Reactivity of 4-Chlorobenzo[*c*][2,7]naphthyridines towards Pd(0) Catalyzed Coupling Reactions and Nucleophilic Substitutions. Aroylation by Nucleophilic Substitution with Analogues of Acyl Anions

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Various 4-substituted benzo[*c*][2,7]naphthyridines were prepared from the corresponding 4-chloro derivative by Pd(0) coupling reaction or nucleophilic substitution. More particularly, 4-aroyl-benzo[*c*][2,7]naphthyridines were synthesized by aroylation with arenecarbaldehydes in the presence of 1,3-dimethylimidazolium iodide.

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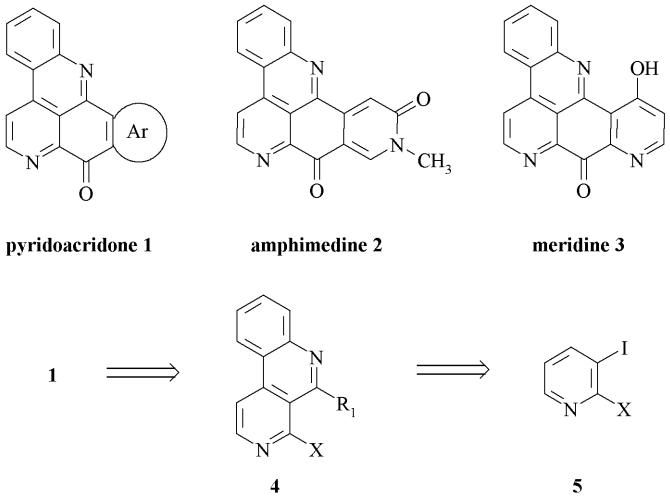
In previous papers [1] we described a new methodology for the synthesis of compounds of the pyridoacridone series **1**. The structure is the basic skeleton of marin alkaloid series of biological interest such as amphimedine **2** or meridine **3** [2]. The strategy implies the preparation of suitably substituted benzo[*c*][2,7]naphthyridines **4**. The latter were synthesized starting from 2-halogeno-3-iodopyridines **5**, by metalation [3], halogen dance and biaryl cross-coupling.

Scheme 1



The 2,9-Diazaphenanthrene **4** we mostly used is the 4-chloro benzo[*c*][2,7]naphthyridine **4a** (X = Cl, R_1 = H) [3b]. This compound was readily obtained in two steps from the easily available 2-chloro-3-iodopyridine **5a** (X = Cl) (overall yield : 60%) (Scheme 2).

In order to transform the naphthyridine **4a** in suitable intermediates for the synthesis of marine alkaloids we undertook the study of different ways of functionalization of **4a** at C-4. Two reactions proved to be efficient: coupling reactions and nucleophilic substitutions.

Suzuki and Stille cross coupling reactions in usual conditions led to biaryl compounds **6** in good yields (51-80%) (Scheme 3-Table 1).

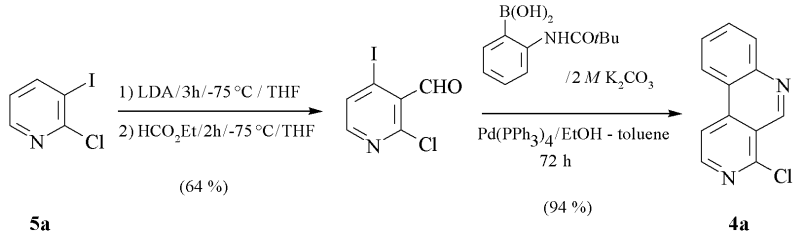
Table 1

Cross-coupling Reactions by using Suzuki (a) or Stille (b) Protocols

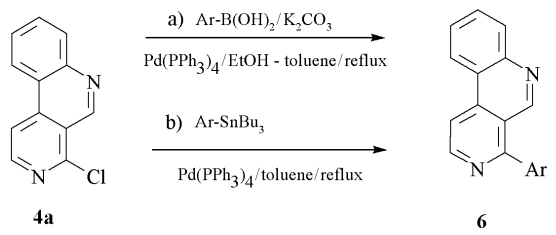
Compound	Ar	Method	Yield [%]
6a	phenyl	(a)	73
6b	2-thienyl	(a)	51
6c	2-benzofuryl	(a)	80
6a	phenyl	(b)	52
6d	2-pyridyl	(b)	57

4-Formylbenzo[*c*][2,7]naphthyridine **8** provides a suitable starting material for the synthesis of functionalized benzo[*c*][2,7]naphthyridine. It was prepared by ozonolysis of 4-vinylbenzo[*c*][2,7]naphthyridine **7** which was synthesized by coupling reaction (Scheme 4).

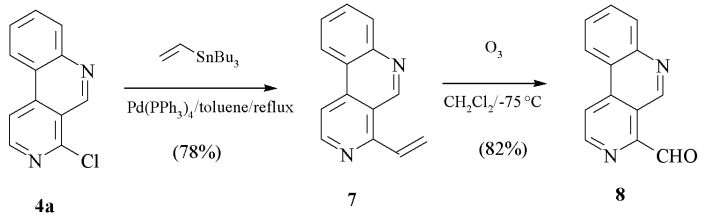
Scheme 2



Scheme 3



Scheme 4



Nucleophilic substitutions of the chlorine of benzonaphthyridine **4a** were carried out first by alcoholates then by carbanions.

Reaction of alcoholates afforded 4-alkoxybenzo[*c*]-[2,7]naphthyridines **9** in good yields (Scheme 5, Table 2).

