



Synthesis and Cytotoxic Activity Evaluation of Indolo-, Pyrrolo-, and Benzofuro-Quinolin-2(1*H*)-Ones and 6-Anilinoindoloquinoline Derivatives

Yeh-Long Chen,* Chao-Ho Chung, I.-Li Chen, Po-Hsu Chen and Haw-Yaun Jeng

School of Chemistry, Kaohsiung Medical University, Kaohsiung City 807, Taiwan

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Abstract—Certain indolo-, pyrrolo-, and benzofuro-quinolin-2(1*H*)-ones **4a,b**, **6**, **8**, **16a–c** and 6-anilinoindoloquinoline derivatives **10a,b**, **11a,b**, **12a,b** have been synthesized and evaluated in vitro against a 3-cell lines panel consisting of MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS). Those active compounds **4a,b**, **6**, **8**, **10a,b**, **11a,b**, **12a,b** were then evaluated in the full panel of 60 human tumor cell lines derived from nine cancer cell types. The results have shown that cytotoxicity decreases in the order of 6-anilinoindoloquinolines > indoloquinolin-2(1*H*)-ones > pyrroloquinolin-2(1*H*)-ones > benzofuroquinolin-2(1*H*)-ones. Among them, 1-[3-(11*H*-indolo[3,2-*c*]quinolin-6ylamino)phenyl]ethanone oxime hydrochloride (**11a**) and its 2-chloro derivative (**11b**) were most active, with mean GI₅₀ values of 1.70 and 1.35 μM, respectively. Both compounds **11a,b** were also found to inhibit the growth of SNB-75 (CNS cancer cell) with a GI₅₀ value of less than 0.01 μM, and, therefore, were selected for further evaluation for in vivo antitumor activity. © 2002 Published by Elsevier Science Ltd.

Introduction

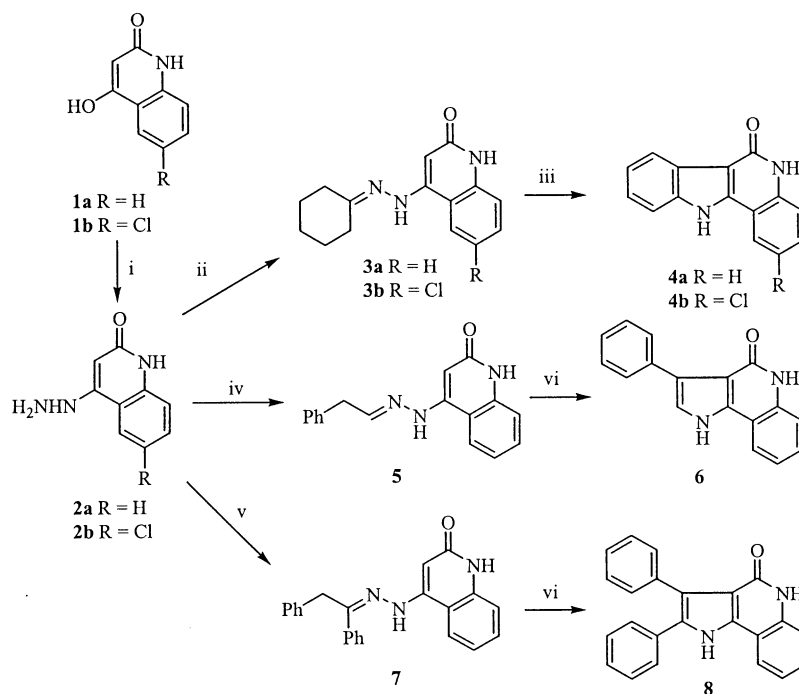
Quinolin-2(1*H*)-one (carbostyryl) skeleton is present in a large number of biologically active compounds.^{1–12} Among them, carteolol had been used clinically as a β-adrenergic blocking agent.⁸ Over the past few years, we were particularly interested in synthesizing α-methylidene-γ-butyrolactones bearing heterocycles (quinoline, coumarin, flavone, xanthone, and quinolin-2(1*H*)-one) and evaluating their cardiovascular and cytotoxic activities.^{9–12} Our results indicated that quinolin-2(1*H*)-one derivatives were the most potent cytotoxic agents among them.¹² On the other hand, the indole skeleton is a basic structure of certain natural alkaloids such as vinblastine¹³ and vincristine¹⁴ which have been used clinically as anticancer drugs. The present report describes the preparation and cytotoxic evaluation of indolo[3,2-*c*]quinolin-2(1*H*)-ones **4a,b** whose structures belong to potential DNA intercalators in which 2-phenyl group and bicyclic quinolin-2(1*H*)-one are locked through a nitrogen bridge to form a coplanar tetracyclic structure. This type of structure can also be considered as potential antitumor 2-phenyl-naph-

thalene-type skeleton with a restricted conformation.¹⁵ The isomeric pyrroloquinolin-2(1*H*)-ones **6** and **8** in which the phenyl group is appended instead of fused on the pyrrole moiety and the isosteric benzofuro-quinolin-2(1*H*)-ones **16a–c** were also synthesized and evaluated. Besides, a number of 9-anilinoacridines have been extensively studied as potential anticancer agents,^{16–20} we have also prepared certain anilino bearing indoloquinolines **10a,b**, **11a,b** and **12a,b** for cytotoxic evaluation.

