Synthesis of 7*H*-Pyrido[2,3-*c*]carbazoles from 5-Bromo-8-methoxyquinolines *via* Coupling and Azide Cyclization Reactions

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A new strategy for the synthesis of substituted 7*H*-pyrido[2,3-*c*]carbazoles has been developed from substituted 5-bromoquinolines by using cross-coupling reaction with (2-aminophenyl)boric acids, followed by a regioselective azide cyclization.

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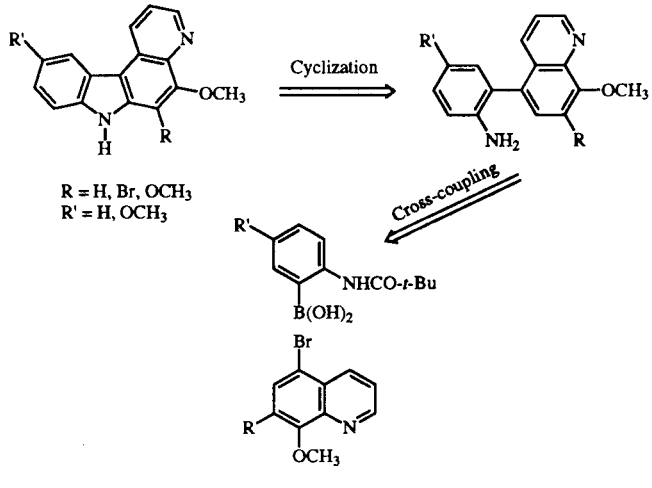
Introduction.

It is well established that the pyridocarbazole ring is an appropriate skeleton to design DNA intercalating drugs [1]. Some compounds such as ellipticines and olivacines elicit high antitumor properties [1-2]. Since the discovery of the potent activity of 7*H*-pyridocarbazoles [2a-b,3], numerous syntheses have been reported [2a-c,4]; indoles [2a-b,4a], but also carbazoles [2c,4b-d] or benzenes [4e] were often used as starting materials.

Because of the usually low yields obtained in the methods described, mainly due to the large number of steps, we chose to construct 7*H*-pyrido[2,3-*c*]carbazoles from suitably substituted quinoline and benzene moieties (Scheme I).

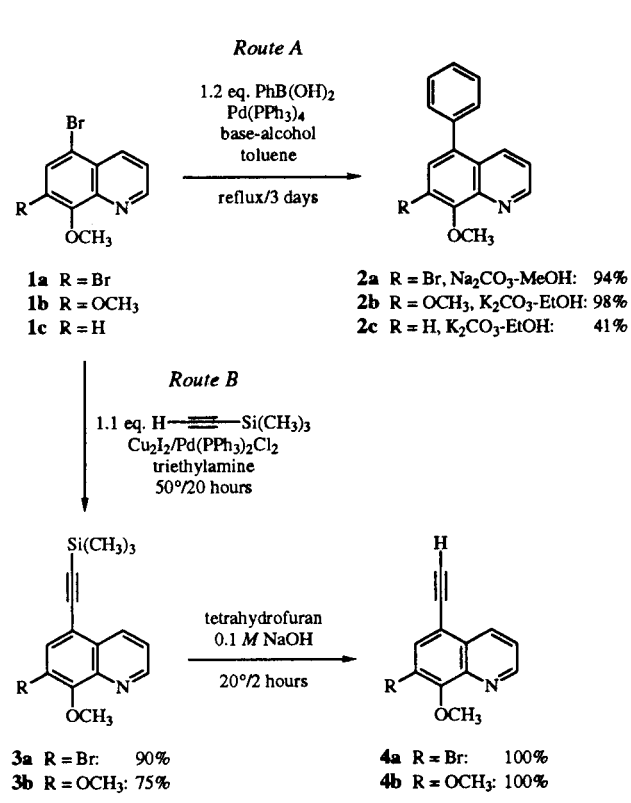
Scheme I



Results.

The cross-coupling reaction [5], largely described in the literature to create a C-C bond, was investigated with the easily available 5-bromoquinolines **1a-c** [6] under Suzuki's [5a] (Scheme II, *Route A*) and Sakamoto's [7] conditions (Scheme II, *Route B*). *Route A* conditions, tested with 5-bromoquinolines **1a-c** and commercial phenylboric acid, led to the corresponding 5-phenylquinolines **2a-c**. Even if quinolines bear two bromo groups, such as in **1a**, a total regioselectivity was observed at C-5 by using sodium carbonate-methanol pair [8]. *Route B* conditions, used with the 7-substituted 5-bromo-8-methoxyquinolines **1a-b** and commercial (trimethylsilyl)acetylene, gave the corresponding 5-(trimethylsilylethynyl)-quinolines **3a-b** in good yields. The trimethylsilyl cleavage under basic conditions led quantitatively to the 5-ethynylquinolines **4a-b**.

Scheme II



Under Suzuki's conditions [5a], the coupling reaction was also achieved with the (2-pivaloylaminophenyl)boric acids **5a-b** [9] to give the amides **6a-f** (Scheme III, Table I). As far as monobromoquinolines **1b-c** are concerned,

yields were improved by using potassium carbonate-ethanol pair (Table I, Entries 3-6).

Scheme III

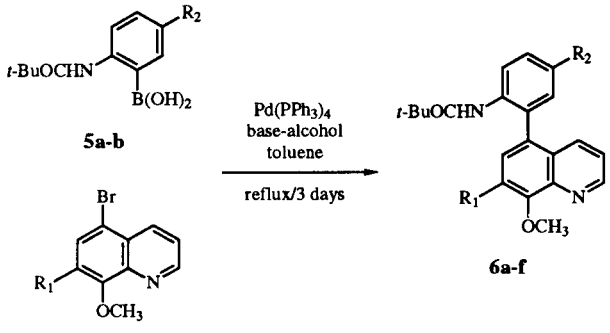


Table I

Entry	R_1	R_2	Base	Alcohol	Product	Yield %
1	Br	H	Na_2CO_3	MeOH	**6a**	90
2	Br	OCH_3	Na_2CO_3	MeOH	**6b**	52
3	OCH_3	H	K_2CO_3	EtOH	**6c**	94
4	OCH_3	OCH_3	K_2CO_3	EtOH	**6d**	76
5	H	H	K_2CO_3	EtOH	**6e**	36
6	H	OCH_3	K_2CO_3	EtOH	**6f**	40

Amides **6a-e** thus obtained were hydrolyzed under acidic conditions to the corresponding amino derivatives **7a-e** (Scheme IV, Table II).