Scheme 5

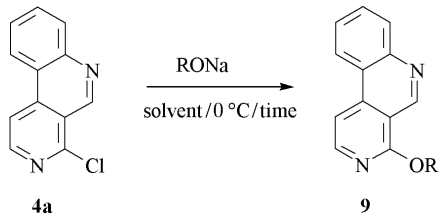


Table 2

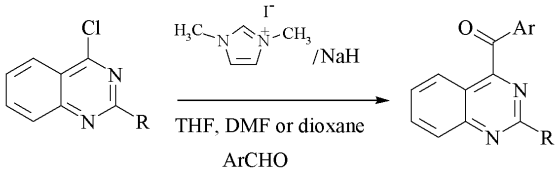
Nucleophilic Substitutions by Alcoholates

	R	Solvent/temperature/time	Yield [%]
9a	Me	MeOH/reflux/18h	65
9b	Et	EtOH/reflux/20h	81
9c	Ph	DMF/60°C/19h	79
9d	2-BrC_6H_4	DMF/60°C/19h	87

Miyashita and colleagues [4] developed a methodology of catalytic aroylation of chloropyrimidines using arene carbaldehydes as aroyl sources. The aroyl groups are introduced by nucleophilic substitution of the chlorine by sodium carbanions with the catalytic action of azolium salts as shown in Scheme 6.

It was of interest to carry out the reaction with 4-chlorobenzo[*c*][2,7]naphthyridine **4a** as substrate**.** In these conditions sodium carbanions substitute the chlorine of

Scheme 6



compound **4a**. It should be noted that in a previous paper, we reported the addition of different lithium carbanions to the 5-6 imine bond [3b]. (Benzo[*c*][2,7]naphthyridin-4-yl)arylketones **11** were obtained in fairly to good yields (Scheme 7-Table 3).

Scheme 7

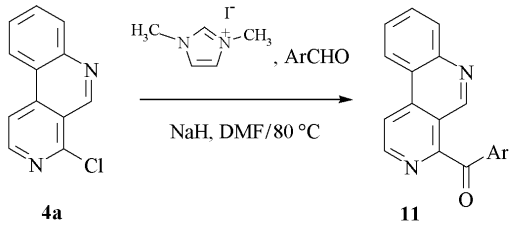


Table 3

Aroylation of 4-Chlorobenzo[*c*][2,7]naphthyridine **4a** with Aromatic Aldehydes in the Presence of Imidazolium Salt

Compound	Aromatic aldehyde	Time [hours]	Aroylbenzo naphthyridine **11**	Yield [%]
11a	benzaldehyde	15	Ar = phenyl	66
11b	1-naphthaldehyde	15	Ar = 1-naphthyl	73
11c	2-naphthaldehyde	15	Ar = 2-naphthyl	44
11d	2-thienaldehyde	20	Ar = 2-thienyl	69
11e	3-thienaldehyde	20	Ar = 3-thienyl	52
11f	2-furaldehyde	20	Ar = 2-furyl	64
11g	3-furaldehyde	20	Ar = 3-furyl	63
11h	picolinadehyde	15	Ar = 2-pyridyl	58

In conclusion, the compounds that are described in this paper possess structures that are very similar to those of known natural products and represent suitable precursors for the elaboration of such compounds. As a continuation of this work, the strategy is used for the synthesis of polycyclic compounds of the series.

EXPERIMENTAL

General Data.

Melting points were determined on Kofler apparatus and are uncorrected. Infrared (ir) spectra were obtained on a Perkin-Elmer FTIR 1650 spectrometer, and only noteworthy frequencies are given in cm^{-1}. The ^1H nmr spectra were recorded at 300 MHz on a Bruker Avance-300 NMR spectrometer. Chemical shifts (δ)

are quoted in parts per million (ppm) downfield from an internal standard, tetramethylsilane in deuteriochloroform, or hexamethyldisiloxane in d_6-dimethylsulfoxide. Coupling constants (*J*) are given in hertz (Hz). Elemental analyses were performed on a Carlo-Erba CHN apparatus. Mass spectra were recorded on a JEOL JMS-AX500 mass spectrometer; samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2, Merck - Geduran SI 60 (70-230 mesh).

The light sensitive tetrakis(triphenylphosphine) palladium(0) catalyst was prepared by hydrazine reduction of palladium chloride, as described by Coulson [5], and stored under a dehydrated and deoxygenated atmosphere at -10 °C. Tributylvinyltin was obtained, as described by Seyferth and Stone, by action of vinylmagnesium bromide on tributyltin chloride [6]. 1,3-Dimethylimidazolium iodide was prepared by the methylation of 1-methylimidazole with methyl iodide according to Benac's method [7].

Suzuki Cross-coupling Reaction of the 4-Chlorobenzo[*c*][*2,7*]-naphthyridine **4a** with Aromatic Boronic Acids.

4-Phenylbenzo[*c*][*2,7*]naphthyridine (**6a**).

4-Chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 108 mg, 0.5 mmole), phenylboronic acid (67 mg, 0.55 mmole), potassium carbonate (0.5 ml of a 2 *M* aqueous solution) in ethanol (0.25 ml) and deoxygenated toluene (8 ml) were stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmole). The reaction mixture was then refluxed for 22 hours. The solution was then cooled at room temperature. Water (10 ml) was added and the aqueous layer was separated, neutralized and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether, 30:70, R_f = 0.35) afforded **6a** (94 mg, 73%) as yellow crystals. **6a**: mp 163 °C; ir (potassium bromide): ν 3050, 1596, 1553 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.47-8.07 (m, 7H, phenyl-H, 8-H, 9-H), 8.27 (dd, 1H, 7-H, $J_{7\text{-}8}$ = 7.8 Hz, $J_{7\text{-}9}$ =1.5 Hz), 8.35 (d, 1H, 1-H, $J_{1\text{-}2}$ = 5.5 Hz), 8.60 (dd, 1H, 10-H, $J_{8\text{-}10}$ = 1.5 Hz, $J_{9\text{-}10}$ = 7.8 Hz), 9.02 (d, 1H, 2-H, $J_{1\text{-}2}$ = 5.5 Hz), 9.55 (s, 1H, 5-H).