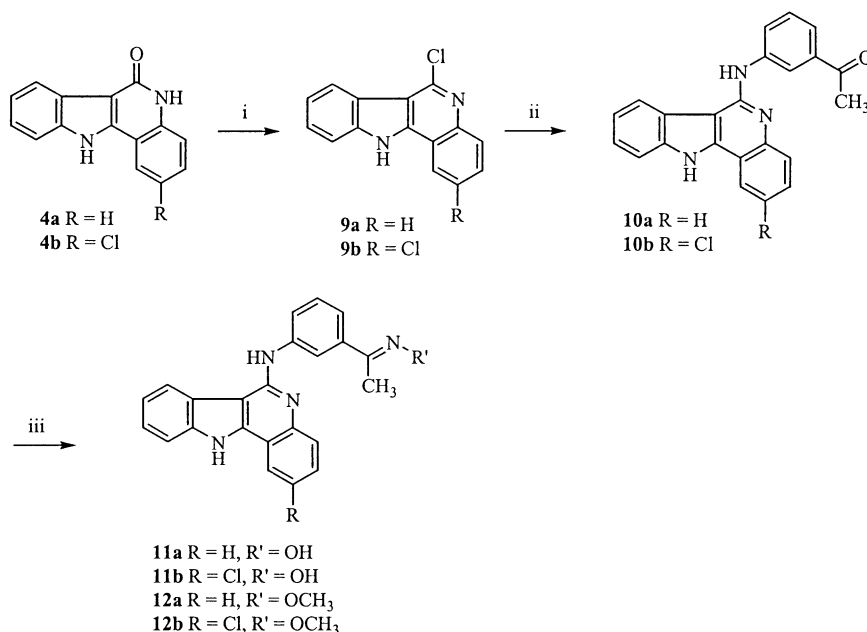
Chemistry

A general synthesis of indolo- and pyrrolo-quinolin-2(1*H*)-ones **4a,b**, **6** and **8** are shown in Scheme 1. 4-Hydrazinoquinolin-2(1*H*)-ones **2a,b** were prepared by the reaction of hydrazine with the corresponding 4-hydroxyquinolin-2(1*H*)-ones **1a,b**.^{21,22} Treatment of **2a,b** respectively with cyclohexanone gave the corresponding hydrazones **3a,b**. Their thermal Fischer indolization followed by the dehydrogenation afforded the desired indoloquinolin-2(1*H*)-ones **4a,b**. The pyrrolo-quinolin-2(1*H*)-ones **6** and **8** were obtained via the thermal cyclization of their respective hydrazones **5** and **7** which in turn were prepared from **2a** and phenylacetaldehyde and deoxybenzoin, respectively.

*Corresponding author. Tel.: +886-7-3121101x2249; fax: +886-7-3125339; e-mail: yeloch@cc.kmu.edu.tw



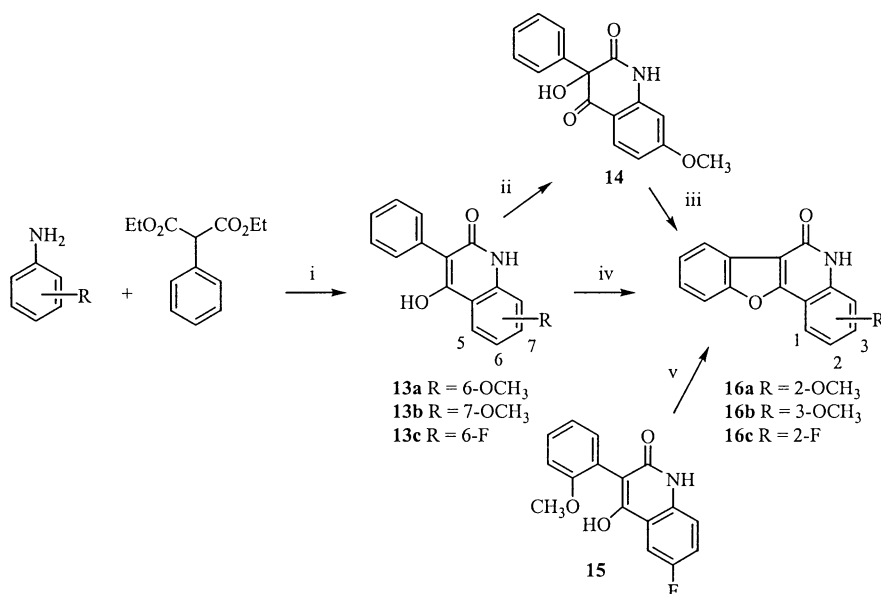
Scheme 1. Reagents: (i) NH_2NH_2 , in ethoxyethanol; (ii) cyclohexanone in AcOH; (iii) Pd/C in Ph_2O ; (iv) phenylacetaldehyde in AcOH; (v) deoxybenzoin in AcOH; (vi) Ph_2O .



Scheme 2. Reagents: (i) POCl_3 ; (ii) 3-aminoacetophenone in 2-BuOH; (iii) NH_2OH or NH_2OCH_3 in MeOH.

Chlorination of **4a** with phosphorus oxychloride gave 6-chloro-11*H*-indolo[3,2-*c*]quinoline (**9a**) as shown in Scheme 2. Reaction of **9a** with 3-aminoacetophenone afforded 1-[3-(11*H*-indolo[3,2-*c*]quinolin-6-ylamino)-phenyl]ethanone hydrochloride (**10a**) which was treated with hydroxylamine and methoxyamine, respectively, in ethanol to give exclusively *E*-form isomer of oxime **11a** and *O*-methyl-oxime **12a**.^{23,24} Accordingly, **11b** and **12b** were prepared from **9b** which in turn was obtained by chlorination of **4b** with POCl_3 .

Preparation of benzofuroquinolin-2(1*H*)-ones **16a–c** is outlined in Scheme 3. 4-Hydroxy-3-phenylquinolin-2(1*H*)-ones **13a–c** were obtained from diethyl 2-phenylmalonate and appropriate anilines in an 1:1 fusion reaction at 250–350 °C.^{25,26} The Pd-catalyzed cyclodehydrogenation²⁷ of **13a–c** afforded their respective benzofuroquinolin-2(1*H*)-ones **16a–c**. Compound **16b** can also be obtained by the acid-catalyzed cyclodehydration of 3-hydroxy-7-methoxy-3-phenyl-1*H*-quinolin-2,4-dione (**14**) which was prepared by the oxidation of **13b**.²⁸



Scheme 3. Reagents: (i) neat, reflux; (ii) alkaline H₂O₂; (iii) P₂O₅, CH₃SO₃H; (iv) Pd/C in Ph₂O; (v) pyridine HCl.

Compound **16c** was also synthesized by the demethylcyclization of 6-fluoro-4-hydroxy-3-(2-methoxyphenyl)-quinolin-2(1*H*)-one (**15**) with pyridine hydrochloride.²⁹

Results and Discussion

All compounds **4a,b**, **6**, **8**, **10a,b**, **11a,b**, **12a,b**, and **16a–c** were evaluated in vitro against a 3-cell lines panel consisting of MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS). In this protocol, each cell line is inoculated and preincubated on a microtiter plate. Test agents are then added at a single concentration (100 μM) and the culture incubated for 48 h. End-point determinations are made with sulforhodamine B, a protein-binding dye. Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds which reduced the growth of any one of the cell lines to 32% or less

(negative numbers indicate cell kill) are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range. Results from Table 1 indicated all of them, with the exception of compounds **16a–c**, pass the 3-cell lines primary screening.

