JOURNAL OF NATURAL PRODUCTS

Volume 63, Number 7 July 2000

Full Papers

Antitumor Agents. 203. Carbazole Alkaloid Murrayaquinone A and Related Synthetic Carbazolequinones as Cytotoxic Agents[1]

Masataka Itoigawa,[†,‡] Yoshiki Kashiwada,[†,§] Chihiro Ito,[⊥] Hiroshi Furukawa,[⊥] Yoko Tachibana,[†] Kenneth F. Bastow,[†] and Kuo-Hsiung Lee*[,†]

Natural Products Laboratory, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599, Faculty of Pharmacy, Meijo University, Tempaku, Nagoya 468-8503, Japan, Tokai Gakuen University, Miyoshi, Aichi 470-0207, Japan, and Niigata College of Pharmacy, Kamishin'ei-cho, Niigata 950-2081, Japan

Received January 14, 2000

Murrayaquinone A (**1**) and murrayafoline A (**3**), isolated from the root bark of *Murraya euchrestifolia*, were identified as cytotoxic compounds. Murrayaquinone A (**1**) demonstrated significant cytotoxicity against SK-MEL-5 and Colo-205 cells, with ED_{50} values of 2.58 and 3.85 μg/mL, respectively. In contrast, murrayafoline A (**3**) exhibited marginal or weak cytotoxicity against SK-MEL-5, Colo-205, HCT-8, KB, and A-549 tumor cell lines, with ED_{50} values ranging from 5.31 to 7.52 μg/mL. In total, 20 carbazole alkaloids (**1**−**20**), isolated previously by Furukawa et al. from various plant sources were also evaluated for their cytotoxic profiles in the NCI's human disease-oriented, 60-cell line, in vitro antitumor screening protocol. Compounds **3** and **15** showed potent cell-line selective cytotoxicity against MOLT-4 cells, with log GI_{50} values of −8.60 and −8.49 M, respectively, while **12** demonstrated better selectivity against the colon cancer subpanel. Moreover, synthetic 2-methyl- or 3-methyl-carbazolequinone derivatives with various substituents in the A-ring were evaluated against KB, SK-MEL-5, Colo-205, and HCT-8 tumor cells. 6-Methoxy- (**21**), 6-methyl- (**22**), and 6-chloro- (**24**) 3-methyl-carbazolequinones demonstrated significant cytotoxicity against SK-MEL-5 cells, with ED_{50} values of 0.55, 0.66, and 0.83 μg/mL, respectively. Compounds **21** and **22** were also significantly cytotoxic toward KB cells, with ED_{50} values of 0.76 and 0.92 μg/mL, respectively, and **21** displayed a similar level of toxicity against Colo-205 cells (ED_{50} 0.87 μg/mL).

We are continuing primary screening of various plant sources against human tumor cell lines in vitro in order to discover novel cytotoxic compounds.[2] Accordingly, the EtOH extract of the root bark of *Murraya euchrestifolia* Hayata (Rutaceae) showed significant cytotoxicity (ED_{50} < 20 μg/mL). Subsequent bioassay-guided fractionation resulted in the isolation of two known carbazole alkaloids, murrayafoline A (**3**) and murrayaquinone A (**1**), as cytotoxic substances. Various carbazole alkaloids (**1**−**20**), isolated previously by Furukawa et al. from *Murraya* sp., were also evaluated against a panel of about 60 tumor cell lines. Furthermore, a series of synthetic carbazolequinone derivatives was prepared and tested.

