, C-5′), 138.5 (C-4a), 141.1 (C-1′), 151.6 (C-1), 151.8 (C-3). Anal. Calcd for $C_{15}H_{11}BrN_2$ (299.16): C, 60.22; H, 3.71; N, 9.36%. Found: C, 60.53; H, 3.76; N, 9.11%.

***N*-(2-Nitrophenyl)isoquinolin-3-amine (2l).** Reaction time 5 h. Eluent: CH_2Cl_2; yield: 94%; dark orange crystals; mp, 148-149 °C; ν_{max} (KBr, cm^{-1}): 3340, 1617, 1509, 1263, 732; δ_H (300 MHz, $CDCl_3$): 6.93 (1H, dd, *J* = 7.7 Hz, 8.4 Hz, H-4′), 7.39 (1H, s, H-4), 7.45-7.56 (2H, m, H-5′, H-7), 7.62-7.75 (2H, m, H-6, H-8), 7.93 (1H, dd, *J* = 8.2 Hz, H-5), 8.27-8.29 (2H, m, H-3′, H-6′), 9.10 (1H, s, H-1), 10.14 (1H, s, NH); δ_C (75 MHz, $CDCl_3$): 107.9 (C-4), 118.7 (C-6′), 119.4 (C-4′), 125.9 (C-7), 126.0 (C-5), 126.2 (C-8a), 126.7 (C-3′), 128.0 (C-8), 131.2 (C-6), 134.9 (C-2′), 135.8 (C-5′), 138.3 (C-4a), 140.1 (C-1′), 148.9 (C-3), 152.1 (C-1). Anal. Calcd for $C_{15}H_{11}N_3O_2$ (265.26): C, 67.92; H, 4.18; N, 15.84%. Found: C, 67.99; H, 4.09; N, 15.78%.

4-Methyl-*N*-(2-nitrophenyl)isoquinolin-3-amine (2m). Reaction time 5 h. Eluent: CH_2Cl_2; yield: 94%; dark orange crystals; mp 130-133 °C; ν_{max} (KBr, cm^{-1}): 3341, 1616, 1509, 1249, 734; δ_H (300 MHz, $CDCl_3$): 2.64 (3H, s, CH_3), 6.87 (1H, dd, *J* = 7.4 Hz, 8.1 Hz, H-4′), 7.45-7.55 (2H, m, H-5′, H-7), 7.72 (1H, dd, *J* = 7.4Hz, 8.0 Hz, H-6), 7.94-8.04 (3H, m, H-5, H-8, H-5′), 8.24 (1H, d, *J* = 8.6 Hz, H-3′), 9.02 (1H, s, H-1), 10.2 (1H, s, NH); δ_C (75 MHz, $CDCl_3$): 12.6 (CH_3), 116.4 (C-4), 118.7 (C-6′), 118.8 (C-4′), 123.2 (C-5), 125.8 (C-7), 126.5 (C-3′), 127.8 (C-4a), 128.5 (C-8), 130.9 (C-6), 134.2 (C-2′), 135.8 (C-5′), 137.4 (C-4a), 141.3 (C-1′), 146.3 (C-3), 149.7 (C-1). Anal. Calcd for $C_{16}H_{13}N_3O_2$ (279.29): C, 68.81; H, 4.69; N, 15.05%. Found: C, 68.62; H, 4.80; N, 14.83%.

4-Benzyl-*N*-(2-nitrophenyl)isoquinolin-3-amine (2n). Reaction time 5 h. Eluent: CH_2Cl_2; yield: 95%; orange crystals; mp 143-146 °C; ν_{max} (KBr, cm^{-1}): 3365, 1613, 1495, 1247, 738; δ_H (300 MHz, $CDCl_3$): 4.53 (2H, s, CH_2), 6.88 (1H, dd, *J* = 7.2, 7.1 Hz, C-4′), 7.15-7.27 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 7.47-7.55 (2H, m, H-5′, H-7), 7.71 (1H, dd, *J* = 8.4, 8.2 Hz, H-6), 7.97-8.03 (3H, m, H-8, H-5, H-6′), 8.20 (1H, d, *J* = 8.6 Hz, H-3′), 9.11 (1H, s, H-1), 10.07 (1H, s, NH); δ_C (75 MHz, $CDCl_3$): 32.2 (CH_2), 118.6 (C-4), 118.7 (C-4′), 118.9 (C-6′), 123.3 (C-5), 125.7 (C-7), 126.2 (C-3′),126.6 (C-8a), 126.7 (C-4″), 128.1 (C-2″, C-6″), 128.4 (C-8), 128.8 (C-3″, C-5″), 131.2 (C-6), 134.3 (C-2′), 135.3 (C-5′), 137.4 (C-4a), 137.9 (C-1″), 140.8 (C-1′), 146.8 (C-3), 150.4 (C-1). Anal. Calcd for $C_{22}H_{17}N_3O_2$ (355.38): C, 74.35; H, 4.82; N, 11.82%. Found: C, 74.52; H, 4.80; N, 11.95%.