Those active compounds **4a,b**, **6**, **8**, **10a,b**, **11a,b**, and **12a,b** were tested in US National Cancer Institute's human tumor cell line screen.³⁰ This assay involves determination of a test agent's effect on growth parameters against a panel of approximately 60 human tumor cell lines, mostly derived from solid tumors. For each compound, dose-response curves for each cell line were measured with five different drug concentration, the concentration causing 50% cell growth inhibition (GI₅₀) compared with the control were calculated and summarized in Table 2. The tetracyclic indolo[3,2-*c*]quinolin-2(1*H*)-ones **4a** and **4b** demonstrated a moderate inhibitory activity with a mean GI₅₀ value of 19.0 and 18.2 μM respectively while the isomeric tricyclic 1*H*-pyrrolo[3,2-*c*]quinolin-2(1*H*)-one (**6**), in which a phenyl ring was appended on the pyrrole moiety, was less active with a mean GI₅₀ of 27.5 μM. Additional phenyl ring appended on the pyrrole moiety slightly decreased cytotoxicity (**6** versus **8**). The anilino-substituent enhanced cytotoxicity of indolo[3,2-*c*]quinolin-2(1*H*)-ones (**10a**, 4.26 μM versus **4a**, 19.0 μM). The cytotoxicity was further enhanced by converting the ketone group of **10a** and **10b** to their respective oximes **11a** (GI₅₀ values of 1.70 μM) and **11b** (1.35 μM). Furthermore, **11a** and **11b** exhibited excellent selective inhibition against CNS cancer cell lines with a GI₅₀ value of 0.93 and 0.78 μM, respectively. However, the methoxy-amino-counterparts **12a** (6.92 μM) and **12b** (7.76 μM), were less active. The inhibitory activity of selective compounds **4b**, **6**, **10a,b**, and **11a,b** against certain cancer cells is illustrated in Table 3. Compound **4b** was not only active against the growth of CCRF-CEM and SR (leukemia), but also active against certain solid tumors

Table 1. Primary anticancer assay of indolo-, pyrrolo-, and benzo-furo-quinolin-2(1*H*)-ones and 6-anilinoindoloquinoline derivatives

Compd	Percentage of growth inhibition		
	NCI-H460 (lung)	MCF7 (breast)	SF-268 (CNS)
4a	29	25	36
4b	3	8	22
6	34	40	18
8	29	19	34
10a	−32	−7	−4
10b	−46	−6	−10
11a	−53	−74	−85
11b	−55	−69	−77
12a	−64	−94	−79
12b	−70	−96	−82
16a	105	122	129
16b	98	108	111
16c	102	150	130

Table 2. Inhibition of in vitro cancer cell lines by indolo- and pyrrolo-quinolin-2(1*H*)-ones and 6-anilinoindoloquinoline derivatives [average GI₅₀ (μM)]^a

Compd	Leuk	Lung	Colon	CNS	Mela	Ovari	Renal	Prosta	Breast	Mean ^b
4a	21.4	16.6	4.79	4.64	19.9	22.9	16.2	18.6	20.4	19.0
4b	11.5	20.4	16.2	20.4	22.4	21.9	12.9	25.7	21.4	18.2
6	10.7	33.9	17.0	47.9	15.8	46.8	31.6	50.1	34.7	27.5
8	11.0	28.8	53.7	28.2	49.0	50.1	25.7	26.3	21.9	30.2
10a	4.37	3.72	3.89	5.01	4.57	3.98	3.98	4.79	5.01	4.26
10b	6.46	3.63	4.36	4.07	4.47	1.86	4.57	5.01	6.92	4.26
11a	1.66	1.82	1.17	0.93	2.04	2.19	1.90	2.57	1.86	1.70
11b	1.29	1.23	0.89	0.78	1.82	1.95	1.58	1.99	1.70	1.35
12a	6.46	6.02	4.90	5.62	8.51	8.91	8.13	11.5	7.08	6.92
12b	6.46	6.92	5.62	11.0	8.32	9.12	5.62	13.2	9.77	7.76

^aData obtained from NCI's in vitro disease-oriented tumor cells screen. GI₅₀: Drug molar concentration causing 50% cell growth inhibition.

^bMean values over all cell lines tested. These cell lines are: Leuk (leukemia: CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); Lung (non-small cell lung cancer: A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); Colon (colon cancer: COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS (CNS cancer: SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); Mela (melanoma: LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); Ovari (ovarian cancer: IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); Renal (renal cancer: 786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); Prosta (prostate cancer: PC-3 and DU-145); and Breast (breast cancer: MCF7, MCF7/ADR-RES, MDA-MB-231/ ATCC, HS 578T, MDA-MB-435, MDA-N and T-47D).

Table 3. Inhibitory activity of indolo- and pyrrolo-quinolin-2(1*H*)-ones and 6-anilinoindoloquinoline derivatives Indolo[3,2-*c*]quinolin-2(1*H*)-one derivatives on the selected cancer cell lines (GI₅₀ (μM))^a

Compd	4b	6	10a	10b	11a	11b
CCRF-CEM	5.13	0.40	5.75	27.5	2.14	nd ^b
SR	5.75	39.8	nd ^b	nd	1.15	0.54
KM12	4.47	20.4	4.68	4.90	1.51	1.15
SW-620	31.6	0.69	4.79	4.37	1.15	1.07
SNB-75	5.01	30.2	nd ^b	nd ^b	<0.01	<0.01
SK-MEL-28	40.7	0.30	nd ^b	nd ^b	nd ^b	nd ^b
OVCAR-3	17.8	40.7	2.45	0.04	2.45	1.90
UO-31	0.55	3.24	3.31	6.02	2.51	2.51
MCF7	15.8	32.4	0.41	0.44	1.26	0.70

^aData obtained from NCI's in vitro disease-oriented tumor cells screen. GI₅₀: drug molar concentration causing 50% cell growth inhibition.

^bNot detected.

such as KM12, SNB-75, and UO-31 with GI₅₀ values of 4.47, 5.01, and 0.55 μM respectively. Compound **6** was especially active against CCRF-CEM, SW-620, SK-MEL-28, and UO-31 with GI₅₀ values of 0.40, 0.69, 0.30, and 3.24 μM respectively. Selective cytotoxicity was also observed for **10a** (MCF7, 0.41 μM) and **10b** (OVCAR-3, 0.04 μM and MCF7, 0.44 μM). Among these compounds, **11a** and **11b** were found to inhibit the growth of SNB-75 with a GI₅₀ value of less than 0.01 μM, respectively and therefore, were selected for further evaluation for in vivo antitumor activity.

