Short communication

Design of antineoplastic agents based on the ‘2-phenylnaphthalene-type’ structural pattern—synthesis and biological activity studies of 11H-indolo[3.2-c]quinoline derivatives

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Abstract

Designed as a new group of planar molecule containing the proposed 2-phenylnaphthalene-type structure, a number of 11H-indolo[3.2-c]quinoline derivatives were synthesized and evaluated biologically. Several compounds were found to possess cytotoxic activity against the growth of human promyelocytic leukemia cells (HL-60), against the small cell lung cancer (SCLC), and showed good response in the National Cancer Institute preclinical antitumor drug discovery 60-cell line panel.

1. Introduction

A number of 3-phenylquinazolones (1) [1], benzoxazolo[2.3-b]quinazolones (2a) [1], benzothiazolo[2.3-b]quinazolones (2b) [1], benzo[b]naptho[2.3-d]furan-6,11-diones (3a) [2] and 5H-benzo[b]naptho[2.3-d]pyrrole-6,11-diones (3b) [3] were designed, synthesized and evaluated biologically to examine the validity of the ‘2-phenylnaphthalene-type’ hypothesis developed in our laboratory. The hypothesis was originated from an observation that many biologically active compounds of natural and synthetic origin possess a tricycle chemical structural pattern consisted of a phenyl ring unit attached to the 2-position of a naphthalene nucleus, or composed of various heterocyclic units with similar structural arrangements [4]. Several compounds designed in such manner were found to exhibit excellent cytotoxic activity in a number of systems [1,2]. Some have been scheduled to undergo further in vivo evaluation.

An examination of the biological activity of compounds 3-phenylquinazolones (1) with that of the benzoxazolo- and benzothiazolo[2.3-b]quinazolones (2) signified the importance of the coplanarity of the ring units for desired biological action [1]. Since the planarity of compounds in-group 2 are achieved through the linkage between the benzene moiety and the 2-position of the naphthalene-type unit, it was decided to alternatively link the benzene ring with the 1-position of the naphthalene-type ring unit. Consequently, a study of compounds containing the 11H-indolo[3.2-c]quinoline (4) ring system was undertaken (Fig. 1).

A search in literature of compounds of this type indicated that some possessed interesting biological activities. There was an elegant study between the antimalarial agent amodiaquine and its ring closed 3-chloro-8-methoxy-9-diethylaminomethyl-11H-indolo[3.2-c]quinoline analogue on DNA binding and RNA polymerase inhibition [5]. Also, a quinolinolinedione...
oxyl compounds 6d, j, l, m, with hydrobromic acid and acetic acid yielded the corresponding hydroxyl compounds 6n–q. Subsequent the ether derivatives 6r–t were obtained from the corresponding hydroxy substituted 11H-indolo[3.2-c]quinolines 6n–p etherification with 2-(dimethylamino)ethyl chloride.

The other synthetic route was carried out as follows: chlorination of 4-hydroxyquinoline (7a) with phosphorus oxychloride gave 4-chloroquinoline (7b), which condensed with appropriate aniline to form 4-(substituted anilino) quinoline (8). This compound was cyclized in refluxing acetic acid in the presence of palladium(II) acetate to the corresponding 11H-indolo[3.2-c]quinolone 6d and 6u [11,12] (Fig. 2).

Theoretically, 4-(substituted anilino) quinolines (8) could also be cyclized to compounds of a different ring system, 7H-pyrido[4.3.2-g]phenanthridine (9). The possibility of forming the general ring system 9 by this route was ruled out by comparison of the NMR data and physical constants of 8-methoxy-11H-indolo[3.2-c]quinoline (6d) prepared by both routes. The NMR interpretation is presented as follows: $^1$H-NMR (DMSO plus CDCl$_3$ ppm: 9.75 (s, 1H, H$_a$), 8.84 (dd, 1H, H$_b$), 8.38 (dd, 1H, H$_b$), 7.94 (td, 1H, H$_b$), 7.88 (td, 1H, H$_b$), 7.80 (d, 1H, H$_c$), 7.75 (d, 1H, H$_c$), 7.26 (dd, 1H, H$_d$), 3.96 (s, 3H, –OCH$_3$).