Scheme IV

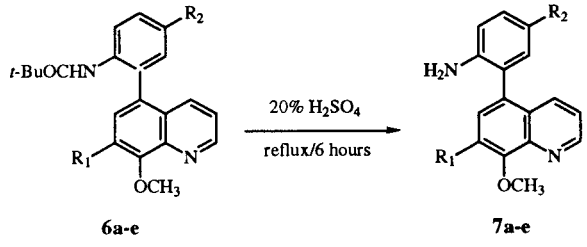
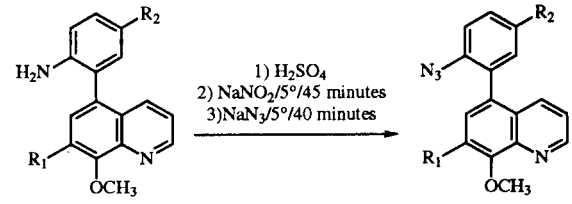


Table II

Entry	R_1	R_2	Amide	Amine	Yield %
1	Br	H	**6a**	**7a**	80
2	Br	OCH_3	**6b**	**7b**	57
3	OCH_3	H	**6c**	**7c**	81
4	OCH_3	OCH_3	**6d**	**7d**	84
5	H	H	**6e**	**7e**	72

A literature survey showed that the cyclization of azido compounds *via* thermolysis has been successfully used to prepare various polycondensed heteroaromatics [10]. Thus, the formation of diazonium salts from amino compounds **7a-e** at 5° [10a], followed by the treatment with sodium azide [10a] afforded compounds **8a-e** with good to quantitative yields (Scheme V, Table III). Thermocyclization attempts [10a] failed from the azide **8d**; the pyridocarbazole **9b** was only obtained in poor yield (13%) from **8b**. In these two cases, the starting material could not be recovered (Table IV, Entries 4 and 2). Nevertheless, a regioselective thermocyclization at C-6 occured from azides **8a,c,e** affording 6-substituted 5-methoxy-7*H*-pyrido[2,3-*c*]carbazoles **9a,c,e** in good yields (Scheme VI, Table IV).

Scheme V



Scheme VI

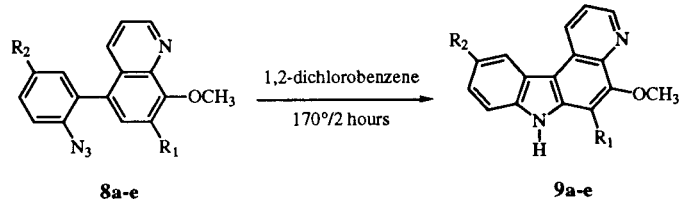


Table III

Entry	R_1	R_2	Amide	Azide	Yield %
1	Br	H	**7a**	**8a**	100
2	Br	OCH_3	**7b**	**8b**	90
3	OCH_3	H	**7c**	**8c**	100
4	OCH_3	OCH_3	**7d**	**8d**	75
5	H	H	**7e**	**8e**	100

Table IV

Entry	R_1	R_2	Azide	Product	Yield %
1	Br	H	**8a**	**9a**	81
2	Br	OCH_3	**8b**	**9b**	13
3	OCH_3	H	**8c**	**9c**	81
4	OCH_3	OCH_3	**8d**	**9d**	—
5	H	H	**8e**	**9e**	70

Conclusion.

Starting from easily available 5-bromo-8-methoxyquinolines **1a-c**, coupling reaction allowed a facile syn-

thesis of 5-(2-aminophenyl)quinolines. Taking advantage, in our case, of a regioselective azide cyclization, new 7*H*-pyrido[2,3-*c*]carbazoles could be prepared. Thus, 6-substituted 5-methoxy-7*H*-pyrido[2,3-*c*]carbazoles were synthesized in four steps in 58, 62 and 18% overall yields, respectively, for compounds **9a**, **9c** and **9e**, which is particularly good, compared to earlier reported syntheses [2a-c,4] in the pyridocarbazole series.

EXPERIMENTAL

Melting points were measured on a Kofler hot stage and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard on a Bruker 200 MHz spectrometer and δ are given in ppm. The ir spectra were obtained as potassium bromide pellets on a Perkin-Elmer FMR 1650 spectrometer. Mass spectra were obtained on a JEOL D700 instrument (electron impact or chemical ionization with ammonia), and elemental analyses were performed on a Carlo Erba CHNOS apparatus.

Starting Materials.

Tetrakis(triphenylphosphine)palladium(0) [11], (2-pivaloylaminophenyl) and (5-methoxy-2-pivaloylaminophenyl)boric acids [9] were synthesized by literature methods. 5-Bromo-8-methoxyquinolines **1a-c** were prepared from 5,7-dibromo-8-hydroxyquinoline [6].

General Procedure for the Reaction of 7-Substituted 5-Bromo-8-methoxyquinoline **1a-b** with (Trimethylsilyl)acetylene.

