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Short communication

Design of antineoplastic agents based on the '2-phenylnaphthalene-type' structural pattern—synthesis and biological activity studies of 11*H*-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 11*H*-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.

Keywords: 2-Phenylnaphthalene-type; 11*H*-Indolo[3.2-*c*]quinoline derivatives; Antitumor activity

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*]naphtho[2.3-*d*]furan-6,11-diones (**3a**) [2] and 5*H*-benzo[*b*]naphtho[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 11*H*-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-11*H*-indolo[3.2-*c*]quinoline analogue on DNA binding and RNA polymerase inhibition [5]. Also, a quinolinedione

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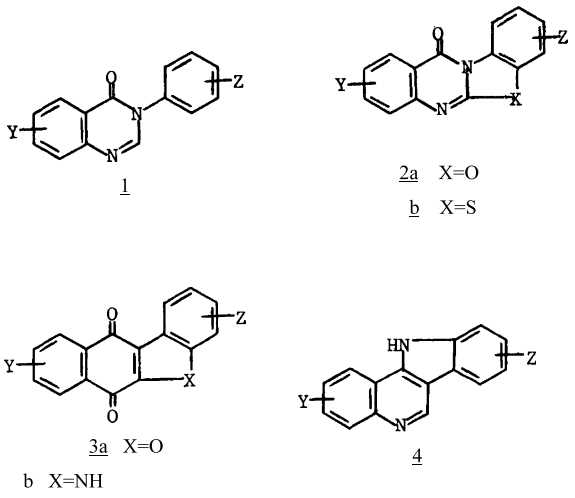

Fig. 1.

derivative, 3-methoxy-11*H*-indolo[3.2-*c*]quinoline-l,4-dione, was found to inhibit DNA topoisomerases [6].

2. Chemistry

Two synthetic approaches for the preparation of 11*H*-indolo[3.2-*c*]quinolines were used. Refluxing **5** [7–10] with an aryl hydrazine gave the cyclized substituted 11*H*-indolo[3.2-*c*]quinoline **6a**–**m** by the Fischer indole synthesis. Demethylation of these methoxyl 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 11*H*-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 11*H*-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, 7*H*-pyrido[4.3.2-*gh*]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-11*H*-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_h), 8.84 (dd, 1H, H_a–), 8.38 (dd, 1H, H_d), 7.94 (td, 1H, H_c), 7.88 (td, 1H, H_b), 7.80 (d, 1H, H_e), 7.75 (d, 1H, H_g), 7.26 (dd, 1H, H_f), 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