***N*-(4-Nitrophenyl)isoquinolin-3-amine (2o).** Reaction time 4 h. Eluent: Hexane /EtOAc (3:1); yield: 55%; brownish yellow crystals; mp 174-176 °C; ν_{max} (KBr, cm^{-1}): 3229, 1582, 1495, 1318, 747; δ_H (300 MHz, $CDCl_3$): 7.31 (1H, s, H-4), 7.40 (1H, dd, *J* = 7.5, 7.6 Hz, H-7), 7.61 (1H, dd, *J* = 7.6 , 7.5 Hz, H-6), 7.70-7.75 (3H, m, H-5, H-2′, H-6′), 7.91 (1H, d, *J* = 7.4 Hz, H-8), 8.12-8.15 (2H, m, H-3′, H-5′), 9.06 (1H, s, H-1), 9.57 (1H, s, NH); δ_C (75 MHz, $CDCl_3$): 104.2 (C-4), 115.4 (C-2′, C-6′), 124.2 (C-7), 124.5 (C-8a), 124.9 (C-3′, C-5′), 125.0 (C-5), 127.2 (C-8), 130.2 (C-6), 137.5 (C-4a), 139.0 (C-4′), 148.5 (C-1′), 149.8 (C-3), 150.6 (C-1). Anal. Calcd for $C_{15}H_{11}N_3O_2$ (265.26): C, 67.92; H, 4.18; N, 15.84%. Found: C, 67.99; H, 4.03; N, 15.69%.

4-Methyl-*N*-(4-nitrophenyl)isoquinolin-3-amine (2p). Reaction time 2 h. Eluent: CH_3Cl; yield: 60%; brownish orange crystals; mp 196-199 °C; ν_{max} (KBr, cm^{-1}): 3354, 1603, 1329, 1114, 743; δ_H (300 MHz, $CDCl_3$): 2.55 (3H, s, CH_3), 6.76 (1H, s, NH), 7.21-7.24 (2H, m, H-2′, H-6′), 7.52 (1H, dd, *J* = 7.6 Hz, 7.4 Hz, H-7), 7.73 (1H, dd, *J* = 7.4 Hz, 7.7 Hz, H-6), 7.95-7.98 (2H, m, H-8, H-5), 8.14-8.18 (2H, m, H-3′, H-5′), 9.00 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 12.8 (CH_3), 114.9

(C-4), 115.7 (C-2′, C-6′), 123.1 (C-5), 125.7 (C-7), 126.0 (C-3′, C-5′), 126.5 (C-8a), 128.6 (C-8), 131.0 (C-6), 137.4 (C-4a), 140.8 (C-4′), 146.4 (C-1′), 149.2 (C-3), 150.0 (C-1). Anal. Calcd for $C_{16}H_{13}N_3O_2$ (279.29): C, 68.81; H, 4.69; N, 15.05%. Found: C, 68.59; H: 4.78; N, 15.25%.

4-Benzyl-*N*-(4-nitrophenyl)isoquinolin-3-amine (2q). Reaction time 2 h. Eluent: CH_2Cl_2; yield: 64%; brownish yellow crystals; mp 120-122 °C; ν_{max} (KBr, cm^{-1}): 3426, 1588, 1310, 1113, 747; δ_H (300 MHz, $CDCl_3$): 4.44 (2H, s, CH_2), 6.65 (1H, s, NH), 7.16-7.34 (7H, m, H-2′, H-6′, H-2″, H-3″, H-4″, H-5″, H-6″), 7.51 (1H, dd, *J* = 7.2 Hz, 7.8 Hz, H-7), 7.70 (1H, dd, *J* = 7.8, 8.0 Hz, H-6), 7.98-8.01 (2H, m, H-5, H-8), 8.11-8.13 (2H, m, H-3′, H-5′), 9.08 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 32.2 (CH_2), 115.7 (C-4), 116.4 (C-2′, C-6′), 122.9 (C-5), 125.5 (C-7), 125.8 (C-3′, C-5′), 126.4 (C-8a), 127.4 (C-4″), 128.3 (C-2″, C-6″), 128.8 (C-8), 129.5 (C-3″, C-5″), 131.5 (C-6), 137.5 (C-4a), 138.1 (C-1″), 140.8 (C-4′), 147.5 (C-1′), 148.5 (C-3), 150.7 (C-1). Anal. Calcd for $C_{22}H_{17}N_3O_2$ (355.38): C, 74.35; H, 4.82; N, 11.82%. Found: C, 74.51; H, 4.75; N, 11.61%.