Results and Discussion

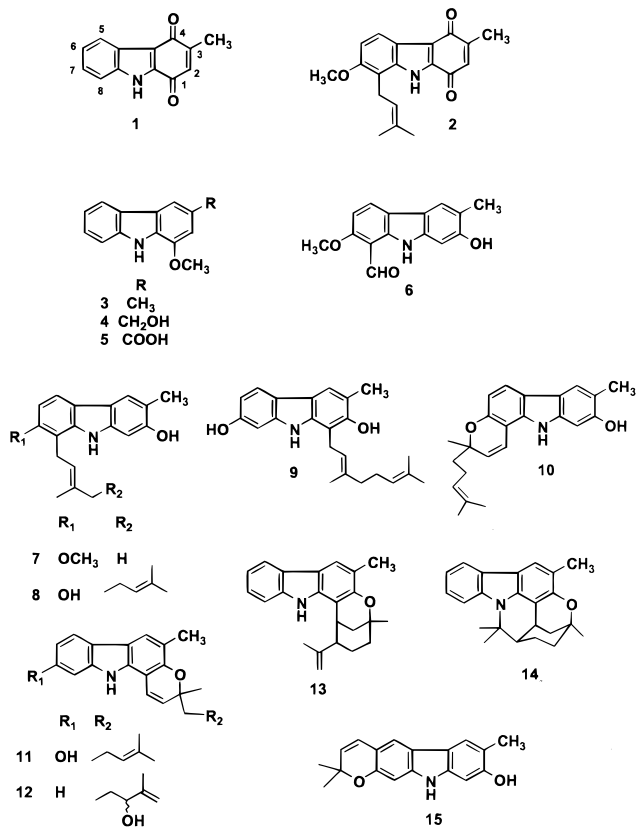
In the course of our continuing screening of various plant extracts for potential cytotoxic antitumor compounds, the EtOH extract of the root bark of *M. euchrestifolia* (Rutaceae) showed significant cytotoxicity (ED_{50} < 20 μg/mL) in SK-MEL-5, Colo-205, HCT-8, A-549, and KB human tumor cell lines. Subsequent solvent partition of this extract with $CHCl_3$ and water yielded a cytotoxic $CHCl_3$-soluble fraction. Further bioassay-guided fractionation resulted in the isola-

* To whom correspondence should be addressed. Tel.: (919) 962-0066. Fax: (919) 966-3893. E-mail: khlee@unc.edu.
[†] Natural Products Laboratory.
[‡] Tokai Gakuen University.
[§] Niigata College of Pharmacy.
[⊥] Faculty of Pharmacy, Meijo University.

10.1021/np000020e CCC: $19.00
Published on Web 06/29/2000

tion of murrayafoline A (**3**),[3] a major carbazole alkaloid of the cytotoxic fraction (1.2% yield from the plant), and murrayaquinone A (**1**)[3] as cytotoxic substances. Murrayafoline A (**3**) exhibited marginal or weak cytotoxicity against all five tumor cell lines, with ED_{50} values ranging from 5.31 to 7.52 μg/mL. In contrast, murrayaquinone A (**1**) demonstrated significant cytotoxicity against SK-MEL-5 and Colo-205 cells, with ED_{50} values of 2.58 and 3.85 μg/mL, respectively, and showed marginal toxicity against HCT-8, KB, and A-549 cells, with ED_{50} values of 5.50, 5.18, and 7.61 μg/mL, respectively.

Following the reports on the synthesis and antitumor activity of ellipticine,[4] numerous studies have focused on pyridocarbazole derivatives and ellipticine and its analogues,[5,6] including studies of their structure−activity relationships, mechanisms of actions, and the design and preparation of new analogues. In contrast, the cytotoxic activities for carbazole derivatives from natural products have been evaluated against only a few tumor cell lines.[7,8] Therefore, 20 carbazole alkaloids, isolated previously by Furukawa et al. from various plant sources,[3,9−15] were evaluated for their cytotoxic profile in the National Cancer Institute's (NCI's) human disease-oriented, 60-cell-line, in vitro antitumor screening protocol. These alkaloids included carbazolequinones (**1**, **2**), monomeric carbazoles (**3**−**6**), prenylcarbazoles (**7**−**15**), and biscarbazoles (**16**−**20**). The cytotoxicity data for selected compounds are shown in Tables 1 and 2.



Murrayaquinone A (**1**) showed a wide-spectrum inhibitory effect on cancer cell growth against all but nine cell lines. The log molar concentration for the median growth inhibitory effects (log GI_{50}) of murrayaquinone A (**1**) ranged from −5.48 to −5.09 in almost all cell lines. In contrast, murrayaquinone B (**2**),[3] which is more lipid soluble because of the methoxy and prenyl groups at C-7 and C-8, respectively, showed only marginal inhibition against leukemia (CCRF−CEM), with a log GI_{50} value of −5.08, and was not cytotoxic (log GI_{50} > −4.60) against the remaining cell lines.