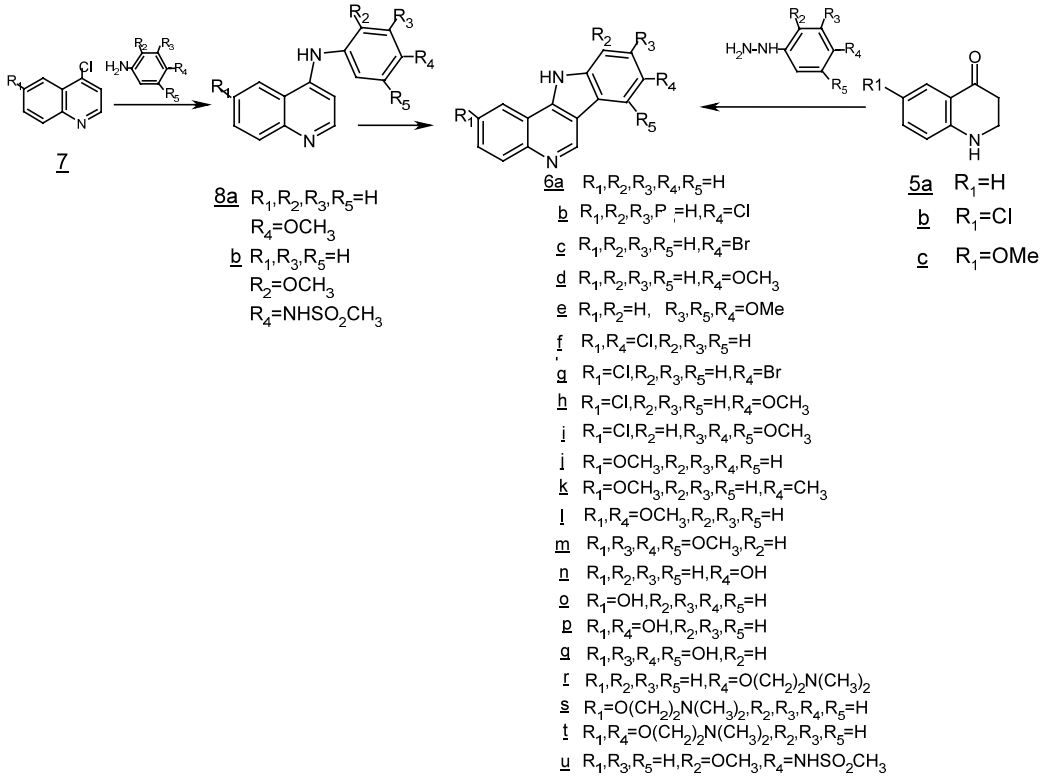

Fig. 2.

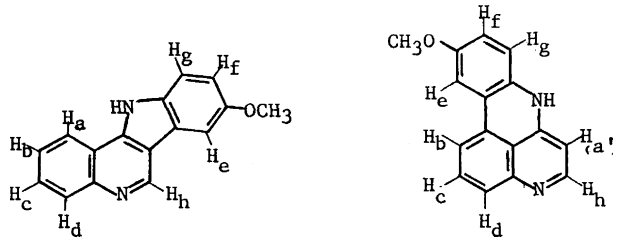

Fig. 3.

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-(dimethylamino) 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-phenylnaphthalene-type' chemical structure. Consequently, we consider that these types of ring system will be of biological importance. The ring system should fulfil two requirements: (1) the basic conformation should be coplanar; (2) the '2-phenyl' ring should be linked to the 'naphthalene' 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.

Table 1
Inhibitory action of 11*H*-indolo[3.2-*c*]quinoline derivatives

Compound	IC_{50} (μM)		NCI screen [c]
	HL-60 [a]	SCLC [b]	
10a	4.16	5.0	+
10b	10.9	0.3	−
10c	17.5	0.3	+
10d	2.03	0.5	+
10e	1.3	0.25	++
10f	0.76	0.075	+
10g	1.66	8	+
10h	77	No effect	+
10i	30.5	No effect	−
10j	5.5	No effect	−
10k	2.66	0.3	+
101	4.48	2.0	++
10m	1.3	1.0	+
10n	0.99	5.0	+
10o	1.06	5.0	+
10p	4.37	0.75	+
10q	3.14	0.75	+
10r	5.79	7.0	−
10s	0.23	0.05	++
10t	0.47	0.075	++
10u	5.0	5.0	−

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

[a] Inhibitory concentration for m-AMSA is 0.055 μM.

[b] Cytotoxicity against SCLC for established anticancer agents (IC_{50} μM) 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-Hoover 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 $C_{16}H_{15}N_2O$ rather than $C_{16}H_{14}N_2O$).

4.2. 4-[(2-Methoxy-4-methanesulfonamido) 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. General procedure for the preparation of 11H-indolo[3,2-c]quinolines (**6**)

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 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-Indole[3.2-c]quinoline hydrochloride (**6a**, R_1, R_2, R_3, R_4, $R_5 = H$)

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 λmax (MeOH): 235 nm (log ε 4.50), 274 (4.52), 290 (4.08), 323 (3.50). MS (*m*/*z*): 218 [M^+]. Anal. ($C_{15}H_{10}N_2 \cdot HC1$) 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**, R_1, R_2, R_3, $R_5 = H$; $R_4 = Cl$)