The COSY spectrum of compound 10d prepared by method A indicates that four aromatic proton peaks (H$_a$, H$_b$, H$_c$ and H$_d$) are derived from one ring and the derivative, 3-methoxy-11H-indolo[3.2-c]quinoline-1,4-dione, was found to inhibit DNA topoisomerases [6].

2. Chemistry

Two synthetic approaches for the preparation of 11H-indolo[3.2-c]quinolines were used. Refluxing 5 [7–10] with an aryl hydrazine gave the cyclized substituted 11H-indolo[3.2-c]quinoline 6a–m by the Fischer indole synthesis. Demethylation of these methyloxyquinolones 6a–m with hydrobromic acid and acetic acid yielded the corresponding hydroxyl compounds 6n–q. Subsequent the ether derivatives 6r–t were obtained from the corresponding hydroxy substituted 11H-indolo[3.2-c]quinolines 6n–p etherification with 2-(dimethylamino)ethyl chloride.

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The COSY spectrum of compound 10d prepared by method A indicates that four aromatic proton peaks (H$_a$, H$_b$, H$_c$ and H$_d$) are derived from one ring and the
other three protons (H_e, H_f, and H_g) are correlated as postulated. Thus the possibility of forming the corresponding ring isomer 9d has been ruled out (Fig. 3). A number of substituted 11\(H\)-indolo[3.2-c]quinolines were prepared and described in Section 4.

3. Results and discussion

The 11\(H\)-indolo[3.2-c]quinolines designed and synthesized were evaluated against the growth of human promyelocytic leukemia cells (HL-60), cytotoxic against the small-cell lung cancer (SCLC), and the National Cancer Institute’s disease-oriented primary antitumor screen 60 cell line panel [13] (see Table 1).

Generally, the 11\(H\)-indolo[3.2-c]quinolines showed inhibitory activity in the NCI 60 cell, and the oxygen-containing compounds (hydroxyl or methoxyl) exhibit inhibitory activity against SCLC (see compounds 6d, 6e, 6k, 6p and 6q). However, substitution with multiple hydroxyl groups on one molecule produced detrimental effect against all three test systems (6o). The three compounds containing one or two of the 2-(dimethyamino) ethoxyl side chain (6f, 6s and 6t) uniformly demonstrated excellent activity in HL-60, SCLC and the NCI tests. Activity of these long chain derivatives is comparable to that against cisplatin, VP-16, vinblastine, adriamycin and mitoxantrone [2] in SCLC tests. However, compound 6u, the structure of which somewhat resembles the acridine m-AMSA [14], exhibited no inhibitory activity in our tests.

The preceding information [1–3] and the presently designed derivatives of the 11\(H\)-indolo[3.2-c]quinoline (4) ring system indicated some interesting biological activities for the compounds containing the proposed ‘2-phenylnapthalene-type’ chemical structure. Consequently, we consider that these types of ring system will be of biological importance. The ring system should fulfill two requirements: (1) the basic conformation should be coplanar; (2) the ‘2-phenyl’ ring should be linked to the ‘napthalene’ unit at position 1 or position 3. We believe that the potential of investigation along this conception is unlimited and perhaps the usefulness of this postulation could be appreciated in the future.

![Fig. 3.](image_url)

Table 1

<table>
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<tr>
<th>Compound</th>
<th>IC(_{50}) ((\mu)M) HL-60</th>
<th>IC(_{50}) ((\mu)M) SCLC</th>
<th>NCI screen</th>
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<tr>
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<td>0.5</td>
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<tr>
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<td>–</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>10u</td>
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<td>5.0</td>
<td>–</td>
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</table>

Descriptions of all the assay tests were given in our previous publications [2].

\(a\) Inhibitory concentration for m-AMSA is 0.055 \(\mu\)M.

\(b\) Cytotoxicity against SCLC for established anticancer agents (IC\(_{50}\) \(\mu\)M) are as follows: cisplatin, 0.67; VP-16, 0.5; vinblastine, 0.004; adriamycin, 0.04; mitoxantrone, 0.02; 5-FU, 5.4.