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.61; H, 4.98; N, 10.72.

4-(2-Thienyl)benzo[*c*][*2,7*]naphthyridine (**6b**).

4-Chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 100 mg, 0.47 mmole), 2-thienylboronic acid (60 mg, 0.47 mmole), potassium carbonate (0.5 ml of a 2 *M* aqueous solution) in ethanol (1 ml) and deoxygenated toluene (10 ml) were stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmole). The reaction mixture was then refluxed for 18 hours. The solution was then cooled at room temperature. Water (10 ml) was added and the aqueous layer was separated, neutralized and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether, 50:50, R_f = 0.5) yielded **6b** (61 mg, 51%) as yellow crystals. **6b**: mp 159 °C; ir (potassium bromide): ν 2924, 1599, 1551 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.21 (dd, 1H, 4'-H, $J_{4'\text{-}3'}$ = 3.7 Hz, $J_{4'\text{-}5'}$ = 5.1 Hz), 7.57 (dd, 1H, 5'-H, $J_{5'\text{-}3'}$ = 1.0 Hz, $J_{5'\text{-}4'}$ = 5.1 Hz), 7.62 (dd, 1H, 3'-H, $J_{3'\text{-}4'}$ = 3.7 Hz, $J_{3'\text{-}5'}$ = 1.0 Hz), 7.70 (ddd, 1H, 9-H, $J_{9\text{-}7}$ = 1.1 Hz, $J_{9\text{-}8}$ = 8.1 Hz, $J_{9\text{-}10}$ = 8.3 Hz), 7.83 (ddd, 1H, 8-H, $J_{8\text{-}7}$ = 8.3 Hz, $J_{8\text{-}9}$ = 8.1 Hz, $J_{8\text{-}10}$ = 1.1 Hz), 8.18 (dd, 1H, 7-H, $J_{7\text{-}8}$ = 8.3 Hz, $J_{7\text{-}9}$ = 1.1 Hz), 8.25 (d, 1H, 1-H, $J_{1\text{-}2}$ = 5.8 Hz), 8.54 (dd, 1H, 10-H, $J_{10\text{-}8}$ = 1.1 Hz, $J_{10\text{-}9}$ = 8.3 Hz), 8.87 (d, 1H, 2-H, $J_{2\text{-}1}$ = 5.7 Hz), 9.84 (s, 1H, 5-H).

Anal. Calcd. for $C_{16}H_{10}N_2S$: C, 73.26; H, 3.84; N, 10.68. Found: C, 73.56; H, 4.04; N, 10.33.

4-(2-Benzo[*b*]furyl)benzo[*c*][*2,7*]naphthyridine (**6c**).

4-Chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 100 mg, 0.47 mmole), benzo[*b*]furylboronic acid (75 mg, 0.47 mmole), potassium carbonate (0.5 ml of a 2 *M* aqueous solution) in ethanol (1 ml) and deoxygenated toluene (10 ml) were stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmole). The reaction mixture was then refluxed for 18 hours. The solution was then cooled at room temperature. Water (10 ml) was added and the aqueous layer was separated, neutralized and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether, 50:50, R_f = 0.5) afforded **6c** (111 mg, 80%) as brown crystals. **6c**: mp 193 °C; ir (potassium bromide): ν 2925, 1598, 1543 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.27 (dd, 1H, 6'-H, $J_{6'\text{-}5'}$ = 7.2 Hz, $J_{6'\text{-}7'}$ = 7.7 Hz), 7.36 (dd, 1H, 5'-H, $J_{5'\text{-}4'}$ = 7.4 Hz, $J_{5'\text{-}6'}$ = 7.2 Hz), 7.6 (d, 1H, 7'-H, $J_{7'\text{-}6'}$ = 7.7 Hz), 7.62 (s, 1H, 3'-H), 7.68 (d, 1H, 4'-H, $J_{4'\text{-}5'}$ = 7.4 Hz), 7.68 (dd, 1H, 9-H, $J_{9\text{-}8}$ = 7.0 Hz, $J_{9\text{-}10}$ = 8.1 Hz), 7.81 (dd, 1H, 8-H, $J_{8\text{-}7}$ = 8.1 Hz, $J_{8\text{-}9}$ = 7.0 Hz), 8.18 (d, 1H, 7-H, $J_{7\text{-}8}$ = 8.1 Hz), 8.28 (d, 1H, 1-H, $J_{1\text{-}2}$ = 5.6 Hz), 8.50 (d, 1H, 10-H, $J_{10\text{-}9}$ = 8.1 Hz), 8.91 (d, 1H, 2-H, $J_{2\text{-}1}$ = 5.6 Hz), 10.31 (s, 1H, 5-H).

Anal. Calcd. for $C_{20}H_{12}N_2O$: C, 81.07; H, 4.08; N, 9.45. Found: C, 81.24; H, 4.41; N, 9.81.

Stille Cross-coupling Reaction of the 4-Chlorobenzo[*c*][*2,7*]-naphthyridine **4a** with Organostannanes.

4-Phenylbenzo[*c*][*2,7*] naphthyridine (**6a**).

4-Chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 100 mg, 0.47 mmole), phenyl tri-*n*-butyl stannane (171 mg, 0.47 mmole), in deoxygenated toluene (10 ml) were stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmole). The reaction mixture was then refluxed for 21 hours. The solution was then cooled at room temperature. Water (10 ml) and ammonia (5 ml, 10% aqueous solution) were added and the aqueous layer was separated and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether, 30:70, R_f = 0.35) afforded **6a** (63 mg, 52%) as yellow crystals. Physical data are in agreement with those previously given.

4-(2-Pyridyl)benzo[*c*][*2,7*]naphthyridine (**6d**).