This compound [18] was obtained by Method A in 51% yield, m.p. >300 °C (from EtOAc, silica gel). UV λmax (MeOH): 242 nm (log ε 4.01), 275 (4.10), 295 (3.73), 328 (3.20). MS (*m*/*z*): 252 [M^+]. Anal. ($C_{15}H_9ClN_2$) 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**, R_1, R_2, R_3, $R_5 = H$; $R_4 = Br$)

This compound was obtained by Method A in 52% yield, m.p. 336–338 °C (from EtOAc, silica gel). MS (*m*/*z*): 296 [$M^+ - 1$]. ^{1}H-NMR (DMSO-d_6) ppm: δ 9.80 (s, 1H), 8.30 (s, 1H), 7.21–7.29 (m, 4H), 6.86–6.93 (m, 3H). Anal. ($C_{15}H_9BrN_2$) 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**, R_1, R_2, R_3, $R_5 = H$; $R_4 = OCH_3$)

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. ($C_{16}H_{12}N_2O$) 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**, R_1, R_2, R_3, $R_5 = H$; $R_4 = OH$)

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 reduced pressure and the yellow solid was recrystallized from EtOH–EtOAc to give 3.73 g (89% yield) of **6e**, m.p. >330 °C. UV λmax (MeOH): 232 nm (log ε 4.27), 260 (4.01), 285 (4.20), 304 (3.94). MS (*m*/*z*): 234 [M^+]. ^{1}H-NMR (DMSO-d_6 plus D_2O) ppm: δ 9.89 (s, 1H), 8.88 (dd, 1H), 8.32 (d, 1H), 7.93 (m, 4H), 7.32 (dd, 1H). Anal. ($C_{15}H_{10}N_2O \cdot HBr \cdot H_2O$) 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**, R_1, R_2, R_3, $R_5 = H$; $R_4 = O(CH_2)_2N(CH_3)_2$)*

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 $CHCl_3$ 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 (3×50 ml). The combined extract was washed successively with 20 ml of 20% NaOH and brine (2×50 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. 292–293 °C. The yield was 850 mg (75%). MS (*m*/*z*): 305 [M^+]. Anal. ($C_{19}H_{19}N_3O \cdot 2HCl$) Calc.: C, 60.32; H, 5.59; N, 11.10; Found: C, 60.42; H, 5.69; N, 11.03%.

*4.10. 7,8,9-Trimethoxy-11H-indolo[3.2-c]quinoline (**6g**, R_1, $R_2 = H$; R_3, R_4, $R_5 = OCH_3$)*

7,8,9-Trimethoxy-11*H*-indolo[3.2-*c*]quinoline (**6g**, R_1, $R_2 = H$; R_3, R_4, $R_5 = OCH_3$) was obtained by Method A in 42% yield, m.p. 285–287 °C (EtOAc). MS (*m*/*z*): 308 [M^+]. ^{1}H-NMR (DMSO-d_6) ppm: δ 9.88 (s, 1H), 8.68–8.51 (m, 3H), 7.93–7.72 (m, 4H). Anal. ($C_{18}H_{16}N_2O_3$) 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**, R_1, $R_4 = Cl$; R_2, R_3, $R_5 = H$)*

3,8-Dichloro-11*H*-indolo[3.2-*c*]quinoline (**6h**, R_1, $R_4 = Cl$; R_2, R_3, $R_5 = H$) was obtained by Method A in 56% yield, m.p. >330 °C (MeOH). MS (*m*/*z*): 286 [$M^+ - 1$]. Anal. ($C_{15}H_8Cl_2N_2$) 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**, $R_1 = Cl$; $R_4 = Br$; R_2, R_3, $R_5 = H$)*