(Trimethylsilyl)acetylene (0.12 ml, 0.82 mmole) was added to a mixture of purified cuprous iodide [12] (0.15 g, 0.8 mmole) and triethylamine (20 ml) and the resulting mixture was stirred at room temperature for 10 minutes. Palladium bis(triphenylphosphine) dichloride (0.28 g, 0.8 mmole) was added and the mixture was stirred for 10 minutes. The required 5-bromoquinoline (8 mmoles) and triethylamine were added. Stirring was continued for 10 minutes before addition of (trimethylsilyl)acetylene (1.17 ml, 8.2 mmoles). The resulting mixture was heated at 50° for 20 hours. After cooling, the mixture was diluted with water (20 ml) and extracted 3 times with 100 ml of ether. Drying over magnesium sulphate and solvents removal afforded a crude product which was purified by preparative flash chromatography on a silica gel column.

7-Bromo-8-methoxy-5-(trimethylsilylethynyl)quinoline (**3a**).

The coupling reaction of **1a** (2.54 g, 8 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of tetrachloromethane and ether (4:1) as an eluent 2.41 g (90%) of **3a** as a yellow oil, bp 120° (0.2 millibar); ir: ν 2960, 2150, 1570, 1490, 1465, 1390, 1370, 1250, 1090, 1060 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.29 (s, 9H, $Si(CH_3)_3$), 4.15 (s, 3H, OCH_3), 7.47 (dd, J = 8.6-3.4 Hz, 1H, H_3), 7.85 (s, 1H, H_6), 8.52 (dd, J = 8.6-1.4 Hz, 1H, H_4), 8.91 (dd, J = 3.4-1.4 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ -0.2, 62.2, 99.9, 100.8, 115.6, 117.5, 121.9, 129.2, 134.7, 134.9, 142.7, 150.3, 154.2.

Anal. Calcd. for $C_{15}H_{16}BrNOSi$ (M = 334.30): C, 53.89; H, 4.82; N, 4.19. Found: C, 53.7; H, 4.8; N, 4.0.

7,8-Dimethoxy-5-(trimethylsilylethynyl)quinoline (**3b**).

The coupling reaction of **1b** (2.14 g, 8 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of trichloromethane and ether (85:15) as an eluent 1.71 g (75%) of **3b** as a yellow oil; ^1H nmr (deuteriochloroform): δ 0.33 (s, 9H, $Si(CH_3)_3$), 4.03 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 7.36 (dd, J = 8.5-4.1 Hz, 1H, H_3), 7.55 (s, 1H, H_6), 8.51 (dd, J = 8.5-1.7 Hz, 1H, H_4), 8.93 (dd, J = 4.1-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ -0.5, 56.3, 61.4, 99.2, 101.0, 115.7, 119.0, 119.4, 124.5, 134.0, 142.4, 143.8, 150.1, 150.1.

Anal. Calcd. for $C_{16}H_{19}NO_2Si$ (M = 285.42): C, 67.33; H, 6.71; N, 4.91. Found: C, 67.2; H, 6.6; N, 4.9.

General Procedure for the Trimethylsilyl Cleavage.

The required 5-(trimethylsilylethynyl)quinoline (2 mmoles) was added to a mixture of tetrahydrofuran (10 ml) and 0.1 *M* aqueous sodium hydroxide (8 ml). Stirring at room temperature for 2 hours, extraction with ether, drying over magnesium sulphate, and solvents removal afforded a crude product which was purified by preparative flash chromatography on a silica gel column.

7-Bromo-5-ethynyl-8-methoxyquinoline (**4a**).

The reaction of **3a** (0.67 g, 2 mmoles) according to the general procedure gave after purification by column chromatography with trichloromethane as an eluent 0.52 g (100%) of **4a** as a yellow solid, mp 128°; ir: ν 3260, 3160, 2940, 2090, 1570, 1490, 1460, 1365, 1085 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.48 (s, 1H, C≡C-*H*), 4.19 (s, 3H, OCH_3), 7.50 (dd, J = 8.5-4.2 Hz, 1H, H_3), 7.90 (s, 1H, H_6), 8.57 (dd, J = 8.5-1.7 Hz, 1H, H_4), 8.97 (dd, J = 4.2-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 62.2, 78.9, 82.9, 115.8, 116.6, 122.0, 129.7, 134.7, 135.2, 143.3, 150.5, 154.9.

Anal. Calcd. for $C_{12}H_8BrNO$ (M = 262.11): C, 54.99; H, 3.08; N, 5.34. Found: C, 54.9; H, 2.9; N, 5.4.

7,8-Dimethoxy-5-ethynylquinoline (**4b**).

The reaction of **3b** (0.57 g, 2 mmoles) according to the general procedure gave after purification by column chromatography with trichloromethane as an eluent 0.43 g (100%) of **4b** as a yellow solid, mp 127°; ^1H nmr (deuteriochloroform): δ 3.47 (s, 1H, C≡C-*H*), 4.02 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 7.36 (dd, J = 8.5-4.2 Hz, 1H, H_3), 7.58 (s, 1H, H_6), 8.54 (dd, J = 8.5-1.7 Hz, 1H, H_4), 8.94 (dd, J = 4.2-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 56.9, 62.0, 80.3, 82.1, 115.2, 120.1, 120.1, 125.3, 134.5, 143.1, 144.7, 150.9, 151.0.

Anal. Calcd. for $C_{13}H_{11}NO_2$ (M = 213.24): C, 73.23; H, 5.20; N, 6.57. Found: C, 73.0; H, 5.1; N, 6.4.

General Procedure for the Reaction of 5,7-Dibromo-8-methoxyquinoline (**1a**) with Phenylboric Acids.

5,7-Dibromo-8-methoxyquinoline (**1a**) (0.32 g, 1 mmole) and the required phenylboric acid (1.2 mmoles) were added to a 2 *M* aqueous solution of sodium carbonate (1 ml) and methanol (0.5 ml) in deoxygenated toluene (10 ml). The resulting mixture was stirred for 30 minutes under an argon atmosphere. Tetrakis(triphenylphosphine)palladium(0) (0.035 g, 0.03 mmole) was added and this mixture was refluxed for 3 days. Cooling, filtration, extraction with toluene, drying over magnesium sulphate, and solvent removal afforded a crude product which was purified by preparative flash chromatography on a silica gel column.