Ethyl 2-(isoquinolin-3-ylamino)benzoate (2r). Reaction time 6 h. Eluent: Hexane /EtOAc (3:1); yield: 43%, green crystals; mp 44-46 °C; ν_{max} (KBr, cm^{-1}): 3298, 3049, 1614, 1451, 745; δ_H (300 MHz, $CDCl_3$): 1.42 (3H, t, *J* = 7.1, 7.1 Hz, CH_3), 4.39 (2H, q, *J* = 7.1, 14.28 Hz, CH_2), 6.88 (1H, dd, *J* = 7.2, 7.9 Hz, H-5′), 7.38 (1H, dd, *J* = 7.0, 7.8 Hz, H-4′), 7.47 (1H, dd, *J* = 7.7, 7.8 Hz, H-7), 7.55 (1H, dd, *J* = 7.8, 7.2 Hz, H-6), 7.60-7.62 (2H, m, H-5, H-4), 7.85 (1H, d, *J* = 8.1 Hz, H-8), 8.05 (1H, d, *J* = 8.0 Hz, H-3′), 8.26 (1H, d, *J* = 8.3 Hz, H-6′), 9.04 (1H, s, H-1), 10.42 (1H, s, NH); δ_C (75 MHz, $CDCl_3$): 14.5 (CH_3), 61.1 (CH_2), 105.0 (C-4), 113.9 (C-1′), 117.0 (C-3′), 119.0 (C-5′), 124.7 (C-7), 125.4 (C-8a), 125.7 (C-5), 127.9 (C-8), 130.7 (C-6′), 131.6 (C-6), 134.2 (C-4′), 138.5 (C-4a), 145.5 (C-2′), 150.7 (C-3), 151.7 (C-1), 168.7 (C=O). Anal. Calcd for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.95; H, 5.52; N, 9.58%. Found: C, 74.06; H, 5.72; N, 9.35%.

Ethyl 3-(isoquinolin-3-ylamino)benzoate (2s). Reaction time 6 h. Eluent: Hexane /EtOAc (3:1); yield: 84%; yellow crystals; mp 107-109 °C; ν_{max} (KBr, cm^{-1}): 3257, 3060, 1721, 1365, 745; δ_H (300 MHz, $CDCl_3$): 1.40 (3H, t, *J* = 6.9, 7.2 Hz, CH_3), 4.39 (2H, q, *J* = 7.2, 14.1 Hz, CH_2), 6.79 (1H, s, NH), 7.19 (1H, s, H-4), 7.33 (1H, dd, *J* = 7.2, 7.2 H-7), 7.42 (1H, dd, *J* = 7.8, 7.5 Hz, H-5′), 7.52-7-59 (3H, m, H-5, H-6, H-4′), 7.72 (1H, d, *J* = 7.2 Hz, H-6′), 7.83 (1H, d, *J* = 7.8 Hz, H-8), 7.99 (1H, s, H-2′), 8.98 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 14.6 (CH_3), 61.3 (CH_2), 100.1 (C-4), 120.6 (C-2′), 123.6 (C-6′), 123.9 (C-5), 124.2 (C-7), 125.0 (C-8a), 125.5 (C-4′), 128.0 (C-8), 129.6 (C-5′), 130.9 (C-6), 132.0 (C-1′), 138.7 (C-4a), 141.5 (C-3′), 151.6 (C-3), 152.3 (C-1), 166.7(C=O). Anal. Calcd for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.95; H, 5.52; N, 9.58%. Found: C, 74.01; H, 5.30; N, 9.63%.

Ethyl 4-(isoquinolin-3-ylamino)benzoate (2t). Reaction time 6 h. Eluent: Hexane /EtOAc (4:1); yield: 83%; yellow crystals; mp 141-144 °C; ν_{max} (Br, cm^{-1}): 3357, 2977, 1679, 1285, 770; δ_H (300 MHz, $CDCl_3$): 1.39 (3H, m, CH_3), 4.38 (2H, m, CH_2), 7.09 (1H. s, NH), 7.34-7.37 (4H, m, H-2′, H-6′, H-4, H-7), 7.60-7.64 (2H, m, H-6, H-5), 7.86 (1H, d, *J* = 7.1 Hz, H-8), 8.02- 8.05 (2H, m, H-3′, H-5′), 9.00 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 14.7 (CH_3), 60.8 (CH_2), 102.1 (C-4), 117.0 (C-3′, C-5′), 123.3 (C-1′), 124.7 (C-7), 125.3 (C-8a), 125.7 (C-5), 127.9 (C-8), 131.1 (C-6), 131.5 (C-2′, C-6′), 138.5 (C-4a), 145.8 (C-4′), 150.3 (C-3), 152.3 (C-1), 166.6 (C=O).

