A New Approach to the Synthesis of Benzofuro[3,2-*b*]quinolines, Benzothieno[3,2-*b*]quinolines and Indolo[3,2-*b*]quinolines

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Dedicated to the memory of Prof. Raymond N. Castle († August 11th, 1999).

Treatment of 2-hydroxy-, 2-mercapto-, and 2-ethoxycarbonylamino-benzonitriles **12** with 2-fluoro- or 2-nitrophenacylbromides **13** under alkaline conditions provided the corresponding benzofuran, benzothiophene, and indole intermediates **10**, respectively. Nucleophilic cyclization of these compounds led to the corresponding tetracyclic quinolinones **7a**, **7b**, and **3**. Denitrocyclization reaction of compounds **10** (R = NO_2) was found especially useful. Compounds **7a**, **7b**, and **3** were converted to their chloro derivatives **14a-c**, which were reduced with hydrogen and a catalyst to the corresponding compounds **8a**, **8b**, and **2**. The presented pathway represents a new method of preparation of quindoline **2** and its O and S analogs **8**. Chloro derivatives **14** are reactive enough to provide the corresponding methoxy derivatives **15** and dimethylamino derivatives **16**. Methylation of compounds **7a** and **7b** with iodomethane providing mixtures of major *N*-methyl derivatives **17** and minor *O*-methyl derivatives **15** were also studied.

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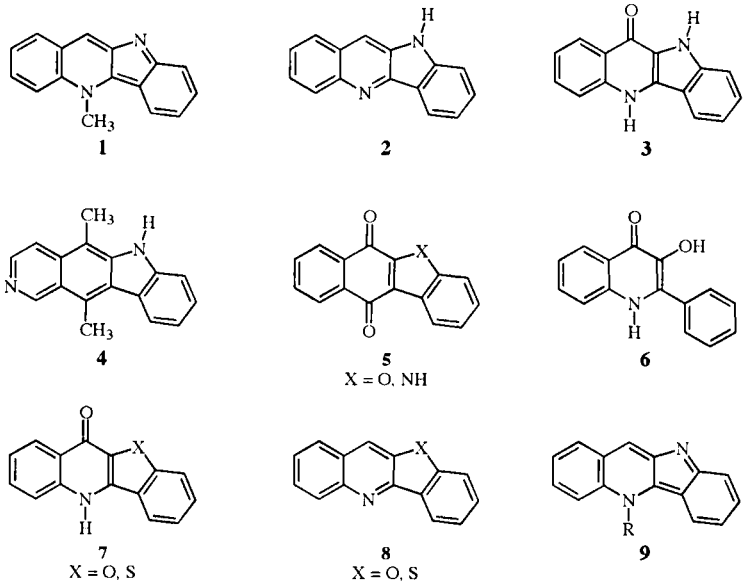
Introduction.

Cryptolepsis sanguinolenta, a twinning and scrambling shrub that grows along the west coast of Africa, still plays a role in traditional medicine in Ghana and is a subject of ethnobotanical studies. It has shown a strong anti-malarial activity in clinical trials and is also effective as a broad-spectrum antibiotic against both gram-negative and gram-positive bacteria [1-5]. Major alkaloids cryptolepine (**1**) [6-8] and quindoline (**2**) [7,9] are accompanied by a number of minor alkaloids. Quindolinone (**3**) is one of the minor alkaloids isolated from this species [10].

Cryptolepine (**1**), as well as its *N*-5 modified analogs are easily available from quindoline (**2**) [11]. There are several different synthetic procedures leading to quindoline (**2**) [2, 12-21], some of them use quindolinone (**3**) as a key intermediate [13,16]. Though some of the known methods of preparation of quindolinone (**3**) seem to be satisfactory [20,22], new methods starting from different materials are desirable for efficient structure modifications of this molecule.

Since both quindoline and, especially, cryptolepine and some of its derivatives have been found to be biologically active, molecular modification of these alkaloids is of interest. Therefore, new methods of preparation with better yields and with the potential to be used for the synthesis of suitable substituted analogs are desirable. In addition, it is a well known fact, that a number of antitumor agents, including elipticine (**4**) and its derivatives, possess tetracyclic skeleton derived from "2-phenylnaphthalene type". Based on this feature, new structures with a pronounced

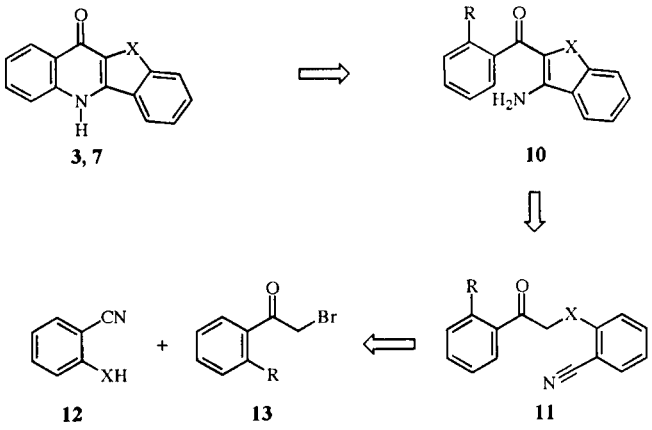


antitumor activity have recently been published, among them, compounds containing skeletons **5** [23-25]. It is evident, that compounds **3**, **7a**, and **7b** comply with the requirements for this type of activity. This theory is also supported by findings that some derivatives containing hydroxyquinolone moiety **6** are fairly cytotoxic [26,27]. Therefore, we decided to study the possibility of alternative methods for the preparation of quindolinone (**3**), as well as its known O [28-30] and S analogs [31,32] **7**. These compounds could also be used as intermediates for the preparation of quindoline (**2**), its analogs **8**, as well as cryptolepine derivatives **9**.

Chemistry.

Our strategy is depicted in retrosynthetic Scheme 1. The target compounds **3** and **7** (X = O, S) should be accessible from the corresponding intermediates **10** bearing suitable leaving groups R. It is expected that these intermediates can be formed by addition of the methane carbanion, formed from the acidic CH_2 group of **11**, to the cyano group. The key intermediates **11** should be easily formed from highly reactive α-bromoketones **13** and the corresponding benzonitriles **12**. All the suggested steps are quite straight forward, some of them have been described in the literature.