7-Bromo-8-methoxy-5-phenylquinoline (**2a**) [7].

2,2-Dimethyl-*N*-(2-(7-bromo-8-methoxy-5-quinolyl)phenyl)propanamide (**6a**).

The coupling reaction of **1a** (0.32 g, 1 mmole) with (2-pivaloylaminophenyl)boric acid (**5a**) (0.27 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of dichloromethane and ether (95:5) as an eluent 0.45 g (90%) of **6a** as a yellow oil; ir: ν 3430, 3330, 2960, 2920, 1670, 1585, 1515, 1460, 1445, 1370, 1310, 1220, 1160, 1085 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.79 (s, 9H, $C(CH_3)_3$), 4.22 (s, 3H, OCH_3), 6.88 (bs, 1H, N*H*), 7.3 (m, 3H, $H_{3\text{-}4\text{-}5}$), 7.37 (dd, J = 8.6-4.1 Hz, 1H, $H_{3'}$), 7.67 (s, 1H, $H_{6'}$), 7.81 (dd, J = 8.6-1.7 Hz, 1H, $H_{4'}$), 8.26 (m, 1H, H_6), 8.96 (dd, J = 4.1-1.7 Hz, 1H, $H_{2'}$); ^{13}C nmr (deuteriochloroform): δ 26.9, 39.3, 62.2, 116.2, 121.8, 121.8, 124.3, 127.4, 127.7, 129.4, 130.4, 132.1, 132.1, 134.6, 134.6, 143.2, 150.5, 153.6, 176.0.

Anal. Calcd. for $C_{21}H_{21}BrN_2O_2$ (M = 413.32): C, 61.03; H, 5.12; N, 6.78. Found: C, 61.0; H, 5.0; N, 6.7.

2,2-Dimethyl-*N*-(2-(7-bromo-8-methoxy-5-quinolyl)-4-methoxyphenyl)propanamide (**6b**).

The coupling reaction of **1a** (0.32 g, 1 mmole) with (5-methoxy-2-pivaloylaminophenyl)boric acid (**5b**) (0.30 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of dichloromethane and ether (9:1) as an eluent 0.23 g (52%) of **6b** as a yellow oil; ir: ν 3348, 2963, 1652, 1578, 1502, 1462, 1368, 1246, 1221, 1083 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.24 (s, 9H, $C(CH_3)_3$), 3.62 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 6.89 (d, J = 8.9 Hz, 1H, H_6), 7.28 (dd, J = 8.5-4.1 Hz, 1H, $H_{3'}$), 7.36 (d, J = 2.7 Hz, 1H, H_3), 7.55 (s, 1H, $H_{6'}$), 7.57 (dd, J = 8.9-2.7 Hz, 1H, H_5), 7.81 (dd, J = 8.5-1.7 Hz, 1H, $H_{4'}$), 8.88 (dd, J = 4.1-1.7 Hz, 1H, $H_{2'}$); ^{13}C nmr (deuteriochloroform): δ 27.4, 39.3, 55.6, 61.9, 111.0, 116.0, 121.1, 121.9, 124.3, 126.5, 127.7, 131.2, 131.3, 133.3, 135.3, 142.7, 149.9, 152.7, 153.4, 176.7.

Anal. Calcd. for $C_{22}H_{23}BrN_2O_3$ (M = 443.35): C, 59.60; H, 5.23; N, 6.32. Found: C, 59.5; H, 5.1; N, 6.2.

General Procedure for the Reaction of other 5-Bromo-8-methoxyquinolines **1b-c** with Phenylboric Acids.

The required 5-bromo-8-methoxyquinoline (1 mmole) and phenylboric acid (1.2 mmoles) were added to a 2 *M* aqueous solution of potassium carbonate (1 ml) and ethanol (0.5 ml) in deoxygenated toluene (10 ml). The resulting mixture was stirred for 30 minutes under an argon atmosphere. Tetrakis(triphenylphosphine)palladium(0) (0.035 g, 0.03 mmole) was added and this mixture was refluxed for 3 days. Cooling, filtration, extraction with toluene, drying over magnesium sulphate, and solvent removal afforded a crude product which was purified by preparative flash chromatography on a silica gel column.

7,8-Dimethoxy-5-phenylquinoline (**2b**).

The coupling reaction of **1b** (0.27 g, 1 mmole) with phenylboric acid (0.15 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of dichloromethane and ether (95:5) as an eluent 0.26 g (98%) of **2b** as a yellow oil; ir: ν 3414, 2933, 1602, 1473, 1398, 1333, 1155, 1078 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.87 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 7.14 (dd, J = 8.6-4.1 Hz, 1H, H_3), 7.27 (s, 1H, H_6), 7.35 (m, 5H, phenyl), 8.07 (dd, J = 8.6-1.7 Hz, 1H, H_4), 8.87 (dd, J = 4.1-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 56.6, 61.6, 116.0, 118.9, 122.4, 127.5, 128.2, 129.7, 134.2, 136.1, 138.9, 142.2, 143.4, 150.1, 150.6.

Anal. Calcd. for $C_{17}H_{15}NO_2$ (M = 265.31): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.8; H, 5.8; N, 5.2.

8-Methoxy-5-phenylquinoline (**2c**).

The coupling reaction of **1c** (0.24 g, 1 mmole) with phenylboric acid (0.15 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of dichloromethane and ether (9:1) as an eluent 0.096 g (41%) of **2c**, mp 120°; ir: ν 1573, 1503, 1466, 1363, 1112 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.06 (s, 3H, OCH_3), 6.99 (d, J = 8.2 Hz, 1H, H_7), 7.24 (dd, J = 8.6-4.0 Hz, 1H, H_3), 7.95 (d, J = 8.2 Hz, 1H, H_6), 7.38 (s, 5H, phenyl), 8.14 (dd, J = 8.6-1.7 Hz, 1H, H_4), 8.88 (d, J = 4.0-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 55.8, 106.9, 121.4, 127.1, 127.1, 127.4, 128.2, 129.9, 132.0, 134.1, 139.2, 140.0, 148.8, 154.6.