We examined three 1-methoxy-carbazoles (**3**−**5**) with variously oxidized groups at position 3. Murrayafoline A (**3**), which possesses a methyl group at C-3, demonstrated significant and selective cytotoxicity against MOLT-4 (leukemia) and HOP-18 (nonsmall cell lung cancer) cells, with log GI_{50} values of < −8.60 and −6.54, respectively. Cytotoxicities against other cell lines were marginal or weak (log GI_{50} values ranging from −5.22 to −4.60). Replacing the methyl group at C-3 with hydroxymethyl and carboxylic acid groups yielded koenoline (**4**)[10] and mukoeic acid (**5**),[3] respectively. Compound **4** showed significant selective cytotoxicity against NCI−H226 (nonsmall cell lung cancer), with a log GI_{50} value of −5.76 and a TGI value of −5.28; however, **4** was not cytotoxic against almost all other tumor cells. Compound **5** was nontoxic (log GI_{50} > −4.60) against all tumor cell lines tested. These results suggest that the methyl group at C-3 is important for increasing anticancer response. However, murrayaline B (**6**),[16] a 3-methyl-carbazole with different ring substituents, showed weak or no cytotoxicity.

Isomurrayafoline B (**7**)[10] and euchrestine C (**8**)[12] contain prenyl and geranyl groups, respectively, at C-8, and showed slightly better toxicity than euchrestine D (**9**),[12] which contains a geranyl group at C-1. However, **7** and **8** showed significant selective cytotoxicity toward only a few cell lines. Formation of a pyrano-ring in **8** and **9** yielded the corresponding pyranocarbazoles **10** and **11**, respectively. Compound **10** demonstrated improved cytotoxicity against NCI−H522, OVCAR-8, and M19-MEL cell lines, with log GI_{50} values of −5.41, −5.42, and −5.16, respectively, and marginal cytotoxicity (log GI_{50} values ranging from −5.38 to −5.26) against half of the tested cell lines. In contrast, **11** displayed weak cytotoxicity against HOP-18 and NCI−H522 cell lines, with log GI_{50} values of −5.13 and −5.17, respectively, and showed no toxicity against the other tested cells. Compound **15**, a linear-type pyranocarbazole, demonstrated significant selective cytotoxicity against the MOLT-4 leukemia cell line, with a log GI_{50} value of −8.49, but had a large log TGI value of > −4.60. It also displayed marginal or weak cytotoxicity toward half of the tested cell lines.

The cytotoxicities for pyranocarbazole analogues, such as **12**, **13**, and **14**, were also evaluated. Compound **12** exhibited significant cytotoxicity, especially against leukemia and colon cancer cell lines, with log GI_{50} values ranging from −5.77 to −5.29. Colon subpanel sensitivity was also shown from comparison of the log TGI values for colon cancer cell lines, which ranged from −5.49 to −5.03, and the full panel average (−4.83). However, **12** was less sensitive against melanoma, ovarian, and breast cancer cell lines (the log TGI values for subpanel averages were −4.75, −4.68, and −4.70, respectively). Growth of cells from more sensitive lines is arrested at a concentration approximately 10fold mol lower than less sensitive lines. This effect was especially noticeable when evaluation of the cytotoxicity data was extended to the log LC_{50} level for two colon cancer cell lines (−5.21 and −5.03 against HT 29 and KM12, respectively). In contrast, **13** and **14** were nontoxic (log LC_{50} > −4.60) against all tumor cell lines.

Among the five biscarbazole compounds, bismurrayafoline A (**16**)[13] and chrestifoline A (**17**)[14] showed weak subpanel selectivity and marginal cytotoxicity against HOP-92, a nonsmall cell lung cancer cell line, with a log GI_{50} value of −5.27, and against LOX IMVI, a melanoma cell line, with a log GI_{50} value of −5.41. Chrestfoline C

Table 1. Inhibition of Human Cancer Cell Lines In Vitro by Selected Carbazoles (**1**, **3**, **7**, **10**, **12**, **15**, **16**, and **17**)