Conclusion

Three benzofuroquinolin-2(1*H*)-ones **16a–c** were found to be void of cytotoxicity. The tetracyclic indolo-[3,2-*c*]quinolin-2(1*H*)-ones **4a,b** were more cytotoxic than the isomeric tricyclic 1*H*-pyrrolo[3,2-*c*]quinolin-2(1*H*)-one **6**, in which a phenyl ring was appended on the pyrrole moiety. Additional phenyl ring appended on the pyrrole moiety as in compound **8** further decreased

cytotoxicity. Among them, 6-anilinoindolo[3,2-*c*]quinolines **11a,b** were the most cytotoxic and found to inhibit the growth of SNB-75 with a GI₅₀ value of less than 0.01 μM.

Experimental

General

TLC: precoated (0.2 mm) silica gel 60 F₂₅₄ plates from EM Laboratories, Inc.; detection by UV light (254 nm). Mp: Electrothermal IA9100 digital melting-point apparatus; uncorrected. UV Spectra (λ_{max} (log ε) in nm): Shimadzu UV-160A UV-vis spectrophotometer. IR spectra (cm⁻¹): Hitachi-260-30 infrared spectrophotometer. ¹H and ¹³C NMR spectra: Varian-Unity-400 spectrometer at 400 and 100 MHz or Varian-Gemini-200 spectrometer at 200 and 50 MHz, chemical shifts δ in ppm with SiMe₄ as an internal standard (=0 ppm), coupling constants *J* in Hz. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer, and results were within ±0.4% of calculated values.

6-Chloro-4-hydrazino-quinolin-2(1*H*)-one (2b). To a suspension of 6-chloro-4-hydroxyquinolin-2(1*H*)-one (**1b**, 0.97 g, 5 mmol) in ethoxyethanol (10 mL) was added 40% hydrazine hydrate (0.5 g, 10 mmol). The reaction mixture was refluxed under N₂ for 48 h. It was then cooled with ice-bath, and the resulting precipitate was collected by filtration and recrystallized from EtOH to give **2b** (0.51 g, 49%) as a pink solid; mp: 308–309 °C; UV λ_{max} nm (log ε): 225 (4.40), 306 (3.86) in 0.1 N MeOH; IR ν_{max} cm⁻¹: 1267, 1397, 1469, 1518, 1608, 1674, 3331, 3439 in KBr. ¹H NMR (DMSO-*d*₆) δ 3.60 (br s, 2H, combined with H₂O), 5.74 (s, 1H), 7.22 (d, 1H, *J*=8.8 Hz), 7.46 (dd, 1H, *J*=8.8, 2.2 Hz), 7.98 (d, 1H, *J*=2.2 Hz), 8.22 (br s, 1H), 10.85 (br s, 2H); ¹³C NMR (DMSO-*d*₆) δ 90.99, 113.68, 117.31, 121.42, 124.71,

129.90, 137.77, 153.20, 163.21. Anal. calcd for $C_9H_8ClN_3O \cdot 0.5H_2O$: C, 49.44; H, 4.15; N, 19.22. Found: C, 49.52; H, 4.20; N, 19.29.

4-(*N'*-Cyclohexylidenehydrazino)quinolin-2(1*H*)-one (3a).

A mixture of **2a**²² (1.75 g, 10 mmol) and cyclohexanone (1.47 g, 15 mmol) in glacial acetic acid (50 mL) was stirred at room temperature for 36 h. The solvent was removed at reduced pressure, and EtOAc was added to the residue. The precipitate that separated was collected by filtration, washed with H_2O , and dried to give **3a** (2.24 g, 88%) as a pink solid; mp: 259–260 °C; UV λ_{max} nm (log ϵ): 224 (4.35), 315 (4.15) in MeOH; IR ν_{max} cm^{-1} : 1216, 1259, 1384, 1518, 1632, 3427 in KBr; 1H NMR (DMSO- d_6) δ 1.58–1.63 (m, 6H), 2.29–2.32 (m, 4H), 6.05 (s, 1H), 7.13 (m, 1H), 7.27 (m, 1H), 7.47 (m, 1H), 7.94 (m, 1H), 9.26 (br s, 1H), 10.98 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 25.55, 26.17, 27.36, 27.68, 35.60, 93.79, 112.72, 116.21, 121.45, 122.75, 130.93, 139.28, 150.42, 161.67, 163.99. Anal. calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.42; H, 6.88; N, 16.51.

6-Chloro-4-(*N'*-cyclohexylidenehydrazino)quinolin-2(1*H*)-one (3b).

This compound was prepared from **2b** according to the method mentioned under the synthesis of **3a** in 90% yield; mp: 357–358 °C; UV λ_{max} nm (log ϵ): 229 (4.16), 322 (4.18) in MeOH; IR ν_{max} cm^{-1} : 1215, 1375, 1412, 1450, 1534, 1595, 1632, 2928, 3433 in KBr; 1H NMR (DMSO- d_6) δ 1.64 (m, 6H), 2.33 (m, 2H), 2.50 (m, 2H), 6.07 (s, 1H), 7.26 (d, 1H, $J=8.8$ Hz), 7.50 (dd, 1H, $J=8.8, 2.2$ Hz), 8.13 (d, 1H, $J=2.2$ Hz), 9.25 (br s, 1H), 11.10 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 25.18, 25.77, 26.97, 27.30, 35.25, 94.82, 113.53, 117.27, 121.93, 124.71, 130.09, 138.01, 148.82, 160.27, 162.93. Anal. calcd for $C_{15}H_{16}ClN_3O$: C, 62.18; H, 5.57; N, 14.50. Found: C, 62.30; H, 5.61; N, 14.42.

5,11-Dihydroindolo[3,2-*c*]quinolin-6-one (4a).

A suspension of **3a** (2.55 g, 10 mmol) in diphenyl ether (20 mL) was heated to 250 °C for 30 min. The mixture was cooled to room temperature, and 10% Pd/C (250 mg) was added, and heated at 250 °C for another 3 h. The reaction mixture was filtered, and the filtrate cooled to room temperature. A large volume of *n*-hexane was added to precipitate a solid that was collected, washed with *n*-hexane and dried under vacuum to give **4a** (1.92 g, 82%); mp: 340 °C; UV λ_{max} nm (log ϵ): 244 (4.63), 295 (4.06), 322 (4.07), 337 (4.35) in MeOH; IR ν_{max} cm^{-1} : 1215, 1341, 1396, 1454, 1552, 1637, 3160, 3210 in KBr; 1H NMR (DMSO- d_6) δ 7.23–7.65 (m, 6H), 8.20 (m, 2H), 11.43 (br s, 1H), 12.58 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 106.48, 111.74, 111.99, 116.10, 120.80, 121.10, 121.59, 122.16, 124.07, 124.40, 129.25, 137.75, 137.98, 140.76, 159.93. Anal. calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 76.89; H, 4.45; N, 11.90.