Anal. Calcd. for $C_{16}H_{13}NO$ (M = 235.29): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.5; H, 5.4; N, 5.9.

2,2-Dimethyl-*N*-(2-(7,8-dimethoxy-5-quinolyl)phenyl)propanamide (**6c**).

The coupling reaction of **1b** (0.27 g, 1 mmole) with (2-pivaloylaminophenyl)boric acid (**5a**) (0.27 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of ethyl acetate and hexane (1:1) as an eluent 0.34 g (94%) of **6c** as a yellow oil; ir: ν 3433, 3342, 2962, 2870, 1677, 1599, 1518, 1474, 1444, 1335, 1155, 1079 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.56 (s, 9H, $C(CH_3)_3$), 3.82 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.78 (bs, 1H, N*H*), 7.01 (dd, J = 8.2-4.1 Hz, 1H, $H_{3'}$), 7.1 (m, 3H, $H_{3\text{-}4\text{-}5}$), 7.16 (s, 1H, $H_{6'}$), 7.53 (dd, J = 8.2-1.7 Hz, 1H, $H_{4'}$), 8.10 (m, 1H, H_6), 8.73 (dd, J = 4.1-1.7 Hz, 1H, $H_{2'}$); ^{13}C nmr (deuteriochloroform): δ 26.4, 38.8, 56.5, 61.4, 116.8, 119.3, 121.1, 122.1, 123.7, 128.5, 128.7, 130.0, 130.7, 133.8, 135.6, 142.7, 142.8, 150.3, 150.6, 175.6.

Anal. Calcd. for $C_{22}H_{24}N_2O_3$ (M = 364.45): C, 72.51; H, 6.64; N, 7.69. Found: C, 72.3; H, 6.6; N, 7.6.

2,2-Dimethyl-*N*-(2-(8-methoxy-5-quinolyl)phenyl)propanamide (**6e**).

The coupling reaction of **1c** (0.24 g, 1 mmole) with (2-pivaloylaminophenyl)boric acid (**5a**) (0.27 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of ethyl acetate and dichloromethane (1:9) as an eluent 0.12 g (36%) of **6e** as a yellow oil; ^1H nmr (deuteriochloroform): δ 0.65 (s, 9H, $C(CH_3)_3$), 3.93 (s, 3H, OCH_3), 7.2 (m, 7H, $H_{3\text{-}4\text{-}5\text{-}3'\text{-}6'\text{-}7'}$, N*H*), 7.66 (dd, J = 8.5-1.7 Hz, 1H, $H_{4'}$), 8.28 (m, 1H, H_6), 8.84 (dd, J = 4.1-1.7 Hz, 1H, $H_{2'}$); ^{13}C nmr (deuteriochloroform): δ 26.8, 39.2, 55.9, 107.1, 120.8, 122.0, 123.8, 126.7, 127.4, 128.3, 128.6, 128.8, 130.6, 133.9, 136.1, 136.1, 149.4, 155.3, 175.9.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$ (M = 334.42): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.3; H, 6.6; N, 8.4.

2,2-Dimethyl-*N*-(2-(7,8-dimethoxy-5-quinolyl)-4-methoxyphenyl)propanamide (**6d**).

The coupling reaction of **1b** (0.27 g, 1 mmole) with (5-methoxy-2-pivaloylaminophenyl)boric acid (**5b**) (0.30 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of dichloromethane and ether (7:3) as an eluent 0.30 g (76%) of **6d** as a yel-

low oil; ir: ν 3330, 2959, 1654, 1598, 1499, 1474, 1334, 1158 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.19 (s, 9H, $C(CH_3)_3$), 3.56 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 6.84 (d, J = 8.9 Hz, 1H, H_6), 7.05 (dd, J = 8.5-4.2 Hz, 1H, $H_{3'}$), 7.17 (s, 1H, $H_{6'}$), 7.35 (d, J = 2.7 Hz, 1H, H_3), 7.56 (dd, J = 8.9-2.7 Hz, 1H, H_5), 7.70 (dd, J = 8.5-1.7 Hz, 1H, $H_{4'}$), 7.83 (bs, 1H, N*H*), 8.77 (dd, J = 4.2-1.7 Hz, 1H, $H_{2'}$); ^{13}C nmr (deuteriochloroform): δ 27.3, 39.2, 55.5, 56.5, 61.5, 111.0, 116.4, 118.8, 121.8, 122.8, 124.5, 127.6, 131.3, 131.6, 132.4, 134.9, 142.0, 142.9, 149.9, 150.6, 153.3.

Anal. Calcd. for $C_{23}H_{26}N_2O_4$ (M = 394.47): C, 70.03; H, 6.64; N, 7.10. Found: C, 69.8; H, 6.6; N, 7.0.

2,2-Dimethyl-*N*-(4-methoxy-2-(8-methoxy-5-quinolyl)phenyl)-propanamide (**6f**).

The coupling reaction of **1c** (0.24 g, 1 mmole) with (5-methoxy-2-pivaloylaminophenyl)boric acid (**5b**) (0.30 g, 1.2 mmoles) according to the general procedure gave after purification by column chromatography with a mixture of dichloromethane and ether (9:1) as an eluent 0.15 g (40%) of **6f** as a yellow oil; ir: ν 3298, 2954, 2836, 1661, 1542, 1500, 1476, 1414, 1210, 1108 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, $C(CH_3)_3$), 3.61 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 6.92 (d, J = 8.9 Hz, 1H, H_6), 7.02 (d, J = 8.0 Hz, 1H, $H_{7'}$), 7.4 (m, 5H, $H_{3-5-3'-6'}$, N*H*), 7.83 (dd, J = 8.5-1.7 Hz, 1H, $H_{4'}$), 8.87 (dd, J = 4.1-1.7 Hz, 1H, $H_{2'}$); ^{13}C nmr (deuteriochloroform): δ 27.4, 39.3, 55.6, 55.8, 106.9, 111.1, 121.2, 121.4, 124.6, 127.6, 127.8, 128.1, 131.2, 131.8, 134.8, 139.6, 148.7, 153.7, 154.7, 176.7.