Scheme 1

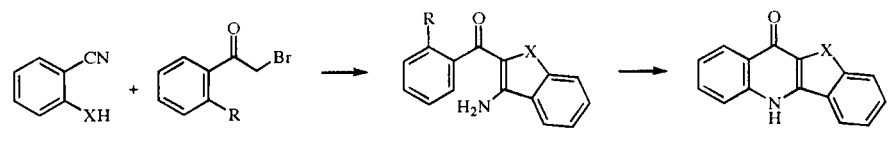


We have recently described the synthesis of a series of substituted benzofurans, including compound **10a**, starting from salicylonitrile **12a** and the corresponding bromo derivative **13a** *via* the corresponding intermediate **11a** (X = O, R = H). Reaction of bromo derivatives with thiosalicylonitrile **12b** provided directly benzothiophene derivatives, including compound **10b**. Unlike with benzofurans, we failed to isolate intermediates **11**. Similar reaction of phenacylbromides with suitably substituted anthranilonitriles, e.g. *N*-methanesulfonyl, *N*-(4-toluenesulfonyl), and *N*-ethoxycarbonyl anthranilonitrile, provided the corresponding indoles. When *N*-ethoxycarbonylanthranilonitrile and compound **13a** were used, the corresponding indole **10c** was directly obtained [33, 34].

For our study, we decided to choose phenacylbromides **13b** and **13c** containing fluoro and nitro groups, respectively, as potential leaving groups. When fluoro derivative **13b** was used for the reaction with salicylonitrile (**12a**) under the described conditions, uncyclized intermediate **11b** (X = O, R = F), which was easily cyclized to **10d** under the described conditions, was obtained. However, using nitro derivative **13c**, depending on the condition used, either a mixture in which the benzofuran **10e** prevailed or exclusively the benzofuran was obtained. Consistent with our previous experience [33,34], phenacylbromides **13b** and **13c** with thiosalicylonitrile (**12b**) provided directly benzothiophenes **10f** and **10g**. Similarly, treatment of anthranilonitrile **12c** with phenacylbromides **13b** or **13c** provided the corresponding compounds **10h** or **10i**.

Nucleophilic cyclization of fluoro derivatives **10d, 10f,** and **10h** with sodium hydride in dimethylformamide provided the required tetracyclic compounds **7a, 7b**, and **3**. With indole **10h**, the *N*-ethoxycarbonyl group was not present in the cyclization product **3.** Denitrocyclization reactions, which use the nitro group as a leaving group, have been successfully used in several cyclization reactions, by us and others, [For a review see ref. 35]; therefore we decided to try this possibility. We found, that the cyclization reaction under identical conditions generally provided

Scheme 2



12	X
a	O
b	S
c	N-CO_2Et

13	R
a	H
b	F
c	NO_2

10	X	R
a	O	H
b	S	H
c	N-CO_2Et	H
d	O	F
e	O	NO_2
f	S	F
g	S	NO_2
h	N-CO_2Et	F
i	N-CO_2Et	NO_2

	X
7a	O
7b	S
3	NH

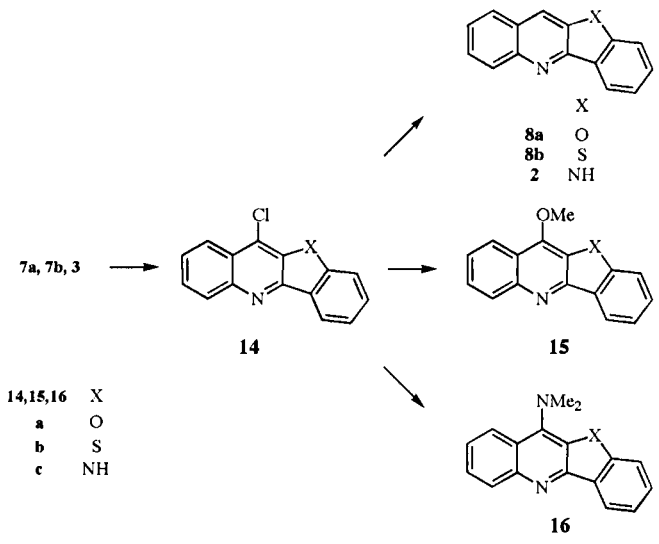
at least comparable yields of the fluoro derivatives of target compounds **7**. Similarly, as with compound **10h**, compound **10i** again provided the *N*-unsubstituted quindolinone (**3**).

Compounds **7a**, **7b**, and **3** were treated with phosphorus oxychloride (in the case of compound **3** with addition of phosphorus pentachloride) by a literature method to give the corresponding chloro derivatives **14a-14c** [13,16,29,30, 32,36]. Catalytic dehalogenation in the presence of hydrogen of **14c** leading to quindoline (**2**) [16] has already been described. We used the same conditions also with **14a** and **14b** and the corresponding benzofuro[3,2-*b*]quinoline (**8a**) benzothieno[3,2-*b*]quinoline (**8b**), respectively, were obtained. Both compound **8a** [30,37] and compound **8b** [38-40] have comparable properties as compounds prepared by other methods. Chloro derivatives **14a-14c** treated with a solution of sodium methanolate in methanol provided the corresponding methoxy derivatives **15**. Similarly, using a solution of dimethylamine in ethanol, compounds **16** were prepared. These compounds form water-soluble salts, for example hydrochlorides, which could be useful for biological testing as water-soluble derivatives of the parent heterocycles.

Having the methoxy derivatives **15a** and **15b**, we decided to study methylation of compounds **7a** and **7b** with iodomethane. In both cases, products of *N*-methylation **17** prevail over the methoxy derivatives **15**. This finding is in contrast with the reported *O*-alkylation of compound **7a** with 3-(dimethylamino)propyl chloride providing the corresponding 3-(dimethylamino)propoxy derivative in 59% yield [29].