2-Chloro-5,11-dihydroindolo[3,2-*c*]quinolin-6-one (4b).

This compound was prepared from **3b** according to the method mentioned under the synthesis of **4a** in 82% yield; mp: 381–384 °C; UV λ_{max} nm (log ϵ): 251 (4.52), 295 (4.08), 322 (4.28), 336 (4.35) in MeOH; IR ν_{max}

cm^{-1} : 1552, 1613, 1637, 3256, 3417 in KBr; 1H NMR (DMSO- d_6) δ 7.22–7.64 (m, 5H), 8.20 (m, 2H), 11.42 (br s, 1H), 12.55 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 106.41, 111.63, 111.91, 115.99, 120.70, 120.98, 121.45, 122.05, 123.94, 124.34, 129.12, 137.67, 137.92, 140.65, 159.80. Anal. calcd for $C_{15}H_9ClN_2O$: C, 67.05; H, 3.38; N, 10.43. Found: C, 66.97; H, 3.46; N, 10.39.

4-(*N'*-Phenethylidenehydrazino)quinolin-2(1*H*)-one (5).

This compound was prepared from **2a** and phenylacetaldehyde according to the method mentioned under the synthesis of **3a** in 91% yield; mp: 248–249 °C; UV λ_{max} nm (log ϵ): 225 (4.48), 312 (4.35) in MeOH; IR ν_{max} cm^{-1} : 1393, 1417, 1493, 1541, 1601, 3447 in KBr; 1H NMR (DMSO- d_6) δ 3.66 (d, 2H, $J=5.8$ Hz), 6.05 (s, 1H), 7.13–7.47 (m, 8H), 7.78 (m, 1H), 7.90 (m, 1H), 10.35 (br s, 1H), 10.99 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 38.37, 93.47, 111.69, 115.65, 120.57, 121.82, 126.54, 128.63 (2C), 128.85 (2C), 130.30, 137.18, 139.33, 146.80, 148.64, 162.85. Anal. calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.49; H, 5.43; N, 15.02.

3-Phenyl-1,5-dihydropyrrolo[3,2-*c*]quinolin-4-one (6).

A suspension of **5** (1.39 g, 5 mmol) in diphenyl ether (10 mL) was heated to 250 °C for 2 h. The mixture was cooled to room temperature and diluted with a large volume of *n*-hexane to precipitate a solid that was collected, washed with *n*-hexane and dried under vacuum to give **6** (1.05 g, 81%); mp: 329–330 °C; UV λ_{max} nm (log ϵ): 239 (4.36), 278 (4.05), 320 (4.20), 333 (4.21) in MeOH; IR ν_{max} cm^{-1} : 1247, 1379, 1419, 1490, 1575, 1601, 1643, 3423 in KBr; 1H NMR (DMSO- d_6) δ 7.16–7.24 (m, 2H), 7.32–7.39 (m, 4H), 7.49 (d, 1H, $J=1.6$ Hz), 7.87 (m, 2H), 8.06 (d, 1H, $J=7.6$ Hz), 11.11 (br s, 1H), 12.46 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 107.12, 110.71, 112.71, 115.41, 120.66, 121.28, 123.16, 125.74, 127.36, 127.63 (2C), 128.85 (2C), 134.47, 135.87, 136.15, 159.72. Anal. calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.41; H, 4.83; N, 10.59.

4-[*N'*-(1,2-Diphenylethylidene)-hydrazino]quinolin-2(1*H*)-one (7).

This compound was prepared from **2a** and deoxybenzoin according to the method mentioned under the synthesis of **3a** in 84% yield; mp: 250–251 °C; UV λ_{max} nm (log ϵ): 227 (4.47), 335 (4.33) in MeOH; 1H NMR (DMSO- d_6) δ 4.52 (s, 2H), 6.37 (s, 1H), 7.14–7.50 (m, 12H), 7.90 (m, 2H), 9.55 (br s, 1H), 11.15 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 31.98, 96.58, 112.41, 115.90, 120.92, 129.33, 130.69 (2C), 128.45 (2C), 128.81 (2C), 129.05 (2C), 129.21, 129.33, 130.76, 136.84, 138.02, 139.55, 149.22, 150.56, 163.06. Anal. calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.02; H, 5.56; N, 11.75.

2,3-Diphenyl-1,5-dihydropyrrolo[3,2-*c*]quinolin-4-one (8).

This compound was prepared from **7** according to the method mentioned under the synthesis of **6** in 82% yield; mp: 327–328 °C; UV λ_{max} nm (log ϵ): 241 (4.48), 326 (4.24), 340 (4.20) in MeOH; IR ν_{max} cm^{-1} : 1207, 1336, 1443, 1488, 1506, 1585, 1639, 3319 in KBr; 1H NMR (DMSO- d_6) δ 7.20–7.38 (m, 13H), 8.27 (d, 1H, $J=8.0$ Hz), 11.07 (br s, 1H), 12.40 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 112.51, 112.93, 115.46, 115.90, 119.68,

121.23, 122.18, 126.16 (2C), 127.37, 128.33 (2C), 128.53 (2C), 131.14 (2C), 131.86, 132.29, 132.68, 134.41, 134.81, 136.31, 159.31. Anal. calcd for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.33. Found: C, 82.04; H, 4.83; N, 8.10.

6-Chloro-11H-indolo[3,2-c]quinoline (9a). A mixture of **4a** (2.34 g, 10 mmol) and $POCl_3$ (20 mL) was refluxed for 18 h. After cooling, the mixture was poured into ice-water (150 mL) and extracted with EtOAc. The EtOAc extract was washed with aqueous K_2CO_3 , brine, and dried over Na_2SO_4 . The organic layer was concentrated in vacuo to give a brown solid, which was recrystallized with acetone to give **9a** (1.72 g, 68%): mp: 280–282 °C; UV λ_{max} nm (log ϵ): 235 (4.56), 256 (4.47), 272 (4.67), 289 (4.28), 323 (3.80) in MeOH; IR ν_{max} cm^{-1} : 1248, 1360, 1450, 1502, 1566, 1593 in KBr; 1H NMR (DMSO- d_6) δ 7.39–7.86 (m, 5H), 8.07 (dd, 1H, $J=2.0$, 7.8 Hz), 8.45 (d, 1H, $J=7.6$ Hz), 8.57 (dd, 1H, $J=2.0$, 7.6 Hz), 13.17 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 106.79, 111.36, 112.18, 116.49, 120.78, 121.22, 122.23, 126.08, 126.30, 128.28, 128.35, 129.21, 138.80, 141.93, 144.35. Anal. calcd for $C_{15}H_9ClN_2$: C, 71.29; H, 3.59; N, 11.09. Found: C, 71.05; H, 3.62; N, 11.12.