Anal. Calcd. for $C_{22}H_{24}N_2O_3$ (M = 364.45): C, 72.51; H, 6.64; N, 7.69. Found: C, 72.3; H, 6.5; N, 7.5.

General Procedure for the Hydrolysis of Pivalamides **6a-f**.

The required pivaloylamino compound (1 mmole) was added to a 20% solution of sulphuric acid (10 ml) and refluxed for 6 hours. The resulting cold solution was poured into a mixture of ice and concentrated ammonia. Extraction with ethyl acetate, drying over magnesium sulphate and solvent removal afforded a crude product which was purified by preparative flash chromatography on a silica gel column.

5-(2-Aminophenyl)-7-bromo-8-methoxyquinoline (**7a**).

The reaction of **6a** (0.41 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ether (9:1) as an eluent 0.26 g (80%) of **7a** as a yellow solid, mp 216°; ir: ν 3380, 3290, 3020, 2920, 1620, 1575, 1500, 1460, 1400, 1255, 1185 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.5 (bs, 2H, NH_2), 4.26 (s, 3H, OCH_3), 7.0 (m, 4H, $H_{3'-4'-5'-6'}$), 7.39 (dd, J = 8.5-4.2 Hz, 1H, H_3), 7.69 (s, 1H, H_6), 7.96 (dd, J = 8.5-1.6 Hz, 1H, H_4), 8.97 (dd, J = 4.2-1.6 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 61.9, 115.1, 116.1, 118.2, 121.4, 122.5, 127.4, 129.3, 131.0, 131.7, 133.9, 135.2, 143.2, 144.2, 150.1, 152.8.

Anal. Calcd. for $C_{16}H_{13}BrN_2O$ (M = 329.20): C, 58.38; H, 3.98; N, 8.51. Found: C, 58.3; H, 3.9; N, 8.5.

5-(2-Amino-5-methoxyphenyl)-7-bromo-8-methoxyquinoline (**7b**).

The reaction of **6b** (0.44 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ethyl acetate (3:1) as an eluent 0.20 g (57%) of **7b** as a yellow viscous solid; ir: ν 3425, 3354, 2931, 1501, 1464, 1232, 1084 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.5 (bs, 2H, NH_2), 3.56 (s, 3H, OCH_3), 4.17 (s, 3H, OCH_3), 6.56 (d, J = 2.7 Hz, 1H, $H_{6'}$), 6.7 (m, 2H, $H_{3'-4'}$), 7.29 (dd, J = 8.6-4.2 Hz, 1H, H_3), 7.57 (s, 1H, H_6), 7.90 (dd, J = 8.6-1.7 Hz, 1H, H_4), 8.88 (dd, J = 4.2-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 55.9, 61.9, 112.4, 116.0, 116.0, 118.9, 121.0, 127.2, 127.7, 131.2, 134.0, 135.6, 140.1, 142.9, 149.8, 149.8, 152.5.

Anal. Calcd. for $C_{17}H_{15}BrN_2O_2$ (M = 359.23): C, 56.84; H, 4.21; N, 7.80. Found: C, 56.7; H, 4.2; N, 7.7.

5-(2-Aminophenyl)-7,8-dimethoxyquinoline (**7c**).

The reaction of **6c** (0.36 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ether (1:1) as an eluent 0.23 g (81%) of **7c** as a yellow solid, mp 131°; ir: ν 3391, 3152, 1603, 1494, 1478, 1332, 1151, 1076 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.4 (bs, 2H, NH_2), 4.00 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 6.82 (dd, J = 8.4-4.2 Hz, 1H, H_3), 7.0 (m, 4H, $H_{3'-4'-5'-6'}$), 7.34 (s, 1H, H_6), 7.87 (dd, J = 8.4-1.8 Hz, 1H, H_4), 8.90 (dd, J = 4.2-1.8 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 56.8, 61.7, 115.3, 116.8, 118.2, 119.3, 122.6, 123.9, 129.2, 131.1, 132.9, 134.7, 142.5, 143.5, 144.3, 150.4, 151.1.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (M = 280.33): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.7; H, 5.6; N, 10.0.

5-(2-Amino-5-methoxyphenyl)-7,8-dimethoxyquinoline (**7d**).

The reaction of **6d** (0.39 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ethyl acetate (1:1) as an eluent 0.26 g (84%) of **7d** as a yellow solid, mp 181°; ir: ν 3344, 2926, 1600, 1498, 1473, 1338, 1234, 1155, 1077 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.5 (bs, 2H, NH_2), 3.55 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 6.58 (d, J = 2.7 Hz, 1H, $H_{6'}$), 6.71 (dd, J = 8.6-2.7 Hz, 1H, $H_{4'}$), 6.82 (d, J = 8.6 Hz, 1H, $H_{3'}$), 7.11 (dd, J = 8.5-4.1 Hz, 1H, H_3), 7.24 (s, 1H, H_6), 7.82 (dd, J = 8.5-1.6 Hz, 1H, H_4), 8.83 (dd, J = 4.1-1.6 Hz, 1H, H_2).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$ (M = 310.36): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.4; H, 5.7; N, 8.9.

5-(2-Aminophenyl)-8-methoxyquinoline (**7e**).