3-Bromo-8-chloro-11*H*-indolo[3.2-*c*]quinoline (**6i**, $R_1 = Cl$; $R_4 = Br$; R_2, R_3, $R_5 = H$) was obtained by Method A in 41% yield, m.p. >340 °C (EtOAc–dimethyl acetamide). MS (*m*/*z*): 330 [$M^+ - 1$]. Anal. ($C_{15}H_8BrClN_2$) 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**, $R_1 = Cl$; $R_4 = OCH_3$; R_2, R_3, $R_5 = H$)*

3-Chloro-8-methoxy-11*H*-indolo[3.2-*c*]quinoline (**6j**, $R_1 = Cl$; $R_4 = OCH_3$; R_2, R_3, $R_5 = H$) was obtained by Method A in 41% yield, m.p. >340 °C (EtOH). MS (*m*/*z*): 282 [M^+]. Anal. ($C_{16}H_{11}ClN_2O \cdot HCl \cdot 0.5H_2O$) 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**, $R_1 = Cl$; $R_2 = H$; R_3, R_4, $R_5 = OCH_3$)*

3-Chloro-7,8,9-trimethoxy-11*H*-indolo[3.2-*c*]quinoline (**6k**, $R_1 = Cl$; $R_2 = H$; R_3, R_4, $R_5 = OCH_3$) was obtained by Method A in 34% yield, m.p. 290–292 °C (EtOAc–dimethyl acetamide). MS (*m*/*z*): 342 [M^+]. Anal. ($C_{18}H_{15}ClN_2O_3$) 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**, $R_1 = OCH_3$; R_2, R_3, R_4, $R_5 = H$)*

3-Methoxy-11*H*-indolo[3.2-*c*]quinoline (**6l**, $R_1 = OCH_3$; R_2, R_3, R_4, $R_5 = H$) 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**, $R_1 = OCH_3$, R_2, R_3, $R_5 = H$; $R_4 = CH_3$)*

3-Methoxy-8-methyl-11*H*-indolo[3.2-*c*]quinoline (**6m**, $R_1 = OCH_3$, R_2, R_3, $R_5 = H$; $R_4 = CH_3$) was obtained by Method A in 60% yield, m.p. 320–321 °C (MeOH) [19]. MS (*m*/*z*): 262 [M^+], 263 [$M^+ + 1$]. Anal. ($C_{17}H_{14}N_2O \cdot 2HC1 \cdot 1/2H_2O$) 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**, R_1, $R_4 = OCH_3$; R_2, R_3, $R_5 = H$)*

3,8-Dimethoxy-11*H*-indolo[3.2-*c*]quinoline (**6n**, R_1, $R_4 = OCH_3$; R_2, R_3, $R_5 = H$) was obtained by Method A in 47% yield, m.p. 307–310 °C (MeOH). MS (*m*/*z*): 273 [M^+]. Anal. ($C_{17}H_{14}N_2O_2 \cdot HCl$) 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**, R_1, R_3, R_4, $R_5 = OCH_3$, $R_4 = H$)*

3,7,8,9-Tetramethoxy-11*H*-indolo[3.2-*c*]quinoline (**6o**, R_1, R_3, R_4, $R_5 = OCH_3$, $R_4 = H$) was obtained by Method A in 50% yield, mp 278–280 °C (EtOH). MS (*m*/*z*): 338 [M^+]. Anal. ($C_{19}H_{18}N_2O_4 \cdot HC1$) 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**, R_1 = OH; R_2, R_3, R_4, R_5 = 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 320–323 °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. ($C_{15}H_{10}N_2O$) 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**, R_1, R_4 = OH; R_2, R_3, R_5 = H)*

3,8-Dihydroxy-11*H*-indolo[3.2-*c*]quinoline (**6q**, R_1, R_4 = OH; R_2, R_3, R_5 = 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. ($C_{15}H_{10}N_2O_2 \cdot 1/2H_2O$) 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**, R_1, R_3, R_4, R_5 = OH; R_2 = H)*

