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SYNTHESIS OF 6-METHYLINDOLE-4,7-QUINONE AND ANTI-TUMOR ACTIVITIES OF ITS RELATED INDOLEQUINONES

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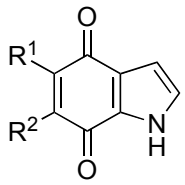
Dedicated to Prof. Steven M. Weinreb on the occasion of his 65th birthday

Abstract−We synthesized 6-methylindole-4,5-quinone (**1b**) in order to clarify the structure of natural product, 5-methylindole-4,5-quinone (**1a**) isolated from *Drupella fragum*. The synthesis features the construction of the indole ring based on an electrocyclic reaction of a 3-alkenyl-2-propargylpyrrole intermediate.
Two synthetic methylindolequinones and their related compounds were examined in human lung cancer cell line NCI-H460 and human breast cancer cell line MDA-MB-231.

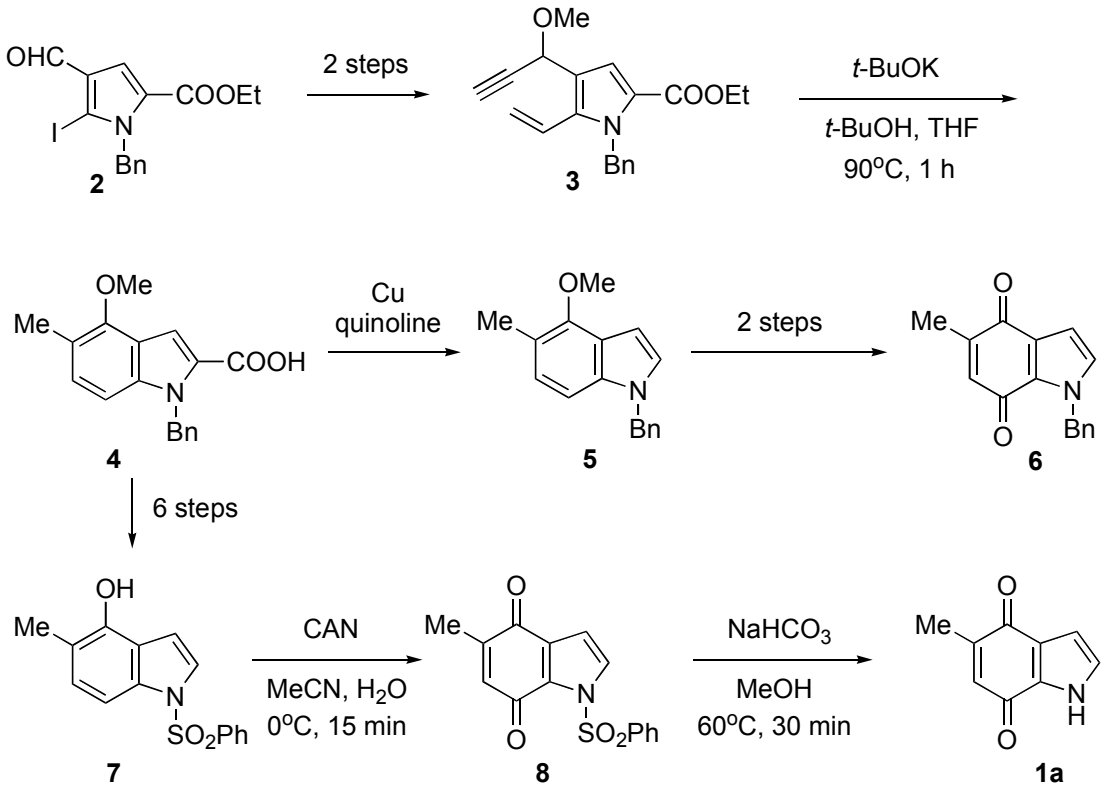
It is well known that many synthetic methodologies of the indole ring have been provided by the construction of a pyrrole ring from the benzene ring. On the other hand, there are not so many reports of indole synthesis by the construction of a benzene ring from pyrrole.[1] We are interested in the development of a new indole synthesis through a benzo-annulation based on an application of an allene-mediated electrocyclic reaction[2] using the pyrrole [*b*]-bond.