4-Chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 108 mg, 0.5 mmole), 2-pyridyl tri-*n*-butyl stannane (204 mg, 0.55 mmole), in deoxygenated toluene (15 ml) were stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (29 mg, 0.025 mmole). The reaction mixture was then refluxed for 24 hours. The solution was then cooled at room temperature. Water (10 ml) and ammonia (5 ml, 10% aqueous solution) were added and the aqueous layer was separated and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*.

Purification by flash chromatography (dichloromethane, R_f = 0.20) afforded **6d** (74 mg, 57%) as light brown crystals. **6d**: mp 175 °C; ir (potassium bromide): ν 3002, 1602, 1586, 1557 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.50 (dd, 1H, 5'-H, $J_{5'-4'}$ = 6.1 Hz, $J_{5'-6'}$ = 4.8 Hz), 7.70-8.04 (m, 3H, 4'-H, 8-H, 9-H), 8.18 (d, 1H, 3'-H, $J_{3'-4'}$ = 7.6 Hz), 8.25 (d, 1H, 7-H, J_{7-8} = 7.6 Hz), 8.45 (d, 1H, 1-H, J_{1-2} = 5.5 Hz), 8.61 (d, 1H, 10-H, J_{10-9} = 7.6 Hz), 8.87 (d, 1H, 6'-H, $J_{6'-5'}$ = 4.8 Hz), 9.01 (d, 1H, 2-H, J_{2-1} = 5.5 Hz), 10.10 (s, 1H, 5-H).

Anal. Calcd. for $C_{17}H_{11}N_3$: C, 79.36; H, 4.31; N, 16.33. Found: C, 79.50; H, 4.30; N, 15.93.

4-Vinylbenzo[*c*][*2,7*]naphthyridine (**7**).

4-Chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 643 mg, 3 mmole), vinyl tri-*n*-butyl stannane (1.08 g, 3.4 mmole), in deoxygenated toluene (60 ml) were stirred under an argon atmosphere for 30 minutes before adding tetrakis(triphenylphosphine)palladium(0) (180 mg, 0.15 mmole). The reaction mixture was then refluxed for 8 hours. The solution was then cooled at room temperature. Water (50 ml) and ammonia (5 ml, 10% aqueous solution) were added and the aqueous layer was separated and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether/diethyl ether, 90:10, R_f = 0.6) afforded **7** (479 mg, 78%) as orange crystals. **7**: mp 147 °C; ir (potassium bromide): ν 3049, 1596, 1554 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.89 (dd, 1H, vinylβ_{cis}-H, $J_{cis\ \beta-\alpha}$ = 10.8 Hz, J_{gem} = 1.8 Hz), 6.67 (dd, 1H, vinylβ_{trans}-H, $J_{trans\ \alpha-\beta}$ = 16.8 Hz, J_{gem} = 1.8 Hz), 7.75 (ddd, 1H, 9-H, J_{9-8} = J_{9-10} = 8.2 Hz, J_{9-7} = 1.4 Hz), 7.78 (dd, 1H, vinylα-H, $J_{cis\ \alpha-\beta}$ = 10.8 Hz, $J_{trans\ \alpha-\beta}$ = 16.8 Hz), 7.84 (ddd, 1H, 8-H, J_{8-7} = J_{8-9} = 8.2 Hz), 8.24 (dd, 1H, 7-H, J_{7-8} = 8.2 Hz, J_{7-9} = 1.4 Hz, J_{8-10} = 1.4 Hz), 8.31 (d, 1H, 1-H, J_{1-2} = 5.7 Hz), 8.55 (dd, 1H, 10-H, J_{10-9} = 8.2 Hz, J_{10-8} = 1.4 Hz), 8.92 (d, 1H, 2-H, J_{2-1} = 5.7 Hz), 9.76 (s, 1H, 5-H).

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.28; H, 5.00; N, 13.62.

Ozonolysis of the 4-Vinylbenzo[*c*][*2,7*]naphthyridine **7**.

4-Formylbenzo[*c*][*2,7*]naphthyridine (**8**).

A solution of 4-vinylbenzo[*c*][*2,7*]naphthyridine (**7,** 400 mg, 1.94 mmole) in dichloromethane (20 ml) and acetic acid (2.5 ml) cooled at – 75 °C was submitted to a flow of ozone until persistence of a blue color, then a flow of oxygen for 10 minutes. The mixture was allowed to warm to room temperature and water (10 ml) was added. The reaction mixture was neutralized with an aqueous solution of sodium carbonate and extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo*. Purification by flash chromatography (ethyl acetate, R_f = 0.4) afforded **8** (333 mg, 82%) as white crystals, mp 186 °C; ir (potassium bromide): ν 1708 (νCO), 1603, 1559 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.79 (ddd, 1H, 9-H, J_{9-7} = 1.5 Hz, J_{9-8} = 8.0 Hz, J_{9-10} = 8.1 Hz), 7.93 (ddd, 1H, 8-H, J_{8-7} = 8.1 Hz, J_{8-9} = 8.0 Hz, J_{8-10} = 1.5 Hz), 8.28 (dd, 1H, 7-H, J_{7-8} = 8.0 Hz, J_{7-9} = 1.5 Hz), 8.58 (dd, 1H, 10-H, J_{10-9} = 8.1 Hz, J_{10-8} = 1.5 Hz), 8.62 (d, 1H, 1-H, J_{1-2} = 5.6 Hz), 9.12 (d, 1H, 2-H, J_{2-1} = 5.6 Hz), 10.44 (s, 1H, CHO), 10.61 (s, 1H, 5-H).

Anal. Calcd. for $C_{13}H_8N_2O$: C, 74.99; H, 3.87; N, 13.45. Found: C, 75.33; H, 3.91; N, 13.53.

Reaction of the 4-Chlorobenzo[*c*][*2,7*]naphthyridine **4a** with Alkoxides and Phenoxides.