3,7,8,9-Tetrahydroxy-11*H*-indolo[3.2-*c*]quinoline (**6r**, R_1, R_3, R_4, R_5 = OH; R_2 = 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. ($C_{15}H_{10}N_2O_4$–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**, $R_1 = O(CH_2)_2N(CH_3)_2$; R_2, R_3, R_4, R_5 = 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 $CHCl_3$ 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 $CHCl_3$ (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. ($C_{19}H_{19}N_3O \cdot 2HCl$) 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-(dimethylanuno) ethoxy]-11H-indolo[3.2-c]quinoline (**6t**, R_1, $R_4 = O(CH_2)_2N(CH_3)_2$), R_2, R_3, R_5 = 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 $CHCl_3$, 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. ($C_{23}H_{28}N_4O_2 \cdot 3HC1$) 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-methanesulfonamido-11H-indolo[3.2-c]quinoline (**6u**, R_1, R_3, R_5 = H; $R_2 = OCH_3$; $R_4 = NHSO_2CH_3$)*

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. ($C_{17}H_{15}N_3O_3S \cdot H_2O$) Calc.: C, 56.81; H, 4.77; N, 11.69. Found: C, 56.99; H, 4.40; N, 11.66%.

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References

[1] C.C. Cheng, D.F. Liu, T.C. Chou, Heterocycles 35 (1993) 775–789.
[2] C.C. Cheng, Q. Dong, D.F. Liu, Y.L. Luo, L.F. Liu, A.Y. Chen, C. Yu, N. Savaraj, T.C. Chou, J. Med. Chem. 36 (1993) 4108–4112.
[3] Y.L. Luo, T.C. Chou, C.C. Cheng, J. Heterocycl. Chem. 33 (1996) 113–117.
[4] (a) C.C. Cheng, Medical Hypotheses 20 (1986) 157–172;
(b) C.C. Cheng, G.P. Ellis, G.B. West (Eds.), Progress in Medicinal Chemistry, vol. 25, Elsevier Science Publishers, B.V. (Biomedical Division), Amsterdam, 1988, pp. 35–83.
[5] V.E. Marquez, J.W. Cranston, R.W. Ruddon, L.B. Kier, J.H. Bukckhalter, J. Med. Chem. 15 (1972) 36–39.
[6] J.F. Riou, P. Helissey, L. Grondard, S. Giorgi-Renault, Molecular Pharmacol. 40 (1991) 699–706.
[7] R.C. Elderfield, W.J. Gensler, T.H. Bembry, C.B. Kremer, F. Brody, H.A. Hageman, J.D. Head, J. Am. Chem. Soc. 68 (1946) 1259–1263.
[8] R.C. Elderfield, A. Maggiolo, J. Am. Chem. Soc. 71 (1949) 1906–1911.
[9] W.S. Johnson, E.L. Woroch, B.G. Buell, J. Am. Chem. Soc. 71 (1949) 1901–1905.
[10] J. Koo, J. Org. Chem. 28 (1963) 1134–1135.
[11] B. Akermark, L. Eberson, E. Jonsson, E. Pettersson, J. Org. Chem. 40 (1975) 1365–1367 (and references cited therein).
[12] S. Bittner, P. Krief, T. Massil, Synthesis (1991) 215–216.
[13] M.R. Boyd, Princ. Pract. Oncol. 3 (1989) 1–12.
[14] B.F. Cain, G.J. Atwell, W.A. Denny, J. Med. Chem. 18 (1975) 1110–1117.
[15] M. Hamana, K. Funakoshi, Yakugaku Zasshi 84 (1964) 42–47.
[16] W.A. Denny, G.J. Atwell, B.C. Baguley, Anti-Cancer Drug Des. 2 (1997) 263–270.
[17] G.R. Clemo, W.H. Perkin, Jr., J. Chem. Soc. 125 (1924) 1608–1622.
[18] L.M. Werbel, S.J. Kesten, W.R. Turner, Eur. J. Med. Chem. 28 (1993) 837.
[19] O. Roussel, N.P. Buu-Hol, P. Jacquignon, J. Chem. Soc. (1965) 5458.