\(c\) National Cancer Institute preclinical 60 human tumor cell lines drug-discovery screen: complete inhibition of cell growth detected [log IC\(_{50}\) (M)] for at least one cell line at [–6: + +, –5: +, inactive: –].

4. Experimental

All melting points were taken on a Thomas-Hoope melting point apparatus. \(^1\)H-NMR spectra in CDCl\(_3\) or DMSO on Bruker AC-E200 (200MHz) using TMS as an internal standard. The \(^1\)H-NMR spectra for compound 6d were acquired on Bruker AM-500 (500 MHz). Mass spectra and ultraviolet absorption spectra were determined, respectively, by the University of Kansas Mass Spectrometry Laboratory and Division of Biological Sciences, Lawrence, KS. The M-H-W Laboratories, Phoenix, AZ, performed elemental analyses.

4.1. 4-(4-Methoxyanilino) quinoline (8a)

A stirring mixture of 0.45 g (2.76 mmol) of 4-chloroquinoline (7), 0.35 g (2.85 mmol) of p-anisidine, 20 mL of EtOH and three drops of methanesulfonic acid was refluxed for 6 h. The reaction mixture was evaporated under reduced pressure. The residual paste was triturated with ether. A yellow solid was formed, which was dissolved in a small amount of MeOH. Cold 20% of NaOH was added to adjust the pH to 10. After
stirring for 10 min, the resulting off-white solid was collected by filtration and washed with water. Yield of the pure product was 95% (0.65 g), m.p. 187–189 °C (lit. [15] m.p. 259–262 °C). The molecular formula given in the reference was C₁₆H₁₅N₂O rather than C₁₆H₁₄N₂O.

4.2. 4-(2-Methoxy-4-methanesulfonyl) anilino]quinoline (8b)

This compound was obtained in a similar manner as for the preparation of 8a. Yield of the light yellow hydrochloride salt was 39%, m.p. 274–276 °C. (lit. [16] m.p. 267–270 °C). Its light gray free base was obtained by treating the salt with aqueous NaOH, m.p. 244–245 °C.


4.3.1. Method A
To a stirring mixture of the appropriate phenyl hydrazine (9, 0.058 mol) in 100 mL of 1-butanol and the appropriate 2,3-dihydroquinoline-4-one (8, 0.052 mol) was added dropwise, with heating, 26 mL of concentrated HCl. The mixture was refluxed for 20 h, then was cooled and refrigerated overnight. The resulting yellow solid was collected by filtration. Dissolving the product in a mixture of water and methanol, and adjusting the pH to 8–9 with 10% NaOH obtained the free base. The product was purified either by recrystallization from EtOH or through a silica gel column using EtOAc as eluent. Most compounds were prepared by this method.

4.3.2. Method B
A stirred mixture of 1 mmol of the appropriate 4-(substituted anilino) quinoline and 1.8 mmol of palladium(II) acetate in 60 mL of acetic acid was heated (substituted anilino) quinoline and 1.8 mmol of palladium(II) acetate in 60 mL of acetic acid was heated under reflux in the presence of nitrogen for 7 h. The resulting solid was collected by filtration and purified through column chromatography. Compounds 6d and 6u were prepared by this method.

4.4. 11H-Indolo[3,2-c]quinoline hydrochloride (6a, R₁, R₂, R₃, R₄, R₅ = H)

This compound was obtained in 40% yield by the general procedure described in Method A, m.p. 328–330 °C (recrystallized from EtOH) [17,18]. UV \( \lambda_{\text{max}} \) (MeOH): 235 nm (log \( \varepsilon \) 4.50), 274 (4.52), 290 (4.08), 323 (3.50). MS (m/z): 218 [M⁺]. Anal. (C₁₅H₁₀N₂HCl) Calc.: C, 70.73; H, 4.35; N, 10.99; Found: C, 70.61; H, 4.41; N, 11.10%.