4-Methoxybenzo[*c*][*2,7*]naphthyridine (**9a**).

A stirred solution of 4-chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 70 mg, 0.33 mmole) in methanol (5 ml), and sodium methylate (25 mg of sodium in 3 ml of methanol, 1.09 mmole) was refluxed for 18 hours then evaporated to dryness. Purification by flash chromatography (dichloromethane/ethyl acetate, 80:20, R_f = 0.6) afforded **9a** (45 mg, 65%) as white crystals. **9a**: mp 88 °C; ir (potassium bromide): ν 1617, 1571 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 4.01 (s, 3H, OCH_3), 7.64 (dd, 1H, 9-H, J_{9-8} = 7.6 Hz, J_{9-10} = 8.2 Hz), 7.80 (dd, 1H, 8-H, J_{8-7} = 8.2 Hz, J_{8-9} = 7.6 Hz), 7.88 (d, 1H, 1-H, J_{1-2} = 5.8 Hz), 8.20 (d, 1H, 7-H, J_{7-8} = 8.2 Hz), 8.31 (d, 1H, 2-H, J_{2-1} = 5.8 Hz), 8.39 (d, 1H, 10-H, J_{10-9} = 8.2 Hz), 9.70 (s, 1H, 5-H).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.06; H, 4.98; N, 13.16.

4-Ethoxybenzo[*c*][*2,7*]naphthyridine (**9b**).

A stirred solution of 4-chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 106 mg, 0.49 mmole) in ethanol (5 ml), and sodium ethylate (35 mg of sodium in 3 ml of ethanol, 1.52 mmole) was refluxed for 20 hours then concentrated to dryness. Purification by flash chromatography (dichloromethane/ethyl acetate, 80:20, R_f = 0.75) afforded **9b** (89 mg, 81%) as beige crystals, mp 104 °C; ir (potassium bromide): ν 2959, 2924, 2855, 1614, 1584 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.56 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 4.63 (q, 2H, OCH_2CH_3, J = 7.1 Hz), 7.64 (dd, 1H, 9-H, J_{9-8} = 7.6 Hz, J_{9-10} = 8.2 Hz), 7.78 (dd, 1H, 8-H, J_{8-7} = 8.2 Hz, J_{8-9} = 7.6 Hz), 7.80 (d, 1H, 1-H, J_{1-2} = 5.9 Hz), 8.18 (d, 1H, 7-H, J_{7-8} = 8.2 Hz), 8.33 (d, 1H, 2-H, J_{2-1} = 5.9 Hz), 8.39 (d, 1H, 10-H, J_{10-9} = 8.2 Hz), 9.61 (s, 1H, 5-H).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.11; H, 5.04; N, 12.41.

4-Phenoxybenzo[*c*][*2,7*]naphthyridine (**9c**).

Into a solution of phenol (132 mg, 1.4 mmole) in dimethylformamide (10 ml) was added sodium hydride (60% in oil, 54 mg, 1.35 mmole). The mixture was stirred for 0.5 hour at room temperature, then 4-chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 100 mg, 0.47 mmole) was added. The mixture was stirred at room temperature for 1 hour then at 60 °C for 19 hours and finally evaporated to dryness. Purification by flash chromatography (dichloromethane, R_f = 0.35) afforded **9c** (101 mg, 79%) as white crystals, mp 154 °C; ir (potassium bromide): ν 1618, 1568 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.21-7.26 (m, 3H, 2'-H, 4'-H, 6'-H), 7.43(dd, 2H, 3'-H, 5'-H, J = 7.7 Hz, J = 8.1 Hz), 7.68 (ddd, 1H, 9-H, J_{9-8} = 7.0 Hz, J_{9-10} = 8.2 Hz, J_{9-7} = 1.2 Hz), 7.82 (ddd, 1H, 8-H, J_{8-7} = 8.3 Hz, J_{8-9} = 7.0 Hz, J_{8-10} = 1.3 Hz), 7.95 (d, 1H, 1-H, J_{1-2} = 5.9 Hz), 8.21 (dd, 1H, 7-H, J_{7-8} = 8.3 Hz, J_{7-9} = 1.2 Hz), 8.32 (d, 1H, 2-H, J_{2-1} = 5.9 Hz), 8.45 (dd, 1H, 10-H, J_{10-9} = 8.2 Hz, J_{10-8} = 1.3 Hz), 9.80 (s, 1H, 5-H).

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.40; H, 4.44; N, 10.29. Found: C, 79.25; H, 4.64; N, 10.55.

4-(2-Bromophenoxy)benzo[*c*][*2,7*]naphthyridine (**9d**).

Into a solution of 2-bromophenol (242 mg, 1.4 mmole) in dimethylformamide (10 ml) was added sodium hydride (60% in oil, 54 mg, 1.35 mmole). The mixture was stirred for 0.5 hour at room temperature, then 4-chlorobenzo[*c*][*2,7*]naphthyridine (**4a**,

100 mg, 0.47 mmole) was added. The mixture was stirred at room temperature for 1 hour then at 60 °C for 19 hours and finally evaporated to dryness. Purification by flash chromatography (dichloromethane, R_f = 0.30) afforded **9d** (143 mg, 87%) as white crystals, mp 168 °C; ir (potassium bromide): ν 1619, 1579, 1570, 1519 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.14 (m,1H, bromophenyl proton), 7.34-7.39 (m, 2H, bromophenyl protons), 7.63 (m, 1H, bromophenyl proton), 7.68 (ddd, 1H, 9-H, J_{9-8} = 7.0 Hz, J_{9-10} = 8.2 Hz, J_{9-7} = 1 Hz), 7.82 (ddd, 1H, 8-H, J_{8-7} = 8.3 Hz, J_{8-9} = 7.0 Hz, J_{8-10} = 1.2 Hz), 7.97 (d, 1H, 1-H, J_{1-2} = 5.9 Hz), 8.21 (dd, 1H, 7-H, J_{7-8} = 8.3 Hz, J_{7-9} = 1 Hz), 8.29 (d, 1H, 2-H, J_{1-2} = 5.9 Hz), 8.45 (dd, 1H, 10-H, J_{10-9} = 8.2 Hz, J_{10-8} = 1.2 Hz), 9.85 (s, 1H, 5-H).