The reaction of **6e** (0.33 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ethyl acetate (1:1) as an eluent 0.18 g (72%) of **7e** as a yellow solid, mp 188°; ir: ν 3410, 3336, 3241, 1630, 1505, 1472, 1448, 1365, 1309, 1111 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.4 (bs, 2H, NH_2), 4.10 (s, 3H, OCH_3), 6.8 (m, 5H, $H_{7-3'-4'-5'-6'}$), 7.33 (dd, J = 8.5-4.1 Hz, 1H, H_3), 7.41 (d, J = 7.9 Hz, 1H, H_6), 7.91 (dd, J = 8.5-1.7 Hz, 1H, H_4), 8.91 (dd, J = 4.1-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 55.9, 107.3, 115.1, 118.2, 121.6, 124.1, 127.6, 127.9, 128.6, 128.8, 131.4, 134.5, 140.2, 144.5, 149.1, 154.9.

Anal. Calcd. for $C_{16}H_{14}N_2O$ (M = 250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.6; H, 5.5; N, 11.0.

General Procedure for the Synthesis of Azides **8a-e** from Amines **7a-e**.

The required amino compound (1 mmole) was added to a solution of water (1 ml) and concentrated sulfuric acid (0.3 ml). The resulting solution was stirred for 10 minutes and ice-cooled before addition of sodium nitrite (0.074 g, 1.05 mmoles) in water (0.2 ml). After stirring for 45 minutes, sodium azide (0.084 g, 1.2 mmoles) in water (0.3 ml) was added and stirring was continued for 40 minutes. Treatment with sodium

hydrogenocarbonate, extraction with dichloromethane, drying over magnesium sulphate and solvent removal afforded a crude product which was purified by preparative flash chromatography on a silica gel column.

5-(2-Azidophenyl)-7-bromo-8-methoxyquinoline (**8a**).

The reaction of **7a** (0.33 g, 1 mmole) according to the general procedure gave after purification by column chromatography with ethyl acetate as an eluent 0.36 g (100%) of **8a** as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 4.27 (s, 3H, OCH_3), 7.4 (m, 5H, $H_{3\text{-}3'\text{-}4'\text{-}5'\text{-}6'}$), 7.61 (s, 1H, H_6), 7.85 (dd, J = 8.6-1.5 Hz, 1H, H_4), 8.98 (dd, J = 4.2-1.5 Hz, 1H, H_2).

Anal. Calcd. for $C_{16}H_{11}BrN_4O$ (M = 355.20): C, 54.10; H, 3.12; N, 15.77. Found: C, 53.9; H, 3.0; N, 15.7.

5-(2-Azido-5-methoxyphenyl)-7-bromo-8-methoxyquinoline (**8b**).

The reaction of **7b** (0.36 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ethyl acetate (85:15) as an eluent 0.35 g (90%) of **8b** as a yellow oil; ir: ν 3005, 2964, 2936, 2835, 2109, 1575, 1500, 1463, 1284, 1242, 1084 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.67 (s, 3H, OCH_3), 4.20 (s, 3H, OCH_3), 7.0 (m, 3H, $H_{3'\text{-}4'\text{-}6'}$), 7.34 (dd, J = 8.5-4.1 Hz, 1H, H_3), 7.58 (s, 1H, H_6), 7.82 (dd, J = 8.5-1.7 Hz, 1H, H_4), 8.93 (dd, J = 4.1-1.7 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 55.7, 61.9, 112.1, 116.0, 119.9, 121.1, 122.2, 127.6, 127.9, 131.4, 132.5, 132.6, 135.0, 143.0, 150.0, 153.0, 154.2.

Anal. Calcd. for $C_{17}H_{13}BrN_4O_2$ (M = 385.23): C, 53.00; H, 3.40; N, 14.54. Found: C, 52.8; H, 3.3; N, 14.4.

5-(2-Azidophenyl)-7,8-dimethoxyquinoline (**8c**).

The reaction of **7c** (0.28 g, 1 mmole) according to the general procedure gave after purification by column chromatography with ethyl acetate as an eluent 0.31 g (100%) of **8c** as a yellow oil; ir: ν 3395, 2934, 2123, 1604, 1473, 1336, 1155, 1078 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.01 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 7.0 (m, 6H, $H_{3\text{-}6\text{-}3'\text{-}4'\text{-}5'\text{-}6'}$), 7.71 (dd, J = 8.5-1.6 Hz, 1H, H_4), 8.87 (dd, J = 4.1-1.6 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 56.7, 61.7, 116.7, 118.3, 119.1, 122.8, 124.7, 129.5, 130.4, 131.9, 132.1, 134.3, 138.4, 142.6, 143.1, 150.2, 150.6.

Anal. Calcd. for $C_{17}H_{14}N_4O_2$ (M = 306.33): C, 66.66; H, 4.61; N, 18.29. Found: C, 66.4; H, 4.7; N, 18.4.

5-(2-Azido-5-methoxyphenyl)-7,8-dimethoxyquinoline (**8d**).

The reaction of **7d** (0.31 g, 1 mmole) according to the general procedure gave after purification by column chromatography with ethyl acetate as an eluent 0.25 g (75%) of **8d** as a yellow oil; ir: ν 2936, 2836, 2112, 1600, 1494, 1473, 1336, 1244, 1157 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.64 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 6.92 (d, J = 2.6 Hz, 1H, $H_{6'}$), 6.97 (d, J = 8.7 Hz, 1H, $H_{3'}$), 7.05 (dd, J = 8.7-2.6 Hz, 1H, $H_{4'}$), 7.16 (dd, J = 8.5-4.1 Hz, 1H, H_3), 7.25 (s, 1H, H_6), 7.74 (dd, J = 8.5-1.5 Hz, 1H, H_4), 8.87 (dd, J = 4.1-1.5 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 55.7, 56.7, 61.6, 112.1, 116.5, 119.0, 119.5, 122.3, 122.8, 129.2, 131.6, 132.3, 134.5, 142.5, 143.1, 150.1, 150.7, 154.3.