4.5. 8-Chloro-11H-indolo[3,2-c]quinoline (6b, R₁, R₂, R₃, R₄ = H; R₅ = Cl)

This compound [18] was obtained by Method A in 51% yield, m.p. > 300 °C (from EtOAc, silica gel). UV \( \lambda_{\text{max}} \) (MeOH): 242 nm (log \( \varepsilon \) 4.01), 275 (4.10), 295 (3.73), 328 (3.20). MS (m/z): 252 [M⁺]. Anal. (C₁₃H₁₃ClN₂) Calc.: C, 71.29; H, 3.59; N, 11.08; Found: C, 70.88; H, 3.80; N, 10.84%.

4.6. 8-Bromo-11H-indolo[3,2-c]quinoline (6c, R₁, R₂, R₃, R₄ = H; R₅ = Br)

This compound was obtained by Method A in 52% yield, m.p. 336–338 °C (from EtOAc, silica gel). MS (m/z): 296 [M⁺ − I]. 1H-NMR (DMSO-d₆) ppm: \( \delta \) 9.80 (s, 1H), 8.30 (s, 1H), 7.21–7.29 (m, 4H), 6.86–6.93 (m, 3H). Anal. (C₁₅H₁₀BrN₂) Calc.: C, 60.63; H, 3.05; N, 9.43; Found: C, 60.81; H, 3.16; N, 9.50%.

4.7. 8-Methoxy-11H-indolo[3,2-c]quinoline (6d, R₁, R₂, R₃, R₄ = H; R₅ = OCH₃)

This compound was obtained by Method A in 45% yield, m.p. 320–322 °C (from EtOH). The compound was also obtained by Method B by refluxing a mixture of 0.6 g of 12a and 0.66 of palladium(II) acetate in 100 mL of acetic acid under nitrogen overnight, and the product was obtained in 57% yield as a light yellow solid (from EtOH and EtOAc), m.p. 319–320 °C. Both products were identical by comparison of their NMR spectra (see discussion in the Chemistry Section). MS (m/z): 248 [M⁺]. Anal. (C₁₅H₁₂N₂O) Calc.: C, 77.26; H, 4.86; N, 11.26; Found: C, 77.10; H, 4.59; N, 10.98%.

4.8. 8-Hydroxy-11H-indolo[3,2-c]quinoline (6e, R₁, R₂, R₃, R₄ = H; R₅ = OH)

A mixture of 5.3 g of 6d, 130 mL of 48% hydrobromic acid and 500 mL of acetic acid was refluxed under nitrogen for 10 h. The pH of the reaction mixture was adjusted to 6 with 20% NaOH and extracted with EtOAc. The organic layer was concentrated under nitrogen and the yellow solid was recrystallized from EtOH–EtOAc to give 3.73 g (89% yield) of 6e, m.p. > 330 °C. UV \( \lambda_{\text{max}} \) (MeOH): 232 nm (log \( \varepsilon \) 4.27), 260 (4.01), 285 (4.20), 304 (3.94). MS (m/z): 234 [M⁺]. 1H-NMR (DMSO-d₆ plus D₂O) ppm: \( \delta \) 9.89 (s, 1H), 8.88 (dd, 1H), 8.32 (d, 1H), 7.93 (m, 4H), 7.32 (dd, 1H). Anal. (C₁₅H₁₀N₂O-HBr-H₂O) Calc.: C, 54.07; H, 3.93; N, 8.41; Found: C, 53.85; H, 3.75; N, 8.25%.
4.9. 8-[2-(Dimethylamino) ethoxy]-11H-indolo[3,2-c]quinoline (6f, R1, R2, R3, R5 = H; R4 = O(\text{CH}_3)\text{N}(\text{CH}_3)\text{J})

A mixture of 0.7 g (3 mmol) of 6e, 0.65 g (4.5 mmol) of 2-(dimethylamino)ethyl chloride hydrochloride, 2.1 g (15 mmol) of potassium carbonate and 150 ml of CHCl3 was refluxed with stirring for 4 h. To the mixture was added 20 ml of water and refluxing was continued for another 24 h. The reaction mixture was cooled and extracted with chloroform (3 x 50 ml). The combined extract was washed successively with 20 ml of 20% NaOH and brine (2 x 50 ml). The organic layer was dried (magnesium sulfate) and the solvent concentrated in vacuo. The resulting yellow–brown solid was acidified with ethanolic hydrogen chloride to give the product as a hydrochloride salt. Recrystallization from ethanol gave yellow crystals, m.p. 285-287 °C. Anal. (C17H14N2O3) Calc.: C, 70.12; H, 5.23; N, 9.08; Found: C, 69.97; H, 5.39; N, 9.00%.