2,6-Dichloro-11H-indolo[3,2-c]quinoline (9b). This compound was prepared from **4b** according to the method mentioned under the synthesis of **9a** in 63% yield: mp: 285–287 °C; UV λ_{max} nm (log ϵ): 235 (4.27), 257 (4.02), 270 (4.42), 287 (3.86), 322 (3.58) in MeOH; IR ν_{max} cm^{-1} : 1265, 1366, 1526, 1589 in KBr; 1H NMR (DMSO- d_6) δ 7.42–7.85 (m, 4H), 8.06 (d, 1H, $J=8.4$ Hz), 8.44 (d, 1H, $J=8.0$ Hz), 8.67 (d, 1H, $J=8.0$ Hz), 13.55 (br s, 1H). ^{13}C NMR (DMSO- d_6) δ 111.37, 112.36, 116.45, 121.25, 121.42, 122.61, 126.24, 126.44, 127.79, 129.15, 129.47, 138.97, 142.20, 143.86, 144.20. Anal. calcd for $C_{15}H_8Cl_2N_2$: C, 62.74; H, 2.81; N, 9.76. Found: C, 62.65; H, 2.93; N, 9.69.

1-[3-(11H-Indolo[3,2-c]quinolin-6-ylamino)phenyl]ethanone hydrochloride (10a). A mixture of **9a** (1.27 g, 5 mmol) and 3-aminoacetophenone (1.01 g, 7.5 mmol) in 2-butanol (10 mL) was refluxed for 4 h (by TLC monitoring). The mixture was then cooled and evaporated in vacuo to give a residue which was treated with H_2O (50 mL). The resulting precipitate was filtered and washed with H_2O . The crude product was chromatographed on a column of silica gel using CH_2Cl_2 :MeOH=10:1 to give 1.38 g (78%) of **10a** as a yellow solid: mp: 310–312 °C; UV λ_{max} nm (log ϵ): 225 (4.43), 264 (4.53), 336 (4.02) in MeOH; IR ν_{max} cm^{-1} : 1213, 1281, 1399, 1456, 1580, 1606, 1638, 1672, 3428 in KBr; 1H NMR (DMSO- d_6) δ 2.63 (s, 3H), 7.32–8.10 (m, 9H), 8.26 (s, 1H), 8.43 (d, 1H, $J=7.6$ Hz), 8.71 (m, 1H), 10.39 (br s, 1H), 13.00 (br s, 1H), 14.08 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 26.82, 102.23, 112.56, 113.50, 119.77, 121.06, 121.83 (2C), 123.07, 123.70, 125.21, 125.76, 125.93, 128.52, 130.11, 130.80, 135.74, 137.90, 138.14, 138.91, 143.13, 148.03, 197.51. Anal. calcd for $C_{23}H_{17}N_3O \cdot HCl$ 0.3H $_2$ O: C, 70.42; H, 4.78; N, 10.71. Found: C, 70.46; H, 4.83; N, 10.66.

1-[3-(2-Chloro-11H-indolo[3,2-c]quinolin-6-ylamino)phenyl]ethanone hydrochloride (10b). This compound was prepared from **9b** according to the method mentioned

under the synthesis of **10a** in 69% yield: mp: 307–309 °C; UV λ_{max} nm (log ϵ): 226 (4.45), 262 (4.55), 338 (4.04) in MeOH; IR ν_{max} cm^{-1} : 1213, 1281, 1360, 1478, 1580, 1606, 1638, 1671, 3416 in KBr; 1H NMR (DMSO- d_6) δ 2.63 (s, 3H), 7.42 (m, 1H), 7.55–8.08 (m, 7H), 8.22 (m, 1H), 8.43 (d, 1H, $J=8.0$ Hz), 8.74 (dd, 1H, $J=8.0$, 1.4 Hz), 10.31 (br s, 1H), 13.00 (br s, 1H), 14.24 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 26.88, 102.17, 112.68, 113.43, 119.34, 121.14, 121.86, 122.00, 123.11, 124.00, 125.46, 126.12 (2C), 128.90, 130.29, 131.02, 135.22, 137.60, 138.28, 138.98, 143.26, 148.00, 197.50. Anal. calcd for $C_{23}H_{16}ClN_3O \cdot HCl$ 0.4H $_2$ O: C, 64.32; H, 4.18; N, 9.78. Found: C, 64.26; H, 4.29; N, 9.76.

(E)-1-[3-(11H-Indolo[3,2-c]quinolin-6-ylamino)phenyl]ethanone oxime hydrochloride (11a). To a suspension of **10a** (1.76 g, 5 mmol) in MeOH (10 mL) was added $NH_2OH \cdot HCl$ (0.52 g, 7.5 mmol). The reaction mixture was refluxed for 1 h and allowed to cool to room temperature. The solvent was removed in vacuo, and the residue was triturated with H_2O (20 mL), filtered, and washed with H_2O . The crude product was recrystallized from EtOH to give 1.39 g (76%) of **11a** as a yellow solid: mp: 286–290 °C; UV λ_{max} nm (log ϵ): 225 (4.45), 260 (4.57), 337 (4.04) in MeOH; IR ν_{max} cm^{-1} : 1218, 1309, 1456, 1579, 1607, 1635, 3420 in KBr; 1H NMR (DMSO- d_6) δ 2.20 (s, 3H), 7.37–7.92 (m, 9H), 8.04 (d, 1H, $J=8.0$ Hz), 8.47 (d, 1H, $J=8.0$ Hz), 8.65 (d, 1H, $J=8.0$ Hz), 10.28 (br s, 1H), 11.35 (br s, 1H), 12.80 (br s, 1H), 14.00 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 11.57, 102.07, 106.79, 112.64, 113.40, 121.21, 121.79, 121.99, 122.88, 123.77, 123.83, 124.52, 125.08, 125.31, 126.06, 129.89, 130.92, 137.12, 138.59, 138.89, 143.03, 148.24, 152.45. Anal. calcd for $C_{23}H_{18}N_4O \cdot HCl$: C, 68.57; H, 4.75; N, 13.91. Found: C, 68.31; H, 4.77; N, 13.80.