In summary, we developed a new procedure of the preparation of quindolinone (**3**) and its O (**7a**) and S (**7b**) analogs providing the target compounds in acceptable yields. This methodology may be useful for the preparation of many substituted analogs of the mentioned compounds, including analogs of the important naturally occurring compounds quindoline (**2**) and cryptolepine (**1**). A large number of substituted salicylonitriles and anthranilonitriles are commercially available for use as starting materials; this is especially true for the preparation of benzofuro[3,2-*b*]quinolines and 10*H*-indolo[3,2-*b*]-quinolines. In addition, a method of exclusive *ortho* cyanation of anilines and phenols leading to the corresponding nitriles published by Adachi and Sugasawa [41] can provide a wide range of the starting nitriles. We also found useful [33] a recently published method of selective monodemethylation of 2-methoxybenzaldehydes [42]. This methodology is especially useful in the case of the readily available polymethoxy benzaldehydes, that provide the corresponding monodemethylation salicylaldehydes, that serve as useful intermediates for the synthesis of many methoxy-substituted silicylonitriles.

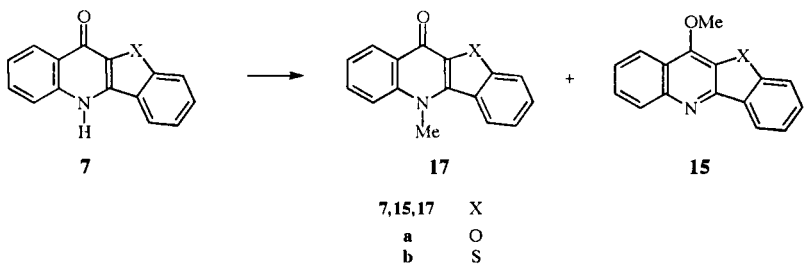
Scheme 3



EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. Infrared spectra (KBr) were recorded on a Perkin-Elmer FT-IR System Spectrum BX spectrometer, wavenumbers are given in cm^{-1}. Ultraviolet spectra were measured on a Shimadzu UV-260 spectrometer in ethanol, wavelengths are given in nm. ^1H nmr spectra were recorded on a Bruker instrument (250 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Mass spectra were measured on a GC-MS Finnigan MAT instrument. Flash chromatography was carried out using silica gel 60 from EM Science. Analytical tlc was performed on tlc aluminum sheets (silica gel 60 F_{254}) and preparative tlc on pre-coated plc plates (silica gel 60 F_{254}) from EM Science.

Scheme 4



2-[2-(2-Fluorophenyl)-2-oxoethoxy]benzonitrile (**11b**).

A solution of sodium hydroxide (0.6 g, 15 mmoles) in water (1 ml) was added dropwise to a stirred solution of salicylonitrile (**12a**) (1.8 g, 15 mmoles) and phenacylbromide **13b** (3.5 g, 16 mmoles) in 2-methoxyethanol and the mixture was refluxed for 20 minutes. Then the mixture was cooled, the insoluble portion was filtered off, washed with a small amount of cold methanol and dried to give the title compound (1.9 g, 50%) as creamy crystals, mp 135-137° (ethanol); ^{1}H nmr (deuteriochloroform): δ 5.37 (AB system, 2H, CH_2), 6.79 (dd, J = 8.5 Hz, J = 1.0 Hz, 1H, C3-H), 7.03 (d.t, J = 7.5 Hz, J = 1.0 Hz, 1H, C5-H), 7.28 (ddd, J = 11.3 Hz, J = 8.2 Hz, J = 1.0 Hz, 1H, C3'-H), 7.30 (m, 1H, C5'-H), 7.47 (ddd, J = 8.5 Hz, J = 7.5 Hz, J = 1.6 Hz, 1H, C4-H), 7.58 (dd, J = 7.5 Hz, J = 1.6 Hz, 1H, C6-H), 7.62 (m, 1H, C4'-H), 7.96 (dt, J = 7.2 Hz, J = 1.9 Hz, 1H, C6'-H); ^{19}F nmr (deuteriochloroform): δ -108.31.

Anal. Calcd. for $C_{15}H_{10}FNO_2$ (255.24): C, 70.58; H, 3.95; F, 7.44; N, 5.49. Found: C, 70.34; H, 4.04; F, 7.15; N, 5.49.

3-Amino-2-(2-fluorobenzoyl)benzofuran (**10d**).

2-[2-(2-Fluorophenyl)-2-oxoethoxy]benzonitrile (1.5 g, 6 mmoles) was added during 1 hour to a stirred solution of sodium (0.3 g, 13 mmoles) in absolute ethanol (15 ml) and the mixture was stirred at room temperature for additional 1 hour. Then the mixture was poured into water (30 ml), the insoluble portion was filtered off, washed with cold water and dried. Crystallization from ethanol provided compound **10d** (1.4 g, 93%) as yellow crystals, mp 162-163°; ms: m/e 255 (M+, 100%), 254 (61%), 236 (55%), 235 (29%), 198 (8%), 160 (9%), 132 (8%), 123 (17%), 104 (21%), 95 (26%), 77 (31%), 51 (15%).

Anal. Calcd. for $C_{15}H_{10}FNO_2$ (255.24): C, 70.58; H, 3.95; F, 7.44; N, 5.49. Found: C, 70.14; H, 4.01; F, 7.80; N, 5.23.

3-Amino-2-(2-nitrobenzoyl)benzofuran (**10e**).

A mixture of salicylonitrile (**12a**) (0.48 g, 4 mmoles) and potassium carbonate (1.6 g, 10 mmoles) in dimethylformamide (10 ml) was stirred at room temperature for 30 minutes. A solution of **13c** (1.2 g, 5 mmole) in dimethylformamide (3 ml) was added dropwise and the mixture was stirred at room temperature overnight. The mixture was poured into water (200 ml) and extracted with diethyl ether (5 x 50 ml). The organic extract was washed with brine (5 x 20 ml), water (20 ml) and dried with magnesium sulfate. The residue after evaporation was purified by flash chromatography (silica gel, petroleum ether:acetone, 8:2) followed by crystallization from ethanol to give **10e** (0.45 g, 40%), mp 127-130°; ^{1}H nmr (deuteriochloroform): δ 5.90 (bs, 2H, NH_2), 7.18-7.28 (m, 2H, C6-H, C7-H), 7.45 (ddd, J = 8.5 Hz, J = 7.0 Hz, J = 1.3 Hz, 1H, C5'-H), 7.57-7.80 (m, 4H, C4-H, C5-H, C4'-H, C6'-H), 8.12 (dd, J = 7.8 Hz, J = 0.9 Hz, 1H, C3'-H).