4.10. 7,8,9-Trimethoxy-11H-indolo[3,2-c]quinoline (6g, R1, R2 = H; R3, R4, R5 = OCH3)

7,8,9-Trimethoxy-11H-indolo[3,2-c]quinoline (6g, R1, R2 = H; R3, R4, R5 = OCH3) was obtained by Method A in 42% yield, m.p. 285–287 °C (EtOAc). MS (m/z): 308 [M+]. 1H-NMR (DMSO-d6) ppm: δ 9.88 (s, 1H), 8.68–8.51 (m, 4H). Anal. (C17H18N2O3) Calc.: C, 70.12; H, 5.23; N, 9.08; Found: C, 69.97; H, 5.39; N, 9.00%.

4.11. 3,8-Dichloro-11H-indolo[3,2-c]quinoline (6h, R1, R4 = Cl; R2, R3, R5 = H)

3,8-Dichloro-11H-indolo[3,2-c]quinoline (6h, R1, R4 = Cl; R2, R3, R5 = H) was obtained by Method A in 56% yield, m.p. > 330 °C (MeOH). MS (m/z): 286 [M+ – Cl]. Anal. (C15H8Cl2N2) Calc.: C, 62.74; H, 2.81; N, 9.76; Found: C, 62.49; H, 2.66; N, 9.97%.

4.12. 3-Bromo-8-chloro-11H-indolo[3,2-c]quinoline (6i, R1 = Cl; R2 = Br; R3, R5 = H)

3-Bromo-8-chloro-11H-indolo[3,2-c]quinoline (6i, R1 = Cl; R2 = Br; R3, R5 = H) was obtained by Method A in 46% yield, m.p. > 340 °C (EtOAc–dimethyl acetamide). MS (m/z): 336 [M+ – Br]. Anal. (C15H8BrClN2) Calc.: C, 54.33; H, 2.43; N, 8.45; Found: C, 54.13; H, 2.66; N, 8.34%.

4.13. 3-Chloro-8-methoxy-11H-indolo[3,2-c]quinoline (6j, R1 = Cl; R4 = OCH3; R2, R3, R5 = H)

3-Chloro-8-methoxy-11H-indolo[3,2-c]quinoline (6j, R1 = Cl; R4 = OCH3; R2, R3, R5 = H) was obtained by Method A in 41% yield, m.p. > 340 °C (EtOH). MS (m/z): 328 [M+]. Anal. (C18H15ClN2O-HCl-0.5H2O) Calc.: C, 58.56; H, 3.99; N, 8.54; Found: C, 58.84; H, 4.23; N, 8.55%.

4.14. 3-Chloro-7,8,9-Trimethoxy-11H-indolo[3,2-c]quinoline (6k, R1, R2 = H; R3, R4, R5 = OCH3)

3-Chloro-7,8,9-Trimethoxy-11H-indolo[3,2-c]quinoline (6k, R1, R2 = H; R3, R4, R5 = OCH3) was obtained by Method A in 34% yield, m.p. 290–292 °C (EtOAc–dimethyl acetamide). MS (m/z): 342 [M+]. Anal. (C18H15ClN2O3) Calc.: C, 63.07; H, 4.41; N, 8.17; Found: C, 62.93; H, 4.65; N, 7.96%.

4.15. 3-Methoxy-11H-indolo[3,2-c]quinoline (6l, R1 = OCH3; R2, R3, R4 = H)

3-Methoxy-11H-indolo[3,2-c]quinoline (6l, R1 = OCH3; R2, R3, R4 = H) was obtained by Method A in 53% yield, m.p. 312–314 °C (EtOH) [18].