Anal. Calcd. for $C_{18}H_{16}N_4O_3$ (M = 336.35): C, 64.28; H, 4.79; N, 16.66. Found: C, 64.0; H, 4.6; N, 16.5.

5-(2-Azidophenyl)-8-methoxyquinoline (**8e**).

The reaction of **7e** (0.25 g, 1 mmole) according to the general procedure gave after purification by column chromatography with ethyl acetate as an eluent 0.28 g (100%) of **8e** as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 4.10 (s, 3H, OCH_3), 7.09 (d, J = 8.0 Hz, 1H, H_7), 7.4 (m, 6H, $H_{3\text{-}6\text{-}3'\text{-}4'\text{-}5'\text{-}6'}$), 7.80 (dd, J = 8.5-1.6 Hz, 1H, H_4), 8.92 (dd, J = 4.1-1.6 Hz, 1H, H_2); ^{13}C nmr (deuteriochloroform): δ 55.9, 106.8, 118.4, 121.6, 124.7, 127.8, 128.3, 129.1, 130.0, 130.8, 132.4, 134.2, 138.7, 139.7, 148.9, 155.1.

Anal. Calcd. for $C_{16}H_{12}N_4O$ (M = 276.30): C, 69.55; H, 4.38; N, 20.28. Found: C, 69.4; H, 4.4; N, 20.1.

General Procedure for the Synthesis of 7*H*-Pyrido[2,3-*c*]carbazoles **9a-d** from Azides **8a-c,e**.

The required azide (1 mmole) in 1,2-dichlorobenzene (7 ml) was slowly heated to 170°. Stirring was continued for 2 hours at 170°, before solvent removal under vacuum. The crude solid was purified by preparative flash chromatography on a silica gel column.

6-Bromo-5-methoxy-7*H*-pyrido[2,3-*c*]carbazole (**9a**).

The reaction of **8a** (0.36 g, 1 mmole) according to the general procedure gave after purification by column chromatography with ethyl acetate as an eluent 0.27 g (81%) of **9a** as a beige solid, mp >250°; ir: ν 3084, 1523, 1455, 1352, 1319, 1277, 1229, 1087 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.28 (s, 3H, OCH_3), 7.5 (m, 4H, $H_{2\text{-}8\text{-}9\text{-}10}$), 8.42 (m, 1H, H_{11}), 8.78 (bs, 1H, N*H*), 8.97 (dd, 1H, H_3), 9.05 (dd, 1H, H_1); ms: (electron impact) m/z 326/328 (M^+).

Anal. Calcd. for $C_{16}H_{11}BrN_2O$ (M = 327.19): C, 58.74; H, 3.39; N, 8.56. Found: C, 58.6; H, 3.2; N, 8.7.

6-Bromo-5,10-dimethoxy-7*H*-pyrido[2,3-*c*]carbazole (**9b**).

The reaction of **8b** (0.39 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ethyl acetate (75/25) as an eluent 0.046 g (13%) of **9b** as a yellow solid, mp >250°; ir: ν 3126, 2931, 1554, 1487, 1464, 1352, 1300, 1215, 1158, 1083 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.02 (s, 3H, OCH_3), 4.26 (s, 3H, OCH_3), 7.15 (dd, 1H, H_9), 7.56 (d, 1H, H_8), 7.65 (dd, 1H, H_2), 7.85 (d, 1H, H_{11}), 8.66 (s, 1H, N*H*), 8.9 (m, 2H, $H_{1\text{-}3}$); ms: (chemical ionization) m/z 357/359 (M^++1).

Anal. Calcd. for $C_{17}H_{13}BrN_2O_2$ (M = 357.21): C, 57.16; H, 3.67; N, 7.84. Found: C, 57.0; H, 3.5; N, 7.7.

5,6-Dimethoxy-7*H*-pyrido[2,3-*c*]carbazole (**9c**).

The reaction of **8c** (0.31 g, 1 mmole) according to the general procedure gave after purification by column chromatography with ethyl acetate as an eluent 0.23 g (81%) of **9c** as a beige solid, mp 179°; ir: ν 2934, 1577, 1529, 1456, 1347, 1294, 1192, 1090 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.22 (s, 3H, OCH_3), 4.29 (s, 3H, OCH_3), 7.5 (m, 4H, $H_{2\text{-}8\text{-}9\text{-}10}$), 8.41 (m, 1H, H_{11}), 8.93 (dd, J = 4.3-1.6 Hz, 1H, H_3), 8.98 (dd, J = 8.3-1.6 Hz, 1H, H_1), 9.12 (bs, 1H, N*H*); ms: (electron impact) m/z 278 (M^+).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (M = 278.31): C, 73.37; H, 5.07; N, 10.07. Found: C, 73.1; H, 4.9; N, 9.9.

5-Methoxy-7*H*-pyrido[2,3-*c*]carbazole (**9e**).

The reaction of **8e** (0.28 g, 1 mmole) according to the general procedure gave after purification by column chromatography with dichloromethane and ethyl acetate (1:1) as an eluent 0.17 g (70%) of **9e** as a beige solid, mp >250°; ir: ν 3046, 1605, 1530, 1458, 1353, 1326, 1278, 1209 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.17 (s, 3H, OCH_3), 7.20 (s, 1H, H_6), 7.4 (m, 3H, $H_{8\text{-}9}$

$_{10}$), 7.63 (dd, J = 8.4-4.2 Hz, 1H, H_2), 8.37 (m, 1H, H_{11}), 8.65 (bs, 1H, N*H*), 8.93 (dd, J = 4.2-1.6 Hz, 1H, H_3), 9.01 (dd, J = 8.4-1.6 Hz, 1H, H_1).

Anal. Calcd. for $C_{16}H_{12}N_2O$ (M = 248.29): C, 77.40; H, 4.87; N, 11.28. Found: C, 77.3; H, 4.9; N, 11.1.

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