1a: R^1=Me, R^2=H
1b: R^1=H, R^2=Me

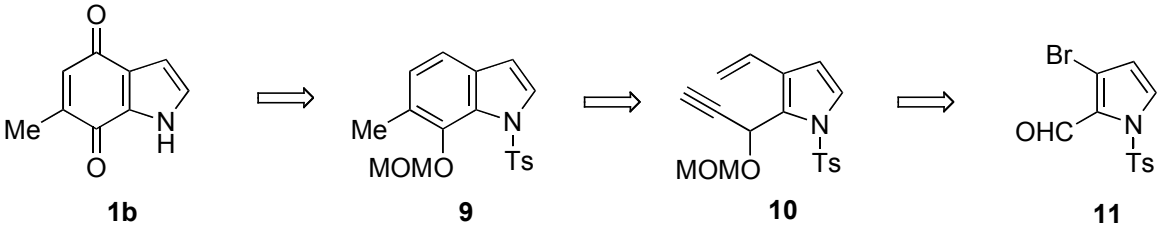
Figure 1

Recently, we reported the synthesis of 5-methylindole-4,7-quinone (**1a**), isolated from *Drupella fragum*,[3] by the construction of a functionalized indole ring based on a thermal electrocyclic reaction of an 2-alkenyl-3-allenylpyrrole intermediate generated from the 2-alkenyl-3-propargylpyrrole (**3**), followed by the oxidation step.[4] The synthetic route of 5-methylindole-4,7-quinone (**1a**) has been depicted in Scheme 1. However, the physical and spectral evidence of the synthetic **1a** did not agree with those of natural **1a**. The structures of our synthetic 5-methylindole-4,7-quinone (**1a**) and its *N*-benzyl derivative (**6**) have been determined by the analysis of their 2D-Nuclear Overhauser Effect (NOESY) and heteronuclear multibond connectivity (HMBC).[4]



Scheme 1

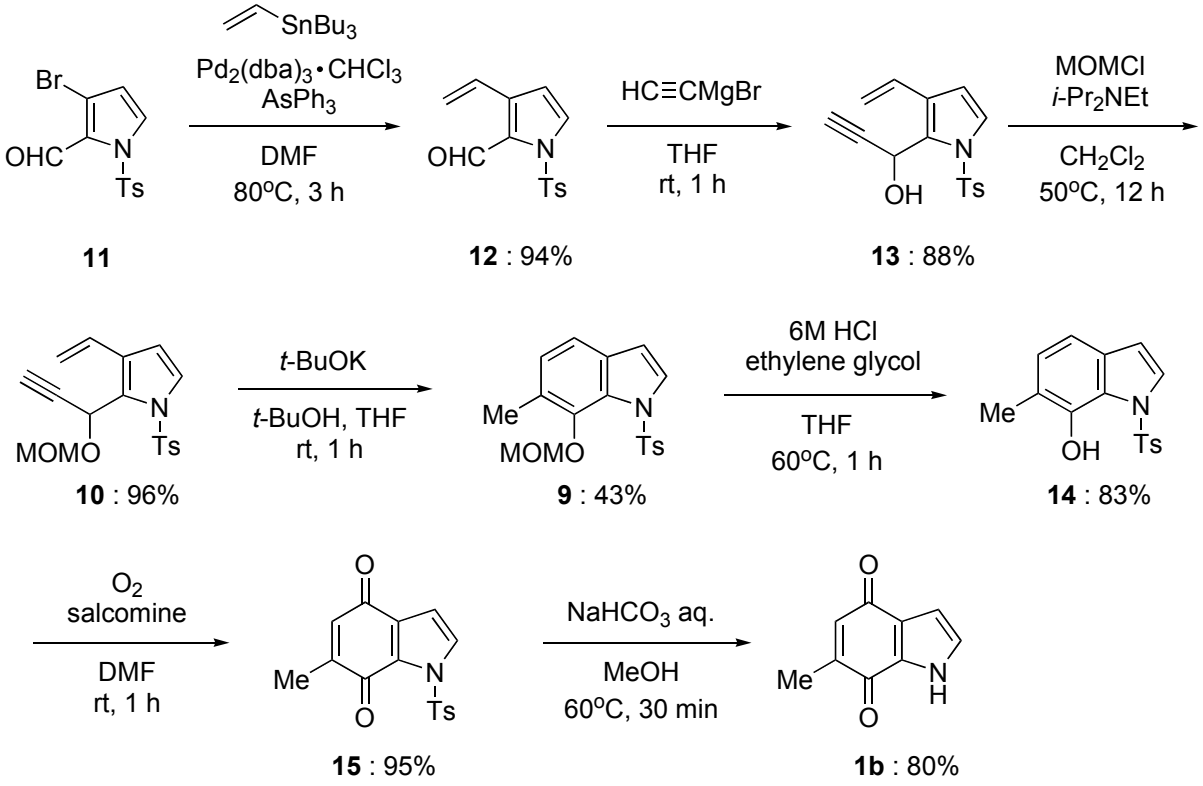
In the present paper, we describe a synthesis of 6-methylindole-4,7-quinone (**1b**) in order to clarify the structure of natural 5-methylindole-4,7-quinone (**1a**). In addition, the antitumor activities of several indole-4,7-quinones, including 5-methylindole-4,7-quinone (**1a**) and its derivatives reported previously,[4] have been also described.