4.16. 3-Methoxy-8-methyl-11H-indolo[3,2-c]quinoline (6m, R1 = OCH3; R2, R3 = H; R4 = CH3)

3-Methoxy-8-methyl-11H-indolo[3,2-c]quinoline (6m, R1 = OCH3; R2, R3 = H; R4 = CH3) was obtained by Method A in 60% yield, m.p. 320–321 °C (MeOH) [19]. MS (m/z): 262 [M+]. 263 [M+ + 1]. Anal. (C17H14N2O2-2HCl-1/2H2O) Calc.: C, 59.31; H, 4.98; N, 8.13; Found: C, 59.73; H, 5.11; N, 7.90%.

4.17. 3,8-Dimethoxy-11H-indolo[3,2-c]quinoline (6n, R1, R4 = OCH3; R2, R3, R5 = H)

3,8-Dimethoxy-11H-indolo[3,2-c]quinoline (6n, R1, R4 = OCH3; R2, R3, R5 = H) was obtained by Method A in 47% yield, m.p. 307–310 °C (MeOH). MS (m/z): 273 [M+]. Anal. (C17H14N2O2-HCl) Calc.: C, 64.87; H, 4.80; N, 8.89; Found: C, 64.68; H, 5.06; N, 8.76%.

4.18. 3,7,8,9-Tetramethoxy-11H-indolo[3,2-c]quinoline (6o, R1, R3, R4 = OCH3, R5 = H)

3,7,8,9-Tetramethoxy-11H-indolo[3,2-c]quinoline (6o, R1, R3, R4, R5 = OCH3, R4 = H) was obtained by Method A in 50% yield, mp 278–280 °C (EtOH). MS (m/z): 338 [M+]. Anal. (C19H18N2O4-HCl) Calc.: C, 60.88; H, 5.11; N, 7.47; Found: C, 60.70; H, 5.22; N, 7.29%.
4.19. 3-Hydroxy-11H-indolo[3.2-c]quinoline (6p, R₁ = OH; R₂, R₃, R₄, R₅ = H)

A mixture of 3 g of 6l, 60 ml of 48% hydrobromic acid and 100 ml of acetic acid was refluxed with stirring under nitrogen for 34 h. The reaction mixture was concentrated under reduced pressure and the residue was neutralized with saturated sodium bicarbonate to pH 7–8. The resulting light brown solid was collected by filtration and recrystallized from EtOAc. The yellow solid product melted at 320°C. The yield was 2.4 g (97%). UV λmax (MeOH): 244 nm (log ε 3.98), 275 (4.25), 290 (3.70). MS (m/z): 234 [M⁺]. Anal. (C₁₅H₁₀N₂O) Calc.: C, 76.91; H, 4.30; N, 11.96; Found: C, 76.78; H, 4.50; N, 11.77%.

4.20. 3,8-Dihydroxy-11H-indolo[3.2-c]quinoline (6q, R₁ = OH; R₂, R₃, R₅ = H)

3,8-Dihydroxy-11H-indolo[3.2-c]quinoline (6q, R₁ = OH; R₂, R₃, R₅ = H) was prepared in a manner similar to that for the preparation of 6p from 2 g of 6n, 40% of 48% hydrobromic acid and 160 ml of acetic acid to give, after neutralization and recrystallization from water, 1.34 g of yellow solid, m.p. 235°C (dec.). MS (m/z): 250 [M⁺]. Anal. (C₁₅H₁₀N₂O₂) Calc.: C, 69.49; H, 4.28; N, 10.81; Found: C, 69.11; H, 4.62; N, 10.62%.