	cytotoxicity log GI_{50} (M)							
cell line	**1**	**3**	**7**	**10**	**12**	**15**	**16**	**17**
leukemia								
CCRF-CEM	−5.48	−4.81	−5.27	−5.30	−5.38	−4.70	−4.92	−5.07
HL-60 (TB)	−5.39	−5.16	−5.10	−5.02	−5.37	−5.16	−4.91	−5.10
K-562	−5.25	−4.60	−5.24	−5.25	−5.56	−4.60	−5.01	−5.14
MOLT-4	−5.27	−8.60	−5.31	−5.38	−5.46	−8.49	−5.07	−5.24
RPMI-8226	−5.23	−5.06	−5.08	−5.18	−5.53	−5.04	−4.60	−5.00
SR	−5.24	−4.99	−5.14	−5.26	−5.35	−5.19	−4.78	−5.11
nonsmall cell lung cancer								
A549/ATCC	−4.60	−5.94	−5.07	−5.18	−5.30	−5.19	−4.63	−5.24
EKVX	−5.39							
HOP-18	−5.47	−6.54						
HOP-62	−4.60	−5.20		−5.32	−5.61	−5.10	−5.18	−5.26
HOP-92	−5.40	−4.63	−5.10	−5.37	−4.99	−5.01	−5.27	−5.12
NCI-H226	−5.18	−5.07	−4.60	−5.15	−5.20	−4.72	−4.77	−5.33
NCI-H23	−5.43				−4.97			
NCI-H322M	−4.60	−4.89	−4.97	−5.18	−5.10	−4.88	−4.60	−5.14
NCI-H460	−5.09	−5.11	−5.25	−5.33	−5.63	−5.27	−4.97	−5.29
NCI-H522	−5.42	−5.37	−5.23	−5.41	−5.48	−5.08	−5.27	−5.30
LXFL 529	−5.37	−4.74	−5.06	−5.29		−5.03	−4.77	−5.38
small cell lung cancer								
DMS144	−5.37	−5.02	−4.68	−5.15		−4.97	−4.70	−4.98
DMS273	−5.37	−5.11	−5.07	−5.30		−5.30	−4.82	−5.12
colon cancer								
Colo-205	−5.39	−4.91	−4.60	−	−5.61	−4.60	−4.60	−4.92
DLD-1	−5.30	−4.98	−5.04	−5.05		−4.89	−4.60	−5.05
HCC-2998	−5.15	−4.83	−5.26	−5.33	−5.66	−5.17	−4.60	−5.27
HCT-116	−5.35	−4.94	−4.92	−5.06	−5.01	−4.89	−4.60	−5.04
HCT-15	−5.38	−5.13	−5.29	−5.30	−5.71	−5.06	−4.77	−5.16
HT29	−4.75	−5.11	−4.14	−5.31	−5.77	−4.93	−4.77	−5.11
KM12	−5.36	−5.09		−5.32	−5.70	−5.28	−4.99	−5.27
KM20L2	−4.60	−5.12	−4.79	−5.28		−5.03	−4.81	−5.28
SW-620	−5.40	−5.08	−5.17	−5.33	−5.29	−5.12	−4.87	−5.09
CNS cancer								
SF-268	−5.36	−4.84	−5.02	−5.30	−5.25	−5.17	−4.76	−5.16
SF-295	−5.36				−5.36			
SF-539	−5.37	−5.22	−5.10	−5.34	−5.44	−5.39	−5.01	−5.34
SNB-19	−4.60	−4.60	−4.60	−4.60	−4.94	−4.60	−4.60	−5.23
SNB-75	−5.36	−4.60	−4.94	−4.89	−5.48	−4.95	−4.64	−5.24
U251	−4.81	−4.98	−5.23	−5.34	−5.27	−5.22	−4.60	−5.30
XF498	−5.36	−4.65	−4.60			−4.60	−4.60	−5.22
melanoma								
LOX IMVI		−4.90	−5.36	−5.34	−5.51	−5.40	−5.09	−5.41
MALME-3M	−5.31	−5.09	−4.76	−5.28	−4.95	−5.00	−4.60	−5.35
M14	−5.38	−5.14	−5.79	−5.41	−5.18	−5.22	−5.20	−5.29
M19-MEL	−5.43	−4.74	−4.91	−5.16		−4.71	−4.60	−5.01
SK-MEL-2	−5.27	−5.13	−4.60	−5.19	−5.68	−4.60	−4.60	−5.40
SK-MEL-28	−5.35	−4.79	−4.60			−4.84	−4.60	−5.06
SK-MEL-5	−5.37	−5.04	−5.09	−5.31	−5.00	−4.76	−4.60	−5.40
UACC-257	−5.34				−5.09			
UACC-62	−5.38	−4.82	−5.04	−5.03	−	−5.17	−4.82	−5.25
ovarian cancer								
IGROV1	−5.18	−4.83	−5.64		−5.08	−4.64	−4.60	−5.04
OVCAR-3	−5.34	−5.05	−5.27	−5.32	−4.99	−5.14	−4.99	−5.27
OVCAR-4	−5.38	−4.60	−4.65	−5.10	−4.78	−4.98		
OVCAR-5	−5.27	−4.61	−4.60	−4.71	−5.68	−4.75	−4.60	−5.30
OVCAR-8	−5.40	−5.13	−5.35	−5.42	−4.97	−5.34	−4.98	−5.34
SK-OV-3	−4.68	−4.68	−4.60		−4.96	−4.60	−4.60	−5.06
renal cancer								
786−0	−5.37	−5.03	−5.36	−5.37	−5.41		−4.60	−5.27
A498					−4.87			
ACHN	−5.38	−4.63	−5.03	−5.17	−5.35	−5.03	−4.91	−5.33
CAKI-1	−4.84							
RXF-393	−5.46	−5.03		−5.28	−5.56	−5.31		
SN12C	−5.34	−4.85		−5.33	−5.02	−5.20	−4.60	−5.19
TK-10	−5.30	−4.60	−5.30	−4.78	−4.85	−4.60	−4.60	−4.92
UO-31	−5.40	−4.82	−4.84		−4.92	−4.94	−4.60	−5.22
prostate cancer								
PC-3					−5.18			
DU-145					−4.90			
breast cancer								
MCF-7					−4.91			
MCF-7/ADR-RES					−5.05			
MDA-MB-231/ATCC					−5.46			
HS 578T					−5.50			
MDA-MB-435					−5.08			
MDA-N					−5.45			
BT-549					−4.89			
T-47D					−5.11			
full panel average[a]	−5.24	−5.05	−5.01	−5.23	−5.26	−5.06	−4.78	−5.20