Scheme 2

We planned a synthesis of 7-oxygenated 6-methylindole (**9**) as a precursor of 6-methylindolequinone (**1b**). 7-Oxygenated 6-methylindole (**9**) would be derived from 3-allenyl-2-propargylpyrrole (**10**) based on an allene-mediated electrocyclic reaction involving the pyrrole [*b*]-bond.[4] The known 3-bromopyrrole-2-carbaldehyde (**11**)[5] as starting material was selected, as shown in retro-synthetic analysis (Scheme 2).

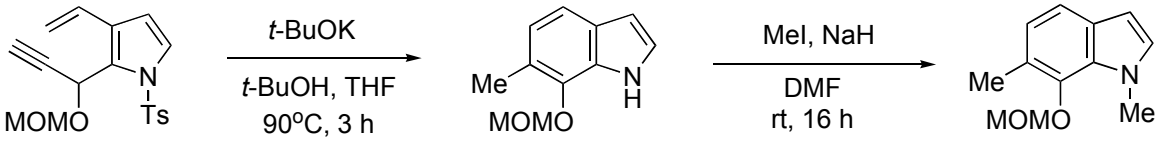
The Stille reaction between 3-bromopyrrole-2-carbaldehyde (**11**) and ethenyl tributylstannane[6] in the presence of tris(dibenzylideneacetone)dipalladium(0)-chloroform [$Pd_2(dba)_3 \cdot CHCl_3$] and triphenylarsine[7] afforded the 3-ethenylpyrrole (**12**) (94%). Grignard reaction of **12** with ethynylmagnesium bromide followed by treatment of the resulting alcohol (**13**) with chloromethyl methyl ether (MOMCl) produced the 2-propargyl ether (**10**) (96%). The 2-propargylpyrrole (**10**) was subjected to an electrocyclic reaction[2,4] in the presence of *t*-BuOK in *t*-BuOH and THF at room temperature to yield the 6-methylindole (**9**) (43%). Subsequent deprotection of the *O*-MOM group of 6-methylindole (**9**) with 6M HCl in THF and ethylene glycol[7a] (**14**: 83%), followed by oxidation of **14** with salcomine under bubbling with oxygen[8] gave the indole-4,7-quinone (**15**) (95%). Finally, hydrolysis of the *N*-tosyl group of **15** with an aqueous $NaHCO_3$ solution in MeOH produced the desired 6-methylindole-4,7-quinone (**1b**) in 80% yield (Scheme 3).