Anal. Calcd. for $C_{18}H_{11}BrN_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 61.66; H, 3.14; N, 8.16.

Reaction of the 4-Chlorobenzo[*c*][*2,7*]naphthyridine **4a** with Aromatic Aldehydes, Catalyzed by 1,3-Dimethylimidazolium iodide, in the Presence of NaH.

General Procedure.

A stirred solution of 4-chlorobenzo[*c*][*2,7*]naphthyridine (**4a**, 200 mg, 0.93 mmole), an aromatic aldehyde (1.02 mmole), and 1,3-dimethylimidazolium iodide (52 mg, 0.23 mmole) in dimethylformamide (15 ml) was treated, under a nitrogen atmosphere, with sodium hydride (60% in oil, 44 mg, 1.12 mmole) and then heated at 90 °C for 15 to 22 hours (the progress of the reaction was checked by thin layer chromatography). After cooling to room temperature, the reaction mixture was poured in ice-water and extracted with dichloromethane and chloroform. The combined organic layers were dried over magnesium sulfate and concentrated to dryness. The residue was purified by flash chromatography on silica gel yielding the ketone **11**.

Benzo[*c*][2,7]naphthyridin-4-yl-phenyl methanone (**11a**).

The general procedure applied to **4a** using benzaldehyde afforded **11a** (175 mg, 66%) as white crystals, after purification by flash chromatography (petroleum ether/ethyl acetate, 40:60). **11a**: mp 176°C; ir (potassium bromide): ν 1619, 1570 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.55 (dd, 2H, 3'-H, 5'-H, J = 8.0 Hz, J = 8.0 Hz), 7.69 (dd, 1H, 9-H, J_{9-8} = J_{9-10} = 7.5 Hz), 7.82 (dd, 1H, 8-H, J_{8-7} = J_{8-9} = 7.5 Hz), 7.95 (dd, 1H, 4'-H, $J_{4'-3'}$ = $J_{4'-5'}$ = 7.6 Hz), 8.02 (d, 2H, 2'-H, 6'-H, J = 8 Hz), 8.30 (d, 1H, 7-H, J_{7-8} = 7.5 Hz), 8.58 (d, 1H, 1-H, J_{1-2} = 5.2 Hz), 8.66 (d, 1H, 10-H, J_{10-9} = 7.5 Hz), 9.03 (d, 1H, 2-H, J_{2-1} = 5.2 Hz), 9.64 (s, 1H, 5-H).

Anal. Calcd. for $C_{19}H_{12}N_2O$: C, 80.26; H, 4.25; N, 9.85. Found: C, 80.12; H, 4.12; N, 9.58.

(Benzo[*c*][*2,7*]naphthyridin-4-yl-1-naphthylmethanone (**11b**).

The general procedure applied to **4a** using 1-naphthaldehyde afforded **11b** (227 mg, 73%) as yellow crystals, after purification by flash chromatography (chloroform/diethyl ether, 95:5, R_f = 0.2), mp 225 °C; ir (potassium bromide): ν 3056, 1665, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): 7.42 (dd, 1H, 3'-H, $J_{3'-2'}$ = 8 Hz, $J_{3'-4'}$ = 7.3 Hz), 7.59 (ddd, 1H, H_{naph}, J = 8.1 Hz, J = 7 Hz, J = 1.4 Hz), 7.60 (dd, 1H, 4'-H, $J_{4'-3'}$ = 7.3 Hz, $J_{4'-2'}$ = 1.5 Hz,), 7.66 (ddd, 1H, H_{naph}, J = 8.4 Hz, J = 7 Hz, J = 1.5 Hz), 7.78 (ddd, 1H, 9-H, J_{9-10} = 8.6 Hz, J_{9-8} = 7.2 Hz, J_{9-7} = 1.4 Hz), 7.90 (ddd, 1H, 8-H, J_{8-7} = 8.6 Hz, J_{8-9} = 7.2 Hz, J_{8-10} = 1.4 Hz), 7.93 (dd, 1H, H_{naph}, J = 8.1 Hz, J = 1.5 Hz), 8.07 (dd, 1H, 2'-H, $J_{2'-3'}$ = 8 Hz, $J_{2'-4'}$ = 1.5 Hz), 8.25 (ddd, 1H, 7-H, J_{7-8} = 8.6 Hz, J_{7-9} = 1.4 Hz, J_{7-10} = 0.7 Hz), 8.52 (dd, 1H, 1-H, J_{1-2} = 5.7 Hz, J_{1-5} = 0.7 Hz), 8.61 (ddd, 1H, H-10, J_{10-9} = 8.6 Hz, J_{10-8} = 1.4 Hz, J_{10-7} = 0.7 Hz), 8.88 (dd, 1H, H_{naph}, J = 8.4 Hz, J = 1.4 Hz), 8.92 (d, 1H, 2-H, J_{2-1} = 5.7 Hz), 9.74 (d, 1H, 5-H, J_{5-1} = 0.7 Hz),

Anal. Calcd. for $C_{23}H_{14}N_2O$: C, 82.62; H, 4.22; N, 8.38. Found: C, 82.95; H, 4.37; N, 8.29.

Benzo[*c*][*2,7*]naphthyridin-4-yl-2-naphthyl methanone (**11c**).