(E)-1-[3-(2-Chloro-11H-indolo[3,2-c]quinolin-6-ylamino)phenyl]ethanone oxime hydrochloride (11b). This compound was prepared from **10b** according to the method mentioned under the synthesis of **11a** in 88% yield: mp: 282–284 °C (recrystallization from EtOH); UV λ_{max} nm (log ϵ): 224 (4.52), 260 (4.65), 337 (4.11) in MeOH; IR ν_{max} cm^{-1} : 1234, 1321, 1385, 1427, 1544, 1580, 1605, 1642, 3418 in KBr; 1H NMR (DMSO- d_6) δ 2.20 (s, 3H), 7.38–7.91 (m, 8H), 8.06 (d, 1H, $J=7.8$ Hz), 8.44 (d, 1H, $J=8.0$ Hz), 8.72 (dd, 1H, $J=7.8$, 1.0 Hz), 10.38 (br s, 1H), 11.36 (br s, 1H), 12.92 (br s, 1H), 14.00 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 11.49, 101.92, 107.01, 112.60, 113.30, 119.27, 121.13, 121.77, 121.93, 122.99, 123.80, 124.55, 125.30, 125.99, 129.84, 130.92, 135.11, 136.96, 138.56, 138.87, 143.06, 148.08, 152.32. Anal. calcd for $C_{23}H_{17}ClN_4O \cdot HCl$ 0.3H $_2$ O: C, 62.40; H, 4.23; N, 12.66. Found: C, 62.38; H, 4.33; N, 12.71.

(E)-1-[3-(11H-Indolo[3,2-c]quinolin-6-ylamino)phenyl]ethanone O-methyloxime hydrochloride (12a). This compound was prepared from **10a** and 40% O-methylhydroxylamine hydrochloride according to the method mentioned under the synthesis of **11a** in 78% yield: mp: 265–268 °C (recrystallization from EtOH); UV λ_{max} nm (log ϵ): 224 (4.53), 260 (4.67), 337 (4.15) in MeOH; IR ν_{max} cm^{-1} : 1407, 1453, 1542, 1600, 1642, 3412 in KBr; 1H NMR (DMSO- d_6) δ 2.23 (s, 3H), 3.94 (s, 3H), 7.39–

8.05 (m, 10H), 8.47 (d, 1H, $J=7.8$ Hz), 8.66 (d, 1H, $J=7.4$ Hz), 10.20 (br s, 1H), 12.90 (br s, 1H), 14.00 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 12.29, 61.61, 102.08, 106.63, 112.49, 113.43, 121.10, 121.70, 121.78, 122.79, 123.45, 123.89, 124.86, 125.07, 125.87, 125.99, 129.80, 130.68, 137.32, 138.80, 139.07, 142.88, 148.24, 153.57. Anal. calcd for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}\cdot\text{HCl}\cdot 0.8\text{H}_2\text{O}$: C, 66.83; H, 5.28; N, 12.99. Found: C, 66.52; H, 5.39; N, 13.04.

(E)-1-[3-(2-Chloro-11H-indolo[3,2-c]quinolin-6-ylamino)-phenyl]ethanone O-methyloxime hydrochloride (12b).

This compound was prepared from **10b** and 40% O-methylhydroxylamine hydrochloride according to the method mentioned under the synthesis of **11a** in 76% yield: mp: 345–346 °C (recrystallization from EtOH); UV λ_{max} nm (log ϵ): 225 (4.56), 260 (4.71), 337 (4.14) in MeOH; IR ν_{max} cm^{-1} : 1426, 1538, 1578, 1603, 1644, 3414 in KBr; ^1H NMR (DMSO- d_6) δ 2.22 (s, 3H), 3.94 (s, 3H), 7.39–8.06 (m, 9H), 8.46 (d, 1H, $J=8.0$ Hz), 8.68 (d, 1H, $J=8.0$ Hz), 10.25 (br s, 1H), 12.98 (br s, 1H), 14.10 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 12.36, 61.69, 102.08, 112.61, 113.47, 119.66, 121.16, 121.69, 121.87, 123.08, 123.90, 124.84, 124.97, 125.22, 125.96, 129.92, 130.85, 135.68, 137.38, 137.44, 138.94, 143.07, 148.22, 153.63. Anal. calcd for $\text{C}_{24}\text{H}_{19}\text{ClN}_4\text{O}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$: C, 62.62; H, 4.60; N, 12.17. Found: C, 62.46; H, 4.82; N, 12.06.

2-Methoxy-5H-11-oxa-5-aza-benzo[a]fluoren-6-one (16a).

A mixture of 4-hydroxy-6-methoxy-3-phenylquinolin-2(1H)-one (**13a**, 1.34 g, 5 mmol)²⁵ and 10% Pd/C (0.015 g) in diphenyl ether (50 mL) was refluxed for 48 h. The mixture was cooled to room temperature, triturated with *n*-hexane, and the resulting precipitate collected, which was then dissolved in hot DMF (100 mL) and filtered to remove Pd/C. The filtrate was concentrated to dryness, and the residual solid recrystallized from EtOH to give 0.48 g (36%) of **16a** as a pale-yellow solid: mp: 294–296 °C (recrystallization from EtOH); UV λ_{max} nm (log ϵ): 239 (4.52), 293 (4.18), 303 (4.23), 346 (4.13), 361 (4.05) in MeOH; IR ν_{max} cm^{-1} : 1223, 1348, 1452, 1562, 1660, 3320 cm^{-1} ; in KBr; ^1H NMR (DMSO- d_6) δ 3.86 (s, 3H), 6.97 (dd, 1H, $J=2.4$, 8.8 Hz), 7.25 (d, 1H, $J=2.0$ Hz), 7.38–7.50 (m, 3H), 7.81 (dd, 1H, $J=1.2$, 8.0 Hz), 7.96 (d, 1H, $J=8.8$ Hz), 8.06 (m, 1H), 11.87 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 54.46, 99.10, 104.59, 111.42, 111.60, 120.84, 122.68, 124.01, 124.50, 125.68, 130.02, 140.40, 154.51, 158.32, 159.30, 161.46. Anal. calcd for $\text{C}_{16}\text{H}_{11}\text{NO}_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.26; H, 4.29; N, 5.16.