4.21. 3,7,8,9-Tetrahydroxy-11H-indolo[3.2-c]quinoline (6r, R₁, R₂, R₃, R₄, R₅ = OH; R₆ = H)

3,7,8,9-Tetrahydroxy-11H-indolo[3.2-c]quinoline (6r, R₁, R₂, R₃, R₅ = OH; R₆ = H) was prepared in a manner similar to that for the preparation of 6p and 6q from 6o, hydrobromic and acetic acid in 83% yield without neutralization. After recrystallization from acetic acid the yellow solid melted at 290°C (dec.). UV λmax (MeOH): 253 nm (log ε 4.26), 280 (3.86), 338 (3.70). MS (m/z): 282 [M⁺]. Anal. (C₁₅H₁₀N₂O₄)·HBr Calc.: C, 49.61; H, 3.05; N, 7.71; Found: C, 49.80; H, 3.21; N, 7.60%.

4.22. 3-[2-(Dimethylamino)ethoxy]-11H-indolo[3.2-c]quinoline (6s, R₁ = O(CH₂)₂N(CH₃)₂; R₂, R₃, R₄, R₅ = H)

A mixture of 1 g (4.3 mmol) of 6p, 1 g (6.5 mmol) of 2-(dimethylamino) ethyl chloride hydrochloride, 5.9 g (43 mmol) of potassium carbonate and 400 ml of CHCl₃ was refluxed with stirring for 24 h. To the suspension was added 60 ml of water and 100 ml of MeOH and the mixture was refluxed again for 24 h with stirring. The suspension gradually dissolved and a yellow solution resulted. The reaction mixture was cooled and, on standing, two layers separated. The organic phase was separated and the aqueous phase was extracted with CHCl₃ (3 × 80 ml). The combined organic solution was washed successively with 20 ml of 20% NaOH and brine (2 × 30 ml), dried (magnesium sulfate) and evaporated. The residue was dissolved in 50 ml of EtOH and acidified with concentrated HCl. The resulting white solid was recrystallized from EtOH to give 1.05 g (65% yield) of 6s, m.p. 300–302°C. MS (m/z): 305 [M⁺]. Anal. (C₁₉H₁₉N₃O·2HCl) Calc.: C, 60.32; H, 5.59; N, 11.10; Found: C, 60.12; H, 5.86; N, 11.08%.

4.23. 3,8-Bis[2-(dimethylamino)ethoxy]-11H-indolo[3.2-c]quinoline (6t, R₁, R₄ = O(CH₂)₂N(CH₃)₂, R₂, R₃, R₅ = H)

A mixture of 1 g (4 mmol) of 6q, 1.73 g (12 mmol) of 2-(dimethylamino) ethyl chloride hydrochloride, 5.52 g (40 mmol) of potassium carbonate, 200 ml of CHCl₃, 50 ml of water and 50 ml of MeOH was refluxed with vigorous stirring for 48 h. The separation and purification and acidification procedures were similar to that for the preparation of 6s, the yield of 6t as a trihydrochloride salt was 1.1 g (55%), m.p. 262–264°C. MS (m/z): 392 [M⁺]. Anal. (C₂₃H₂₈N₄O₂·3HCl) Calc.: C, 55.04; H, 6.23; N, 11.16; Found: C, 54.89; H, 6.23; N, 10.96%.

4.24. 6-Methoxy-8-methanesulfonyl-11H-indolo[3.2-c]quinoline (6u, R₁, R₂, R₃, R₅ = H; R₆ = OCH₃; R₄ = NHSO₂CH₃)

A mixture of 0.4 g (1 mmol) of 8b, 0.4 g (1.8 mmol) of palladium(II) acetate and 60 ml of acetic acid was refluxed under nitrogen for 7 h. The reaction mixture was evaporated to syrup. To the residue was added 50 ml of water and, under cooling; its pH was adjusted to 8. After overnight standing in a refrigerator, the mixture was filtered and the brownish yellow solid was purified by means of silica gel column chromatography using ethyl acetate–methanol (9:1) as eluent. After addition of 10 mL of water to the eluent, the resulting solid was collected by filtration and 0.1 g (28% yield) of 6u of brownish yellow solid was obtained, m.p. 294°C (dec.). MS (m/z): 341 [M⁺]. Anal. (C₁₇H₁₅N₃O₂S·H₂O) Calc.: C, 56.81; H, 4.77; N, 11.69. Found: C, 56.99; H, 4.40; N, 11.66%.

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