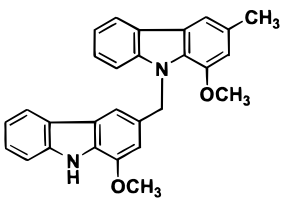
[a] Calculated mean panel log GI_{50}.

Table 2. Cytotoxicities (ED_{50} in μg/mL) for Murrayaquinone A (**1**) and Synthetic 3-Methyl- (**21**−**26**) and 2-Methyl- (**27**−**32**) Carbazolequinones

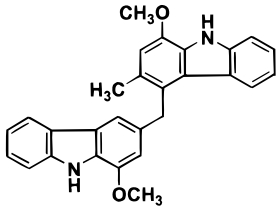
compound	KB	SK-MEL-5	Colo205	HCT-8
1	5.18	2.58	3.85	5.50
21	0.76	0.55	0.87	7.91
22	0.92	0.66	3.52	6.49
23	5.25	2.51	9.19	5.88
24	4.39	0.83	>20	6.45
25	>20	7.25	>20	>20
26	4.95	3.55	4.22	5.30
27	5.08	6.22	>20	6.03
28	4.60	5.29	3.20	5.47
29	2.03	5.50	4.50	4.76
30	3.52	5.50	4.42	5.50
31	4.51	3.92	4.51	5.09
32	0.92	5.50	5.18	4.70

(**18**),[14] bismurrayafoline B (**19**),[13] and murranimbine (**20**)[15] were inactive toward all cell lines.

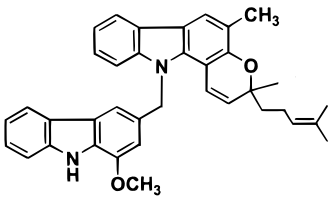
Among all tested compounds, murrayaquinone A (**1**) has the simplest structure and had a broad cytotoxic profile; hence, it was considered as a potential lead for new cytotoxic agents. Therefore, synthetic 2-methyl- or 3-methyl-carbazolequinone derivatives with various substituents in the A-ring were evaluated for cytotoxicity against KB, SK-MEL-5, Colo-205, and HCT-8 tumor cells.