The general procedure applied to **4a** using 2-naphthaldehyde afforded **11c** (137 mg, 44%) as beige crystals, after purification by flash chromatography (chloroform/diethyl ether, 95:5, R_f = 0.6), mp 222 °C; ir (potassium bromide): ν 3052, 1664, 1612, 1560, 1472 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.50 (ddd, 1H, H_{naph}, J = 8.2 Hz, J = 7 Hz, J = 1.4 Hz), 7.58 (ddd, 1H, H_{naph}, J = 8.2 Hz, J = 7 Hz, J = 1.4 Hz), 7.78 (ddd, 1H, 9-H, J_{9-10} = 8.2 Hz, J_{9-8} = 7.1 Hz, J_{9-7} = 1.4 Hz), 7.84 (dd, 1H, H_{naph}, J = 8.2 Hz, J = 1.4 Hz), 7.88 (dd, 1H, H_{naph}, J = 8.2 Hz, J = 1.4 Hz), 7.90 (ddd, 1H, 8-H, J_{8-7} = 8.2 Hz, J_{8-9} = 7.1 Hz, J_{8-10} = 1.5 Hz), 7.96 (d, 1H, 4'-H, $J_{4'-3'}$ = 8.7 Hz), 8.15 (dd, 1H, 3'-H, $J_{3'-4'}$ = 8.7 Hz, $J_{3'-1'}$ = 1.1 Hz), 8.24 (ddd, 1H, 7-H, J_{7-8} = 8.2 Hz, J_{7-9} = 1.5 Hz, J_{7-10} = 0.7 Hz), 8.35 (d, 1H, 1'-H, $J_{1'-3'}$ = 1.1 Hz), 8.56 (dd, 1H, 1-H, J_{1-2} = 5.8 Hz, J_{1-5} = 0.6 Hz), 8.62 (ddd, 1H, H-10, J_{10-9} = 8.2 Hz, J_{10-8} = 1.5 Hz, J_{10-7} = 0.7 Hz), 9.01 (d, 1H, 2-H, J_{2-1} = 5.8 Hz), 9.61 (d, 1H, 5-H, J_{5-1} = 0,6 Hz),

Anal. Calcd. for $C_{23}H_{14}N_2O$: C, 82.62; H, 4.22; N, 8.38. Found: C, 82.66; H, 4.16; N, 8.42.

Benzo[*c*][2,7]naphthyridin-4-yl-2-thienyl methanone (**11d**).

The general procedure applied to **4a** using 2-thienaldehyde afforded **11d** (187 mg, 69%) as beige crystals, after purification by flash chromatography (dichloromethane/ethyl acetate, 90:10, R_f = 0.25). **11d**: mp 197 °C; ir (potassium bromide): ν 3070, 1720, 1635, 1600, 1558, 1416 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.18 (dd, 1H, 4'-H, $J_{4'-3'}$ = 3.9 Hz, $J_{4'-5'}$ = 4.9 Hz), 7.75 (ddd, 1H, 9-H, J_{9-7} = 1.2 Hz, J_{9-8} = 8.2 Hz, J_{9-10} = 8.1 Hz), 7.80 (dd, 1H, 5'-H, $J_{5'-4'}$ = 4.9 Hz, $J_{5'-3'}$ = 1.1 Hz), 7.88 (ddd, 1H, 8-H, J_{8-7} = 8.1 Hz, J_{8-9} = 8.2 Hz, J_{8-10} = 1.2 Hz), 7.95 (dd, 1H, 3'-H, $J_{3'-4'}$ = 3.9 Hz, $J_{3'-5'}$ = 1.1 Hz), 8.23 (dd, 1H, 7-H, J_{7-8} = 8.1 Hz , J_{7-9} = 1.2 Hz), 8.54 (d, 1H, 1-H, J_{1-2} = 5.7 Hz), 8.57 (dd, 1H, 10-H, J_{10-8} = 1.2 Hz, J_{10-9} = 8.1 Hz), 8.97 (d, 1H, 2-H, J_{2-1} = 5.7 Hz), 9.87 (s, 1H, 5-H).

Anal. Calcd. for $C_{17}H_{10}N_2OS$: C, 70.32; H, 3.47; N, 9.65; S, 11.04. Found: C, 70.11; H, 3.62 ; N, 9.40; S, 11.17.

Benzo[*c*][2,7]naphthyridin-4-yl-3-thienylmethanone (**11e**).

The general procedure applied to **4a** using 3-thienaldehyde afforded **11e** (141 mg, 52%) as beige crystals, after purification by flash chromatography (petroleum ether/diethyl ether, 50:50, R_f = 0.20), mp 207 °C; ir (potassium bromide): ν 1651, 1601, 1502, 1401 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.39 (dd, 1H, 5'-H, $J_{5'-4'}$ = 5.1 Hz, $J_{5'-2'}$ = 2.9 Hz), 7.76 (ddd, 1H, 9-H, J_{9-7} = 1.1 Hz, J_{9-8} = 7.1 Hz, J_{9-10} = 8.2 Hz), 7.78 (dd, 1H, 4'-H, $J_{4'-2'}$ = 1.1 Hz, $J_{4'-5'}$ = 5.1 Hz), 7.89 (ddd, 1H, 8-H, J_{8-7} = 8.3 Hz, J_{8-9} = 7.1 Hz, J_{8-10} = 1.3 Hz), 8.24 (dd, 1H, 2'-H, $J_{2'-4'}$ = 1.1 Hz, $J_{2'-5'}$ = 2.9 Hz), 8.24 (dd, 1H, 7-H, J_{7-8} = 8.3 Hz , J_{7-9} = 1.1 Hz), 8.53 (d, 1H, 1-H, J_{1-2} = 5.7 Hz), 8.59 (dd, 1H, 10-H, J_{10-8} = 1.3 Hz, J_{10-9} = 8.2 Hz), 8.97 (d, 1H, 2-H, J_{2-1} = 5.7 Hz), 9.71 (s, 1H, 5-H).