Anal. Calcd. for $C_{15}H_{10}N_2O_4$ (282.26): C, 63.83; H, 3.57; N, 9.92. Found: C, 63.63; H, 4.00; N, 9.64.

3-Amino-2-(2-fluorobenzoyl)benzothiophene (**10f**).

A mixture of thiosalicylonitrile (**12b**) (1.2 g, 8.9 mmoles) and potassium carbonate (3.2 g, 20 mmoles) in dimethylformamide (20 ml) was stirred at room temperature under an argon atmosphere for 30 minutes. A solution of **13b** (2.3 g, 10.5 mmoles) in dimethylformamide (10 ml) was added dropwise and the mixture was stirred at room temperature overnight. The mixture was poured into water (200 ml), the separated solid was filtered (2.5 g, two spots on tlc), dissolved in methanol (50 ml) and sodium methanolate (0.6 g, 11 mmole) was added to the solution. The color rapidly changed from yellow to red and after 5 minutes the solution was evaporated to dryness. The residue was triturated with water and the mixture was extracted with dichloromethane (5 x 20 ml), and extract was dried with magnesium sulfate. After evaporation the residue was crystallized from aqueous ethanol to give **10f** (1.6 g, 66%) as yellow crystals, mp 143-145° (ethanol); ^{1}H nmr (deuteriochloroform): δ 6.98 (bs, 2H, NH_2), 7.15-7.28 (m, 2H, C3'-H, C4'-H), 7.35-7.53 (m, 3H, C5'-H, C6'-H, C6-H), 7.58 (td, J = 8.1 Hz, J = 1.8 Hz, 1H, C5-H), 7.66 (d, J = 8.0 Hz, 1H, C7-H), 7.73 (d, J = 8.1 Hz, 1H, C4-H).

Anal. Calcd. for $C_{15}H_{10}FNOS$ (271.31): C, 66.41; H, 3.72; F, 7.00; N, 5.16; S, 11.82. Found: C, 66.26; H, 4.11; F, 7.17; N, 5.00; S, 11.77.

3-Amino-2-(2-nitrobenzoyl)benzothiophene (**10g**).

A mixture of thiosalicylonitrile (**12b**) (1.2 g, 8.9 mmoles) and potassium carbonate (3.2 g, 20 mmoles) in dimethylformamide (200 ml) was stirred at room temperature for 30 minutes. A solution of **13c** (2.6 g, 10.6 mmoles) in dimethylformamide (10 ml) was added dropwise and the mixture was stirred at room temperature for 1 hour. The mixture was poured into water (200 ml), the insoluble red precipitate was filtered off (2.7 g) and crystallized from 2-propanol (charcoal) to give **10g** (1.1 g, 41%) as orange crystals, mp 151-152° (ethanol); ^{1}H nmr (deuteriochloroform): δ 6.91 (bs, 2H, NH_2), 7.36 (ddd, J = 8.1 Hz, J = 7.1 Hz, J = 1.2 Hz, 1H, C6-H), 7.47 (td, J = 7.1 Hz, J = 1.2 Hz, 1H, C5-H), 7.56-7.66 (m, 3H, C4-H, C7-H, C5'-H), 7.69-7.78 (m, 2H, C4'-H, C6'-H), 8.18 (d, J = 8.2 Hz, 1H, C3'-H).

Anal. Calcd. for $C_{15}H_{10}N_2O_3S$ (298.32): C, 60.39; H, 3.38; N, 9.39; S, 10.75. Found: C, 60.62; H, 3.79; N, 9.45; S, 10.69.

3-Amino-1-ethoxycarbonyl-2-(2-fluorobenzoyl)indole (**10h**).

Sodium hydride (50% suspension in mineral oil, 0.75 g, 15 mmoles) was added to a stirred solution of compound **12c** (3.0 g, 16 mmole) in dimethylformamide (40 ml) and the mixture was stirred at room temperature for 1 hour. Then a solution of **13b** (3.5 g, 16 mmole) in dimethylformamide (15 ml) was added dropwise and the mixture was stirred at room temperature for 2 hours. The mixture was evaporated under reduced pressure, the residue was dissolved in dichloromethane (2 ml) and purified by flash chromatography on silica gel (petroleum ether:acetone, 5:1) followed by crystallization from hexane to give **10h** (1.3 g, 25%) as yellow crystals, mp 128-129°; ^{1}H nmr (deuteriochloroform): δ 1.00 (t, J = 7.1 Hz, 3H, CH_3), 3.82 (q, J = 7.1 Hz, 2H, CH_2), 6.07 (bs, 2H, NH_2), 7.14 (m, 2H, C6-H, C5'-H), 7.31 (dt, 1H, C5-H), 7.41 (m, 1H, C4'-H), 7.57 (m, 3H, C4-H, C3'-H, C6'-H), 8.18 (bd, J = 8.5 Hz, 1H, C7-H).

Anal. Calcd. for $C_{18}H_{15}FN_2O_3$ (326.33): C, 66.25; H, 4.63; F, 5.82; N, 8.58. Found: C, 65.95; H, 5.01; F, 5.87; N, 8.42.

3-Amino-1-ethoxycarbonyl-2-(2-nitrobenzoyl)indole (**10i**).

A mixture of **12c** (1.9 g, 10 mmoles) and potassium carbonate (4.0 g, 25 mmoles) in dimethylformamide (20 ml) was stirred at room temperature for 30 minutes. A solution of **13c** (2.9 g, 12 mmoles) in dimethylformamide (10 ml) was added dropwise and the mixture was stirred at room temperature for 2 hours. The mixture was poured to water (200 ml), the separated solid was filtered (1.7 g) and crystallized from ethanol (charcoal) to give **10i** (1.4 g, 40%) as yellow crystals, mp 203-205°; ^{1}H nmr (deuteriochloroform): δ 1.00 (t, J = 7.1 Hz, 3H, CH_3), 3.90 (q, J = 7.1 Hz,

2H, CH_2), 6.30 (bs, 2H, NH_2), 7.35 (ddd, J = 8.0 Hz, J = 6.9 Hz, J = 1.1 Hz, 1H, C6-H), 7.56-7.64 (m, 5H, C4-H, C5-H, C3'-H, C4'-H, C5'-H), 7.95 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H, C6'-H), 8.13 (bd, 1H, C7-H).