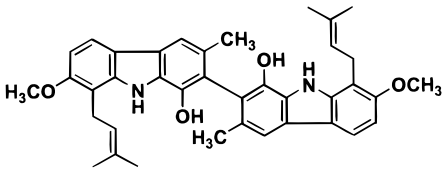
16



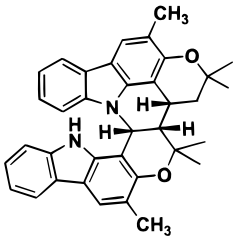
17



18



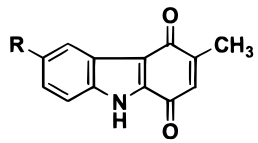
19



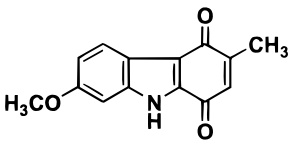
20

3-Methyl-6-methoxy-carbazolequinone (**21**) demonstrated significant cytotoxicity against KB, SK-MEL-5, and Colo-205 cell lines, with ED_{50} values of 0.76, 0.55, and 0.87 μg/mL, respectively, while the cytotoxicity against HCT-8 was weak (7.91 μg/mL). In contrast, 3-methyl-7-methoxy-carbazolequinone (**25**) was nontoxic (ED_{50} > 20 μg/mL), except against SK-MEL-5 (ED_{50} 7.25 μg/mL), while marginal cytotoxicity (ED_{50} values ranging from 3.55 to 5.30 μg/mL) toward these tumor cell lines was observed with **26**, the 8-methoxy analogue.

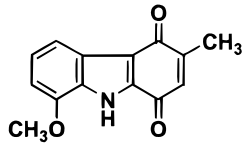
However, in the case of 2-methylcarbazolequinone derivatives, 2-methyl-8-methoxy-carbazolequinone (**32**) showed significant cytotoxicity against KB cells, with an ED_{50} value of 0.92 μg/mL, and also exhibited marginal cytotoxicity against the other cell lines (ED_{50} values ranging from 4.70 to 5.50 μg/mL). In contrast, 2-methyl-6-methoxy- and 2-methyl-7-methoxy-carbazolequinones (**27** and **31**, respectively) displayed marginal cytotoxicity (ED_{50} values ranging from 3.92 to 6.22 μg/mL).



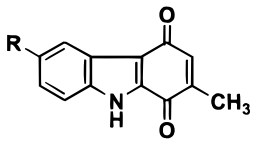
	R
21	OCH_3
22	CH_3
23	F
24	Cl



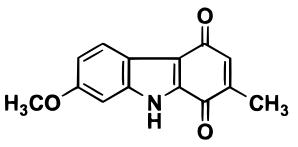
25



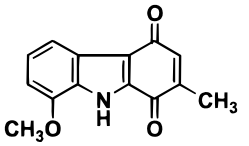
26



	R
27	OCH_3
28	CH_3
29	F
30	Cl



31



32

When the methoxy group of **21** was replaced with a methyl group, as seen in **22**, cytotoxicity against Colo-205 cells decreased, but **22** still exhibited significant cytotoxicity against KB and SK-MEL-5 cells, with ED_{50} values of 0.92 and 0.66 μg/mL, respectively. Furthermore, replacing the OMe group of **21** with a Cl or F group yielded **24** and **23**, respectively, which exhibited significant selective cytotoxicity against the SK-MEL-5 cell line, with ED_{50} values of 0.83 and 2.51 μg/mL, and showed marginal or weak toxicities against the other cells. The same replacements in the 2-methyl-carbazolequinone series (**27**−**30**) had little effect on cytotoxicity.

Comparing the 2-methyl- and 3-methyl-carbazolequinone derivatives, the former series was more toxic than the latter when methoxy substituents were present at the 7- and 8-positions (compare **32** and **31** with **26** and **25**). However, in general, 2-methyl-6-substituted derivatives were less toxic than the corresponding 3-methyl-carbazolequinone derivatives (compare **27**, **28**, and **30** with **21, 22**, and **24**). In summary, these results suggest that carbazolequinone derivatives have potential as cytotoxic agents with cell-line selectivity.

Experimental Section

General Experimental Procedures. Melting points were measured on a Fisher-Johns or a Yanako micromelting point apparatus and are uncorrected. Mass spectra were determined on a JEOL HX-110 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on Bruker AC-300, JEOL A-400, and JEOL A-500 spectrometers using TMS as internal standard.

Plant Materials. The dried root bark of *M. euchrestifolia* was collected at Kuantaochi, Nantou Hsien, Taiwan, and the voucher specimens are deposited in the Herbarium of Meijo University.