3-Methoxy-5H-11-oxa-5-aza-benzo[a]fluoren-6-one (16b).²⁸

This compound was prepared from **13b** according to the method mentioned under the synthesis of **16a** in 32% yield: mp: 282–285 °C (recrystallization from EtOH); UV λ_{max} nm (log ϵ): 232 (4.49), 260 (4.16), 297 (4.24), 327 (4.33), 343 (4.36) in MeOH; IR ν_{max} cm^{-1} : 1235, 1346, 1448, 1558, 1663, 3328 cm^{-1} ; in KBr; ^1H NMR (DMSO- d_6) δ 3.89 (s, 3H), 7.27 (dd, 1H, $J=2.8$, 9.0 Hz), 7.44–7.57 (m, 4H), 7.84 (m, 1H), 8.12 (m, 1H), 11.91 (br s, 1H); ^{13}C NMR (DMSO- d_6) δ 55.60, 102.11, 107.07, 110.24, 111.03, 111.76, 117.77, 120.48, 121.28, 123.90, 124.58, 126.32, 132.96, 154.60, 154.74, 161.55.

2-Fluoro-5H-11-oxa-5-aza-benzo[a]fluoren-6-one (16c).

This compound was prepared from **13c** according to the method mentioned under the synthesis of **16a** in 27% yield: mp: 287–290 °C (recrystallization from EtOH; lit.²⁹ mp: 298–300 °C); UV λ_{max} nm (log ϵ): 231 (4.47), 287 (4.08), 299 (4.15), 335 (4.12), 350 (4.04) in MeOH; IR ν_{max} cm^{-1} : 1220, 1341, 1449, 1572, 1662, 3332 cm^{-1} ; in KBr; ^1H NMR (DMSO- d_6) δ 7.47–7.61 (m, 4H), 7.86 (m, 2H), 8.15 (m, 1H), 12.08 (br s, 1H).

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References and Notes

1. Tominaga, M.; Tone, H.; Nakagawa, K.; Takada, K.; Hoshino, Y.; Watanabe, K. *Chem. Pharm. Bull.* **1981**, *29*, 2166.
2. Nishi, T.; Yamamoto, K.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 798.
3. Nishi, T.; Tabusa, F.; Tanaka, T.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 1151.
4. Nishi, T.; Tabusa, F.; Tanaka, T.; Ueda, H.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 852.
5. Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1988**, *31*, 2048.
6. Alabaster, C. T.; Bell, A. S.; Campbell, S. F.; Ellis, P.; Henderson, C. G.; Morris, D. S.; Roberts, D. A.; Ruddock, K. S.; Samuels, G. M. R.; Stefaniak, M. H. *J. Med. Chem.* **1989**, *32*, 575.
7. Fujioka, T.; Teramoto, S.; Mori, T.; Hosokawa, T.; Sumida, T.; Tominaga, M.; Yabuuchi, Y. *J. Med. Chem.* **1992**, *35*, 3607.
8. Lipworth, B. J.; Grove, A. *Br. J. Clin. Pharm.* **1997**, *43*, 9.
9. Tzeng, C. C.; Wang, T. C.; Chen, Y. L.; Wang, C. J.; Chang, Y. L.; Teng, C. M. *Helv. Chim. Acta* **1997**, *80*, 1161.
10. Wang, T. C.; Chen, Y. L.; Tzeng, C. C.; Liou, S. S.; Tzeng, W. F.; Chang, Y. L.; Teng, C. M. *Helv. Chim. Acta* **1998**, *81*, 1038.
11. Chen, Y. L.; Wang, T. C.; Fang, K. C.; Chang, N. C.; Tzeng, C. C. *Heterocycles* **1999**, *50*, 453.
12. Tzeng, C. C.; Lee, K. H.; Wang, T. C.; Han, C. H.; Chen, Y. L. *Pharmaceut. Res.* **2000**, *17*, 715.
13. Rowinsky E. K.; Donehower R. C. In *The Chemotherapy Source Book*; Perry, M. C., Ed.; Williams and Wilkins Baltimore, 1998; Vol. 2; p 387.
14. Donehower R. C.; Rowinsky E. K. In *Cancer: Principles and Practice of Oncology*; De Vita, V. T.; Hellman, S.; Rosenberg, S. A., Eds.; J. B. Lippincott Company Philadelphia, 1993; p 409.
15. Chen, C. C.; Liu, D. F.; Chou, T. C. *Heterocycles* **1993**, *35*, 775.
16. Atwell, G. J.; Cain, B. F.; Seelye, R. N. *J. Med. Chem.* **1972**, *15*, 611.
17. Denny, W. A.; Atwell, G. J.; Cain, B. F. *J. Med. Chem.* **1978**, *21*, 5.

18. Denny, W. A.; Atwell, G. J.; Cain, B. F.; Leo, A.; Panthananickal, A.; Hansch, C. *J. Med. Chem.* **1982**, 25, 276.
19. Gamage, S. A.; Tepsiri, N.; Wilairat, P.; Wojcik, S. J.; Figgitt, D. P.; Ralph, R. K.; Denny, W. A. *J. Med. Chem.* **1994**, 37, 1486.
20. Gamage, S. A.; Figgitt, D. P.; Wojcik, S. J.; Ralph, R. K.; Ransijn, A.; Mauel, J.; Yardley, V.; Snowden, D.; Croft, S. L.; Denny, W. A. *J. Med. Chem.* **1997**, 40, 2634.
21. Fadda, A. A.; Khahil, A. M.; El-Habbal, M. M. *J. Indian Chem. Soc.* **1991**, 68, 393.
22. Nguyen, C. H.; Marchand, C.; Delage, S.; Sun, J.-S.; Garestier, T.; Helene, C.; Bisagni, E. *J. Am. Chem. Soc.* **1998**, 120, 2501.
23. Fang, K. C.; Chen, Y. L.; Sheu, J. Y.; Wang, T. C.; Tzeng, C. C. *J. Med. Chem.* **2000**, 43, 3809.
24. Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, 44, 2374.
25. Stadlbauer, W.; Laschober, R.; Lutschounig, H.; Schindler, G.; Kappe, Th. *Monatsh. Chem.* **1992**, 123, 617.
26. Stadlbauer, W.; Kappe, Th. *Monatsh. Chem.* **1985**, 116, 1005.
27. Stadlbauer, W.; Laschober, R.; Kappe, Th. *Liebigs Ann. Chem.* **1990**, 531.
28. Kappe, Th.; Brandner, A.; Stadlbauer, W. *Monatsh. Chem.* **1987**, 118, 1177.
29. Yamaguchi, S.; Tsuzuki, K.; Kinoshita, M.; Oh-hira, Y.; Kawase, Y. *J. Heterocycles Chem.* **1989**, 26, 281.
30. Monks, A.; Scudiero, D.; Skehaan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaingro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, 83, 757.