Anal. Calcd for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.95; H, 5.52; N, 9.58%. Found: C, 73.61; H, 5.52; N, 9.67%.

2-(Isoquinolin-3-ylamino)benzaldehyde (2u). Reaction time 2 h. Eluent: Hexane /EtOAc (2:1); yield: 84%; brownish yellow; mp 92-95 °C; ν_{max} (KBr, cm^{-1}): 2819, 2741, 1602, 1447, 754; δ_H (300 MHz, $CDCl_3$): 6.98 (1H, dd, *J* = 7.3, 7.3 Hz, H-5′), 7.31 (1H, s, H-4), 7.41 (1H, dd, *J* = 7.3, 7.4, H-7), 7.54-7.71 (4H, m, H-5, H-6, H-4′, H-6′), 7.89 (1H, d, *J* = 8.1 Hz, H-8), 8.45 (1H, d, *J* = 8.4 Hz, H-3′), 9.08 (1H, s, H-1), 9.95 (1H, s, CHO), 10.90 (1H, s, NH); δ_C (75 MHz, $CDCl_3$): 106.4 (C-4), 116.3 (C-3′), 119.0 (C-5′), 120.5 (C-1′), 125.1 (C-7), 125.6 (C-8a), 125.8 (C-5), 127.9 (C-8), 130.9 (C-6), 136.0 (C-4′), 136.8 (C-6′), 138.4 (C-4a), 145.6 (C-2′), 150.1 (C-3), 151.6 (C-1), 194.9 (CHO). Anal. Calcd for $C_{16}H_{12}N_2O$ (248.27): C, 77.40; H, 4.87; N, 11.28%. Found: C, 77.25; H, 4.82; N, 11.41%.

***N*-(3-Bromopyridin-2-yl)isoquinolin-3-amine (2v).** Reaction time 10 h. Eluent: Hexane /EtOAc (2:1); yield: 80%; brownish yellow; mp 107-110 °C; ν_{max} (KBr, cm^{-1}): 3386, 1584, 1512, 1014, 742; δ_H (300 MHz, $CDCl_3$): 6.72 (1H, m, H-5′), 7.39 (1H, dd, *J* = 7.8, 7.3 Hz, H-7), 7.59 (1H, dd, *J* = 8.1, 7.1 Hz, H-6), 7.78-7.87 (3H, m, H-4′, H-5, H-8), 7.99 (1H, s, NH), 8.31 (1H, d, *J* = 4.7 Hz, H-6′), 8.78 (1H, s, H-4), 8.98 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 105.3 (C-4), 107.2 (C-3′), 116.5 (C-5′), 124.9 (C-7), 125.9 (C-8a), 126.8 (C-5), 127.7 (C-8), 130.7 (C-6), 138.5 (C-4a), 140.5 (C-4′), 146.5 (C-6′), 148.4 (C-3), 151.1 (C-2′), 151.3 (C-1). Anal. Calcd for $C_{14}H_{10}BrN_3$ (300.15): C, 56.02; H, 3.36; N, 14.00%. Found: C, 56.06; H, 3.48; N,13.88%.

4-Benzyl-*N*-(3-bromopyridin-2-yl)isoquinolin-3-amine (2w). Reaction time 10 h. Eluent: Hexane /EtOAc (2:1); yield: 70%;brownish yellow crystals; mp 116-118 °C; ν_{max} (KBr, cm^{-1}): 3396, 1590, 1488, 1012, 728; δ_H (300 MHz, $CDCl_3$): 4.45 (2H, s, CH_2), 6.64 (1H, m, H-5′), 7.03 (1H, s, NH), 7.15-7.25 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 7.52 (1H, dd, *J* = 7.6, 7.5 Hz, H-7), 7.65 (1H, dd, *J* = 7.8, 8.0 Hz, H-6), 7.73 (1H, d, *J* = 7.8 Hz, H-4′), 7.97-8.02 (2H, m, H-5, H-8), 8.1 (1H, d, *J* = 4.7 Hz, H-6′), 9.16 (1H, s, H-1); δ_C (75 MHz, $CDCl_3$): 33.1 (CH_2), 107.2 (C-3′), 116.6 (C-5′), 122.2 (C-4), 123.7 (C-5), 126.0 (C-7), 126.6 (C-4″), 127.5 (C8a), 128.5 (C-3″, C-5″), 128.5 (C-8), 128.9 (C-2″, C-6″), 130.9 (C-6), 137.4 (C-4a), 139.4 (C-1″), 140.5 (C-4′), 146.7 (C-3), 147.1 (C-6′), 151.2 (C-1), 153.1 (C-2′). Anal. Calcd for $C_{21}H_{16}BrN_3$ (390,27): C, 64.63; H, 4.13; N, 10.77%. Found: C, 64.91; H, 4.21; N: 10.39%.

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