Anal. Calcd. for $C_{18}H_{15}N_3O_5$ (353.33): C, 61.19; H, 4.28; N, 11.89. Found: C, 61.11; H, 4.38; N, 11.84.

General Procedure for the Preparation of Compounds **7a** and **7b**.

Sodium hydride (50% suspension in mineral oil, 0.25 g, 5 mmoles) was added to a stirred solution of the corresponding compound **10** (2 mmoles) in dimethylformamide (10 ml) and the mixture was stirred at room temperature (in case of **10d** at 100°) for 2 hours. The cold mixture was poured into water (50 ml), the solution was acidified with acetic acid, the insoluble portion was filtered off, washed with water and crystallized from 2-methoxyethanol to give the corresponding tetracyclic compound **7**.

Benzofuro[3,2-*b*]quinolin-11(5*H*)-one (**7a**).

This compound was obtained in yields of 91% (from **10d**) and 80% (from **10e**) as white crystals that do not melt below 360° [29]; ir (KBr) ν 742, 1217, 1362, 1524, 1584, 1645, 2820, 3020 and 3420 cm^{-1}; uv (EtOH): λ_{max} 205 nm (log ε 4.33), 218 nm (log ε 4.25), 258 nm (log ε 4.58), 307 nm (log ε 4.27), 331 nm (log ε 3.86), 345 nm (log ε 4.14), 362 nm (log ε 4.23); ^1H nmr (dimethyl-d_6-sulfoxide, 60°): δ 7.34 (m, 1H), 7.46 (m, 1H), 7.68 (m, 4H), 8.21 (bd, 1H), 8.40 (bd, 1H); ^{13}C nmr (dimethyl-d_6-sulfoxide, 160°): δ 111.74 (C-1), 117.31 (C-6), 118.19 (C-4a), 120.77 (C-4), 120.85 (C-8), 122.33 (C-3), 124.64 (C-9), 125.29 (C-9a, C-10a), 128.83 (C-2), 130.29 (C-7), 137.31 (C-4b), 138.99 (C-5a), 154.73 (C-11a), and 164.60 (C-10).

Anal. Cald. for $C_{15}H_9NO_2$ (235.24): C, 76.59; H, 3.86; N, 5.95. Found: C, 76.30; H, 4.07; N, 5.69.

Benzothieno[3,2-*b*]quinolin-11(5*H*)-one (**7b**).

This compound was obtained in yields of 88% (from **10f**) and 84% (from **10g**) as white crystals, not melting up to 360° (lit [28] gives mp > 350°); uv (EtOH): λ_{max} 218 nm (log ε 4.48), 254 nm (log ε 4.50), 268 nm (log ε 4.62), 302 nm (log ε 3.92), 352 nm (log ε 4.02), 375 nm (log ε 4.24);^1H nmr (dimethyl-d_6-sulfoxide): δ 7.38 (td, 1H), 7.59-7.81 (m, 4H), 8.03 (d, J = 7.9 Hz, 1H), 8.31 (dd, J = 7.9 Hz, J = 0.9 Hz, 1H), 8.52 (dd, J = 7.9 Hz, J = 1.1 Hz, 1H), 12.24 (bs, 1H, NH).

Anal. Calcd. for $C_{15}H_9NOS$ (251.31): C, 71.69; H, 3.61; N, 5.57; S, 12.76. Found: C, 72.02; H, 3.40; N, 5.32; S, 12.55.

10*H*-Indolo[3,2-*b*]quinolin-11(5*H*)-one (**3**).

Sodium hydride (50% suspension in mineral oil, 0.15 g, 3.1 mmoles) was added to a stirred solution of compound **10h** or **10i** (1.5 mmoles) in THF (10 ml) and the mixture was stirred at room temperature for 1 hour. The cold mixture was poured into water (50 ml) and the solution was acidified with acetic acid, the insoluble portion was filtered off and washed with water. The crystals, which contain two compounds (tlc), were dissolved in ethanol (10 ml) and a solution of sodium hydroxide (1.5 g) in water (10 ml) was added. The mixture was refluxed for 30 minutes, the mixture was evaporated to dryness, the residue was triturated with water and the insoluble portion was filtered, washed with water and crystallized from ethanol to give **3** as monohydrate in yields of 77% (from **10h**) and 90% (from **10i**). The compound does not melt up to 360° (lit [13] gives mp > 330°); ir (KBr): ν 1631, 3159 and 3391 cm^{-1}; uv (EtOH): λ_{max} 232 nm (log ε 4.32), 269 nm (log ε 4.48), 308 nm (log ε 4.12), 323 nm (log ε 4.11), 378 nm (log ε 3.88), 396 nm (log ε 4.03); ^1H nmr (dimethyl-d_6-sulfoxide): δ 7.30 (td, 2H), 7.48-7.58 (m, 2H), 7.68 (dt, 1H), 7.78 (d, J = 7.9 Hz, 1H), 8.25 (d, J = 7.9 Hz, 1H), 8.38 (dd, J = 8.1 Hz, J = 1.1 Hz, 1H), 11.54 (bs, 1H, NH), 12.45 (bs, 1H, NH).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.51; H, 4.74; N, 11.18.

General Procedure for the Preparation of 11-Chloro Derivatives **14a-14c**.

A mixture of oxo derivative **7a, 7b, 3** (4 mmoles), phoshorus oxychloride (10 ml), and in case of **3**, phosphorus pentachloride (1 g, 5 mmoles) was refluxed for 3 hours. The excess phosphorus oxychloride was evaporated under reduced pressure, the residue was poured into ice-cold water and basified with a 10% solution of sodium hydroxide. The formed precipitate was filtered off, washed with water and crystallized from ethanol (charcoal) to give the corresponding chloro derivative **14**.

11-Chlorobenzofuro[3,2-*b*]quinoline (**14a**).