Anal. Calcd. for $C_{17}H_{10}N_2OS$: C, 70.32; H, 3.47; N, 9.65; S, 11.04. Found: C, 70.04; H, 3.40 ; N, 9.64; S, 11.22.

Benzo[*c*][2,7]naphthyridin-4-yl-2-furylmethanone (**11f**).

The general procedure applied to **4a** using 2-furaldehyde afforded **11f** (163 mg, 64%) as beige crystals, after purification by flash chromatography (dichloromethane/diethyl ether, 90:10, R_f = 0.50). **11f**: mp 190°C; ir (potassium bromide): ν 2922, 1651, 1604, 1560, 1463 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.63 (dd, 1H, 4'-H, $J_{4'-3'}$ = 3.6 Hz, $J_{4'-5'}$ = 1.7 Hz), 7.46 (dd, 1H, 3'-H, $J_{3'-4'}$ = 3.6 Hz, $J_{3'-5'}$ = 0.4 Hz), 7.77 (ddd, 1H, 9-H, J_{9-7} = 0.9 Hz, J_{9-8} = 8.1 Hz, J_{9-10} = 8.2 Hz), 7.79 (dd, 1H, 5'-H, $J_{5'-4'}$ = 1.7 Hz, $J_{5'-3'}$ = 0.4 Hz), 7.89 (ddd, 1H, 8-H, J_{8-7} = 8.3 Hz, J_{8-9} = 8.1 Hz, J_{8-10} = 1.1 Hz), 8.25 (dd, 1H, 7-H, J_{7-8} = 8.2 Hz, J_{7-9} = 0.9 Hz), 8.56 (d, 1H, 1-H, J_{1-2} = 5.7 Hz), 8.59 (dd, 1H, 10-H, J_{10-8} = 1.1 Hz, J_{10-9} = 8.2 Hz), 8.98 (d, 1H, 2-H, J_{2-1} = 5.7 Hz), 9.83 (s, 1H, 5-H).

Anal. Calcd. for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.67; N, 10.21. Found: C, 74.82; H, 3.75; N, 10.16.

Benzo[*c*][2,7]naphthyridin-4-yl-3-furylmethanone (**11g**).

The general procedure applied to **4a** using 3-furaldehyde afforded **11g** (161 mg, 63%) as brown crystals, after purification by flash chromatography (dichloromethane/diethyl ether, 90:10, R_f = 0.35), mp 202 °C; ir (potassium bromide): ν 1654, 1602, 1558, 1509 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.03 (dd, 1H, 4'-H, $J_{4'-2'}$ = 0.8 Hz, $J_{4'-5'}$ = 1.9 Hz), 7.51 (dd, 1H, 5'-H, $J_{5'-4'}$ = 1.9 Hz, $J_{5'-2'}$ = 1.5 Hz), 7.75 (ddd, 1H, 9-H, J_{9-7} = 1 Hz, J_{9-8} = 8.1 Hz, J_{9-10} = 8.2 Hz), 7.88 (ddd, 1H, 8-H, J_{8-7} = 8.1 Hz, J_{8-9} = 8.1 Hz, J_{8-10} = 1.2 Hz), 8.24 (dd, 1H, 7-H, J_{7-8} = 8.1 Hz , J_{7-9} = 1 Hz), 8.32 (dd, 1H, 2'-H, $J_{2'-4'}$ = 0.8 Hz, $J_{2'-5'}$ = 1.5 Hz), 8.52 (d, 1H, 1-H, J_{1-2} = 5.7 Hz), 8.57 (dd, 1H, 10-H, J_{10-8} = 1.2 Hz, J_{10-9} = 8.2 Hz), 8.95 (d, 1H, 2-H, J_{2-1} = 5.7 Hz), 9.92 (s, 1H, 5-H).

Anal. Calcd. for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.67; N, 10.21. Found: C, 74.69; H, 3.63; N, 10.49.

Benzo[*c*][2,7]naphthyridin-4-yl-2-pyridyl methanone (**11h**).

The general procedure applied to **4a** using picolinaldehyde afforded **11h** (154 mg, 58%) as yellow crystals, after purification by flash chromatography (dichloromethane/diethyl ether, 80:20, R_f = 0.25), mp 222 °C; ir (potassium bromide): ν 1685, 1602, 1560 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.46 (ddd, 1H, 5'-H, $J_{5'-3'}$ = 1.2 Hz, $J_{5'-4'}$ = 7.7 Hz, $J_{5'-6'}$ = 4.7 Hz), 7.72 (ddd, 1H, 9-H, J_{9-7} = 1.3 Hz, J_{9-8} = 8.2 Hz, J_{9-10} = 8.2 Hz), 7.81 (ddd, 1H, 8-H, J_{8-7} = 8.2 Hz, J_{8-9} = 8.2 Hz, J_{8-10} = 1.3 Hz), 7.89 (ddd, 1H, 4'-H, $J_{4'-3'}$ = 7.8 Hz, $J_{4'-5'}$ = 7.7 Hz, $J_{4'-6'}$ = 1.7 Hz), 8.18 (dd, 1H, 7-H, J_{7-8} = 8.2 Hz, J_{7-9} = 1.3 Hz), 8.27 (dd, 1H, 3'-H, $J_{3'-4'}$ = 7.8 Hz, $J_{3'-5'}$ = 1.2 Hz), 8.47 (d, 1H, 1-H, J_{1-2} = 5.8 Hz), 8.56 (dd, 1H, 10-H, J_{10-9} = 8.2 Hz, J_{10-8} = 1.3 Hz), 8.58 (dd, 1H, 6'-H, $J_{6'-5'}$ = 4.7 Hz, $J_{6'-4'}$ = 1.7 Hz), 8.93 (d, 1H, 2-H, J_{2-1} = 5.8 Hz), 9.43 (s, 1H, 5-H).

Anal. Calcd. for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.61; H, 3.57; N, 14.42

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