Isolation of Carbazoles. The dried root-bark of *M. euchrestifolia* (2 kg) was chipped and extracted with EtOH at reflux. After removal of the solvent by evaporation, the extract was partitioned with $CHCl_3$ and H_2O. The $CHCl_3$ layer, which showed cytotoxicity in the SK-MEL-5, Colo-205, HCT-8, A-549, and KB human tumor cell lines, was concentrated and subjected to Si gel column chromatography. Elution with hexane gave mainly murrayafoline A (**3**), which was purified by Si gel chromatography with hexane−isopropyl ether (4:1) to yield pure sample (11 g, 1.2% yield from total plant material). Subsequent elution with benzene also furnished a cytotoxic fraction, which was further repeatedly chromatographed on Si gel with hexane−EtOAc (4:1) to give murrayaquinone A (**1**) (5 mg) together with murrayaquinone B (**2**) (200 mg). The remaining compounds (**4**−**20**) were found in the stem bark and fruit of *M. euchrestifolia*.[9−16]

Synthesis of 2-Methyl- and 3-Methyl-carbazolequinone Derivatives. 2-Methyl- and 3-methyl-carbazolequinone derivatives (**21**−**32**) were prepared by palladium-assisted intermolecular cyclization of substituted 2-anilino-5-methyl- or substituted 2-anilino-6-methyl-1,4-benzoquinones with palladium(II) acetate [Pd(OAc)] as reported previously.[17]

Cytotoxicity Assays. The in vitro cytotoxicity assay was carried out according to an NCI protocol, as previously described.[18] The assay was conducted using a panel of human tumor cell lines. The cell lines are epidermoid carcinoma of the nasopharynx (KB), melanoma (SK-MEL-5), colon carcinoma (Colo-205), ileocecal adenocarcinoma (HCT-8), and lung carcinoma (A-549). In general, assay methods were the same as those described by Monks et al.[19] The human disease-oriented, 60-cell-line, in vitro antitumor screening was carried out at the NCI. Details of the assay procedures have been reported.[20]

Acknowledgment. The authors are indebted to Dr. Anthony Mauger, Drug Synthesis and Chemistry Branch, NCI, and Dr. Bonnie L. Roberson, Starks, C. P., Rockville, MD, for the in vitro human-tumor cell-line assay. This investigation was supported by a grant from the NCI (CA 17625) awarded to K. H. Lee.

References and Notes

(1) For Antitumor Agents 202, see: Xia, Y.; Yang, Z. Y.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Lee, K. H. *Bioorg. Med. Chem. Lett.*, submitted.
(2) Fujioka, T.; Sakurai, A.; Mihashi, K.; Kashiwada, Y.; Chen, I. S.; Lee, K. H. *Chem. Pharm. Bull.* **1997**, *45*, 68−74.
(3) Furukawa, H.; Wu, T. S.; Ohta, T.; Kuoh, C. S. *Chem. Pharm. Bull.* **1985**, *33*, 4132−4138.
(4) Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. *Aust., J. Chem.* **1967**, *20*, 2715−2727.
(5) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, 1990; Vol. 39, pp 239−352.
(6) Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: Orlando, 1985; Vol. 25, pp 89−142.
(7) Wu, T. S.; Huang, S. C.; Wu, P. L.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2395−2398.
(8) Chakrabarty, M.; Nath, A.; Khasnobis, S.; Chakrabarty, M.; Konda, Y.; Harigaya, Y.; Komiyama, K. *Phytochemistry* **1997**, *46*, 751−755.
(9) Furukawa, H.; Ito, C.; Yogo, M.; Wu, T. S. *Chem. Pharm. Bull.* **1986**, *34*, 2672−2675.
(10) Ito, C.; Wu, T. S. Furukawa, H. *Chem. Pharm. Bull.* **1987**, *35*, 450−452.
(11) Ito, C.; Kanbara, H.; Wu, T. S. Furukawa, H. *Phytochemistry* **1992**, *31*, 1083−1084.
(12) Ito, C.; Nakagawa, M.; Wu, T. S. Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 1668−1671.
(13) Furukawa, H.; Wu, T. S.; Ohta, T. *Chem. Pharm. Bull.* **1983**, *31*, 4202−4205.
(14) Ito, C.; Wu, T. S. Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 1143−1146.
(15) Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 1355−1357.
(16) Ito, C.; Nakagawa, M.; Wu, T. S.; Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 2525−2528.
(17) Yogo, M.; Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 328−334.
(18) Kuo, S. C.; Lee, H. Z.; Juang, J. P.; Lin, Y. T.; Wu, T. S.; Chang, J. J.; Lednicer, D.; Paull, K. D.; Lin, C. M., Hamel, E.; Lee, K. H. *J. Med. Chem.* **1993**, *36*, 1146−1156.
(19) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757−766.
(20) Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Semin. Oncol.* **1992**, *19*, 622−638.

NP000020E