This compound was obtained in 77% yield as white crystals, mp 157-158° (lit [29] gives mp 159-160°); ir (KBr): ν 732, 1465, 1595, and 3036 cm^{-1}; uv (EtOH): λ_{max} 217 nm (log ε 4.58), 261 nm (log ε 4.75), 328 nm (log ε 4.27), 338 nm (log ε 4.27); ^1H nmr (deuteriochloroform): δ 7.50 (m, 1H), 7.65-7.72 (m, 3H), 7.78 (ddd, J = 8.9 Hz, J = 6.7 Hz, J = 1.7 Hz, 1H), 8.31 (dd, J = 8.3 Hz, J = 1.1 Hz, 1H), 8.37 (d, J = 7.7 Hz, 2H).

Anal. Calcd. for $C_{15}H_8ClNO$ (253.69): C, 71.02; H, 3.18; Cl, 13.98; N, 5.52. Found: C, 71.38; H, 3.22; Cl, 13.91; N, 5.78.

11-Chloro[1]benzothieno[3,2-*b*]quinoline (**14b**).

This compound was obtained in 33% yield as white needles, mp 154-155° (lit [32] gives mp 157-158°); ir (KBr): ν 732, 764, 1485, 1595, and 3038 cm^{-1}; uv (EtOH): λ_{max} 239 nm (log ε 4.52), 273 nm (log ε 4.81), 337 nm (log ε 4.03), 355 nm (log ε 3.68), 374 nm (log ε 3.72); ^1H nmr (deuteriochloroform): δ 7.52-7.70 (m, 3H), 7.81 (m, 2H), 8.29 (m, 2H), 8.60 (m, 1H).

Anal. Calcd. for $C_{15}H_8ClNS$ (269.75): C, 66.79; H, 2.99; Cl, 13.14; N, 5.19; S, 11.89. Found: C, 67.12; H, 3.25; Cl, 13.19; N, 4.89; S, 11.42.

11-Chloro-10*H*-indolo[3,2-*b*]quinoline (**14c**).

This compound was obtained in 70% yield as white crystals, mp 219-221° (lit [13] gives mp 225-228°); ir (KBr): ν 739, 1220, 1339, 1397, 1487, 1614, 3040, 3188, and 3638 (NH) cm^{-1}; uv (EtOH): λ_{max} 223 nm (log ε 4.37), 274 nm (log ε 4.66), 344 nm (log ε 4.16); ^1H nmr (dimethyl-d_6-sulfoxide): δ 7.31 (ddd, J = 8.4 Hz, J = 6.9 Hz, J = 1.1 Hz, 1H), 7.57-7.75 (m, 4H), 8.24 (m, 2H), 8.33 (d, J = 8.9 Hz, 1H), 11.78 (bs, 1H, NH).

Anal. Cald. for $C_{15}H_9ClN_2$ (252.70): C, 71.30; H, 3.59; Cl, 14.03; N, 11.09. Found: C, 71.64; H, 3.33; Cl, 14.41; N, 10.77.

General Procedure for the Preparation of Compounds **8a**, **8b**, and **3**.

A suspension of chloro derivative **14a-14c** (1 mmole) in methanol (5 ml) was acidified with a saturated solution of hydrogen chloride in ethanol and the solution was evaporated. The residue was dissolved in methanol (10 ml), 10% Pd on carbon (0.05 g) was added and the mixture was hydrogenated at atmospheric pressure for 2 hours. The catalyst was filtered off through Celite and washed with methanol. The filtrate was evaporated and crystallized from the appropriate solvent to give compound **8a** as its hydrochloride and compounds **8b** and **3** as bases.

Hydrochloride of Benzofuro[3,2-*b*]quinoline (**8a**).

This compound was obtained in 40% yield as yellow crystals, mp 149-153° (ethyl acetate). uv (EtOH): λ_{max} 215 nm (log ε 4.60), 259 nm (log ε 4.73), 328 nm (log ε 4.29), 337 nm (log ε 4.29); ^{1}H nmr (dimethyl-d_6-sulfoxide): δ 7.57 (ddd, J = 8.3 Hz, J = 6.6 Hz, J = 1.6 Hz, 1H), 7.69 (ddd, J = 8.3 Hz, J = 6.7 Hz, J = 1.2 Hz, 1H), 7.77-7.87 (m, 3H), 8.19 (dd, J = 8.3 Hz, J = 1.2 Hz, 1H), 8.28 (bd, J = 8.5 Hz, 1H), 8.39 (bd, J = 7.8 Hz, 1H), 8.66 (s, 1H); ms: *m/z* 219 (molecular ion of the base).

Anal. Calcd. for $C_{15}H_{10}ClNO$ (255.70): C, 70.46; H, 3.94; Cl, 13.86; N, 5.48. Found: C, 70.58; H, 4.11; Cl, 13.74; N, 5.55.

[1]Benzothieno[3,2-*b*]quinoline (**8b**).

This compound was obtained in 63% yield as yellow crystals, mp 166-168 °C (ethanol:water, 1:1); refs [38-40] give mp 171.5-172.5°; uv (EtOH): λ_{max} 206 nm (log ε 4.30), 241 nm (log ε 4.63), 272 nm (log ε 4.69), 336 nm (log ε 4.12); ^{1}H nmr (dimethyl-d_6-sulfoxide): δ 7.60-7.75 (m, 3H), 7.87 (ddd, J = 8.2 Hz, J = 6.8 Hz, J = 1.3 Hz, 1H), 8.07 (bd, J = 8.3 Hz, 2H, 1-H), 8.22 (bd, J = 8.5 Hz, 1H), 8.56 (bd, J = 7.9 Hz, 1H), 9.02 (s, 1H).

Anal. Cald. for $C_{15}H_9NS$ (235.31): C, 76.57; H, 3.86; N, 5.95; S, 13.62. Found: C, 76.50; H, 4.22; N, 5.94; S, 13.51.

10*H*-Indolo[3,2-*b*]quinoline (**2**).

This compound was obtained in 80% yield as yellow crystals, mp 250-253° (ethanol:water, 1:1); references [6] and [12] give mp 249-251° and 251-252°, respectively; uv (EtOH): λ_{max} 224 nm (log ε 4.45), 274 nm (log ε 4.20), 364 nm (log ε 3.96), 392 nm (log ε 3.56); ^{1}H nmr (dimethyl-d_6-sulfoxide): δ 7.28 (t, J = 7.5 Hz, 1H), 7.56-7.68 (m, 4H), 7.88 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 7.7 Hz, 1H), 8.25 (s, 1H), 8.44 (d, J = 7.5 Hz, 1H), 11.60 (bs, 1H, NH).

Anal. Calcd. for $C_{15}H_{10}N_2$ (218.26): C, 82.55; H, 9.62; N, 12.84. Found: C, 82.22; H, 9.77; N, 12.38.

General Procedure of Preparation of 11-Methoxy Derivatives **15a-15c.**

A mixture of chloro derivative **14a-14c** (0.4 mmoles) and sodium methanolate (40 mg, 0.8 mmole) in methanol (10 ml) was refluxed till the starting chloro derivative was absent by tlc (40 - 60 hours). The mixture was poured into ice-cold water, the insoluble portion was filtered off and crystallized from ethanol to give the corresponding methoxy derivative **15**.

11-Methoxybenzofuro[3,2-*b*]quinoline (**15a**).

This compound was obtained in 30% yield as white crystals, mp 112-115°; ir (KBr): ν 744, 1198, 1356, 1575, and 1640 cm^{-1}; uv (EtOH): λ_{max} 220 nm (log ε 4.47), 253 nm (log ε 4.60), 262 nm (log ε 4.76), 287 nm (log ε 3.56), 323 nm (log ε 4.25), 350 nm (log ε 3.88); ^{1}H nmr (deuteriochloroform): δ 4.63 (s, 3H, CH_3), 7.43 (bt, 1H), 7.56 (m, 3H), 7.68 (bt, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H).

Anal. Calcd. for $C_{16}H_{11}NO_2$ (249.27): C, 77.10; H, 4.45; N, 5.62. Found: C, 77.25; H, 4.75; N, 5.73.

11-Methoxy[1]benzothieno[3,2-*b*]quinoline (**15b**).

This compound was obtained in 51% yield as slightly yellowish crystals, mp 111-118°; uv (EtOH): λ_{max} 222 nm (log ε 4.35), 260 nm (log ε 4.62), 280 nm (log ε 3.31), 332 nm (log ε 4.22), 364 nm (log ε 3.68); ^{1}H nmr (deuteriochloroform): δ 4.43 (s, 3H, CH_3), 7.61-7.71 (m, 3H), 7.82 (t, J = 8.0 Hz, 1H), 8.04 (bd, J = 8.2 Hz, 1H), 8.16 (bd, J = 8.0 Hz, 1H), 8.25 (bd, J = 8.3 Hz, 1H), 8.52 (bd, J = 7.9 Hz, 1H).

Anal. Calcd. for $C_{16}H_{11}NOS$ (265.33): C, 72.43; H, 4.18; N, 5.28; S, 12.08. Found: C, 72.68; H, 4.53; N, 5.17; S, 11.96.

11-Methoxy-10*H*-indolo[3,2-*b*]quinoline (**15c**).

This compound was obtained in 48% yield as yellowish crystals, mp 207-212° ; uv (EtOH): λ_{max} 225 nm (log ε 4.21), 275 nm (log ε 4.48), 324 nm (log ε 3.92), 336 nm (log ε 4.03), 372 nm (log ε 3.58); ^{1}H nmr (deuteriochloroform): δ 4.30 (s, 3H, CH_3), 7.30 (t, J = 7.6 Hz, 1H), 7.52-7.75 (m, 4H), 8.22 (m, 2H), 8.33 (d, J = 7.5 Hz, 1H), 11.55 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{12}N_2O$ (248.29): C, 77.40; H, 4.87; N, 11.28. Found: C, 77.02; H, 4.52; N, 10.84.

General Procedure for the Preparation of 11-Dimethylamino Derivatives **16a-16c.**

A mixture of chloro derivative **14a-14c** (0.5 mmole) and dimethylamine (0.23 g, 5 mmoles) in ethanol (3.5 ml) was heated in a sealed tube at 150° for 10 hours. The mixture was evaporated to dryness, the residue was dissolved in ethanol and the base was converted to its hydrochloride with an ethanolic solution of hydrogen chloride. Crystallization from the appropriate solvent (charcoal) provided the hydrochloride of the corresponding 11-dimethylamino derivative **16**.

Dihydrochloride of 11-Dimethylaminobenzofuro[3,2-*b*]quinoline (**16a**).

This compound was obtained in 51% yield as yellow crystals, mp 239-242° (2-propanol); ir (KBr): ν 761, 1096, 1192, 1398, 1590, 1639, 2487, and 3033 cm^{-1}; uv (EtOH): λ_{max}: 214 nm (log ε 4.52), 263 nm (log ε 4.68), 334 nm (log ε 4.72), 377 nm (log ε 4.29), 393 nm (log ε 4.32); ^{1}H nmr (dimethyl-d_6-sulfoxide): δ 3.66 (s, 6H, CH_3), 7.58 (ddd, J = 8.2 Hz, J = 7.4 Hz, J = 1.2 Hz, 2H), 7.82 (m, 3H), 8.41 (bd, J = 7.9 Hz, 2H), 8.82 (bd, J = 8.2 Hz, 1H).

Anal. Cald. for $C_{17}H_{16}Cl_2N_2O$ (335.23): C, 60.91; H, 4.81; Cl, 21.15; N, 8.36. Found: C, 60.96; H, 5.05; Cl, 20.77; N, 8.70.

Hydrochloride of 11-Dimethylamino[1]benzothieno[3,2-*b*]-quinoline (**16b**).

This compound was obtained in 77% yield as yellow crystals, mp 235-238° (ethanol); ir (KBr): ν 757, 1238, 1400, 1534, 1570, 1620, and 3027 cm^{-1}; uv (EtOH): λ_{max}: 26 nm (log ε 4.5 4), 228 nm (log ε 4.52), 281 nm (log ε 4.60), 396 nm (log ε 4.03); ^{1}H nmr (dimethyl-d_6-sulfoxide): δ 3.55 (s, 6H, CH_3), 7.62 (m, 2H), 7.74 (ddd, J = 8.0 Hz, J = 7.2 Hz, J = 1.3 Hz, 1H), 7.87 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.4 Hz, 1H), 8.06 (ddd, J = 8.0 Hz, J = 1.1 Hz, J = 0.7 Hz, 1H), 8.30 (ddd, J = 8.7 Hz, J = 1.4 Hz, J = 0.6 Hz, 1H), 8.56 (dd, J = 8.5 Hz, J = 0.6 Hz, 1H), 9.17 (d, J = 8.0 Hz, 1H).

Anal. Calcd. for $C_{17}H_{15}ClN_2S$ (314.83): C, 64.86; H, 4.80; Cl, 11.26; N, 8.90; S, 10.18. Found: C, 64.61; H, 5.08; Cl, 11.55; N, 8.44; S, 9.88.

Hydrochloride of 11-Dimethylamino-10*H*-indolo[3,2-*b*]quinoline (**16c**).

This compound was obtained in 80% yield as yellow crystals, mp 264-267° (ethanol:water, 1:1); ir (KBr): ν 761, 1248, 1400, 1527, 1585, 1639, 2804, 3020 and 3197 cm^{-1}; uv (EtOH): λ_{max}: 204 nm (log ε 4.52), 228 nm (log ε 4.49), 237 nm (log ε 4.52), 287 nm (log ε 4.70), 348 nm (log ε 4.41), 435 nm (log ε 4.18); ^{1}H nmr (dimethyl-d_6-sulfoxide): δ 3.66 (s, 6H, CH_3), 7.31 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.80

(d, J = 9.0 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 8.37 (m, 2H), 8.78 (d, J = 7.6 Hz, 1H), 11.78 (bs, 1H, NH).

Anal. Calcd. for $C_{17}H_{16}ClN_3$ (297.80): C, 68.57; H, 5.42; Cl, 11.91; N, 14.11. Found: C, 68.19; H, 5.41; Cl, 12.25; N, 13.75.

Methylation of Compounds **7a** and **7b**.

Sodium hydride (50% suspension in mineral oil, 0.1g, 2 mmoles) was added to a stirred solution of **7** (1 mmole) in dimethylformamide (5 ml) and the mixture was stirred at room temperature for 1 hour and then iodomethane (0.1 ml, 1.6 mmole) was added and the mixture was stirred for additional 10 hours. The mixture was then poured into water (25 ml), the insoluble portion was filtered off, washed with water and dried to give a crude mixture, which was purified by preparative tlc using hexane:acetone 7:3 (v/v) to give the corresponding *N*-methyl derivative **17** and 11-methoxy derivative **15.**

5-Methylbenzofuro[3,2-*b*]quinolin-11(5*H*)-one (**17a**).

This compound was obtained in 74% yield as white crystals, that do not melt below 360° (ethanol); ir (KBr): ν 750, 1185, 1258, 1508, 1592, 1635, and 3400 cm^{-1}; uv (EtOH): λ_{max} 207 nm (4.09), 220 nm (log ε 4.08), 260 nm (log ε 4.42), 310 nm (log ε 4.06), 339 nm (log ε 3.67), 354 nm (log ε 4.00), 371 nm (log ε 4.10); ^1H nmr (dimethyl-d_6-sulfoxide, 60°): δ 4.32 (s, 3H, CH_3), 7.43-7.50 (m, 2H), 7.70 (m, 1H), 7.81 (m, 2H), 7.97 (bd, 1H), 8.44 (bd, 2H); ^{13}C nmr (dimethyl-d_6-sulfoxide, 60°): δ 37.57 (CH_3), 114.84 (C-1), 117.95 (C-6), 120.88 (C-4a), 123.88 (C-8), 127.48 (C-9), 128.07 (C-9a), 128.28 (C-3), 128.58 (C-4), 131.63 (C-2), 133.72 (C-7), 136.65 (C-10a), 139.74 (C-5a), 142.50 (C-4b), 157.01 (C-11a), and 166.71 (C-10).

Anal. Cald. for $C_{16}H_{11}NO_2$ (249.27): C, 77.10; H, 4.45; N, 5.62. Found: C, 76.66; H, 4.74; N, 5.60.

11-Methoxybenzofuro[3,2-*b*]quinoline (**15a**).

This compound was obtained in 14% yield as white crystals, mp 117-119° (hexane). The compound is identical (tlc, mp, ir, uv, ^1H nmr) with the sample prepared from **14a**.

Anal. Calcd. for $C_{16}H_{11}NO_2$ (249.27): C, 77.10; H, 4.45; N, 5.62. Found: C, 77.25; H, 4.66; N, 5.33.

5-Methyl[1]benzothieno[3,2-*b*]quinolin-11(5*H*)-one (**17b**).

This compound was obtained in 75% yield as yellow crystals, mp 281-282° (ethanol); ir (KBr): ν 751, 1184, 1273, 1512, 1586, 1616, and 3064 cm^{-1}; uv (EtOH): λ_{max} 202 nm (log ε 4.44), 213 nm (log ε 4.52), 269 nm (log ε 4.58), 279 nm (log ε 4.66), 376 nm (log ε 4.12), 395 nm (log ε 4.24); ^1H nmr (dimethyl-d_6-sulfoxide): δ 4.40 (s, 3H, CH_3), 7.40 (ddd, J = 7.9 Hz, J = 6.1 Hz, J = 1.7 Hz, 1H), 7.48- 7.62 (m, 2H), 7.74 –7.86 (m, 2H), 8.00 (bd, J = 7.8 Hz, 1H), 8.37 (bd, J = 7.9 Hz, 1H), 8.52 (bd, J = 7.6 Hz, 1H).

Anal. Calcd. for $C_{16}H_{11}NOS$ (265.33): C, 72.42; H, 4.18; N, 5.28; S, 12.08. Found: C, 72.72; H, 4.29; N, 5.36; S, 11.90.

11-Methoxy[1]benzothieno[3,2-*b*]quinoline (**15b**).

This compound was obtained in 23% yield as slightly yellowish crystals, mp 121-122° (hexane). The compound has identical (tlc, mp, ir, uv, ^1H nmr) with the sample prepared from **14b**.

Anal. Calcd. for $C_{16}H_{11}NOS$ (265.33): C, 72.42; H, 4.18; N, 5.28; S, 12.08. Found: C, 72.55; H, 3.96; N, 5.08; S, 11.77.

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