Scheme 3

Furthermore, the 7-methoxymethyloxy-*N*-methyl-6-methylindole (**17**) was prepared from the propargyl ether (**10**) in order to utilize the structure analysis of 6-methylindole-4,7-quinone (**1b**) in several NMR

experiments. Namely, propargyl ether (**10**) was subjected to a thermal electrocyclic reaction in the presence of *t*-BuOK in *t*-BuOH at 90ºC to give the *N*-deprotected indole (**16**) in this case (39%), which was treated with methyl iodide with NaH to produce *N*-methylindole (**17**) (94%) (Scheme 4).



10 **16** : 39% **17** : 94%

Scheme 4

The structures of 6-methylindole-4,7-quinone (**1b**) and 7-methoxymethyloxy-*N*-methyl-6-methylindole (**17**) were determined by ^{1}H-NMR and ^{13}C-NMR, HMBC and NOESY experiments as illustrated by arrows (Figure 2). Although it has been reported that the correlation between C3-H and C4-C of natural **1a** was observed in the HMBC spectrum, a correlation between C3-H and C4-C of synthetic **1b** was not observed in a similar spectrum. The spatial connectivity between the methyl proton of *N*-methyl group and the C2-H of *N*-methylindole (**17**) was indicated in the NOESY spectrum, and then the structure of **17** was confirmed in the HMBC spectrum. On the basis of this experiment, the structure of synthetic **1b** has been also supported indirectly. As a result, the physical and spectral evidence of synthetic 6-methylindole-4,7-quinone (**1b**) did not agree with those of natural **1a** reported by the Fukuyama group.[3] It was found that the structure of natural **1a** is not 6-methylindole-4,7-quinone (**1b**).

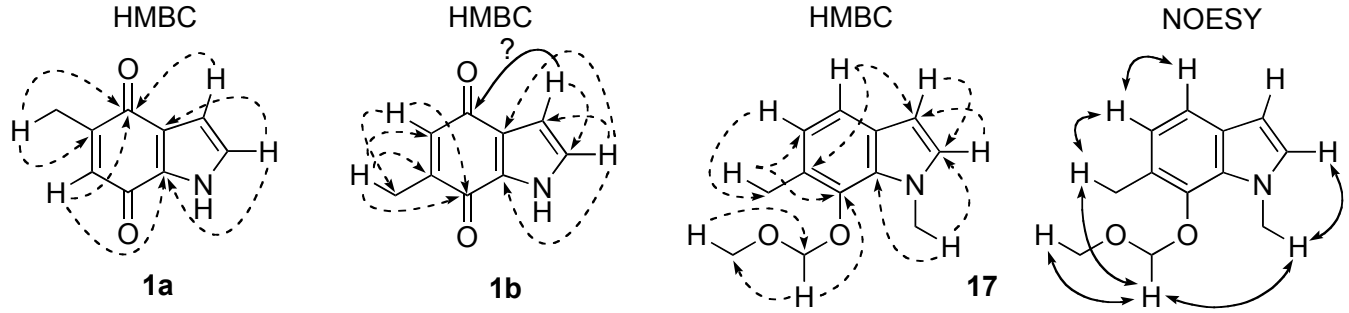


Figure 2

Two synthetic methylindole-4,7-quinones were examined in *in-vitro* growth inhibition assay using human non-small cell lung cancer cell line NCI-H460 and human breast cancer cell line MDA-MB-231 (Table 1). In comparison with CDDP (on NCI-H460: IC_{50} 0.483 μM and on MDA-MB-231: IC_{50} 11.6 μM), 5-methylindolequinone (**1a**) hardly showed the activity (on NCI-H460: IC_{50} 16.6 μM and on MDA-MB-231: IC_{50} 17.4 μM). 6-Methylindolequinone (**1b**) showed slightly stronger activity against MDA-MB-231 (IC_{50} 3.51 μM) than CDDP. In addition, the activity of related compounds (**6**, **8**, **15**) having the benzyl or the arylsulfonyl group in the 1-position of methylindolequinone was examined

(Schemes 1 and 3, Table 1). *N*-Phenylsulfonyl-5-methylindolequinone (**8**) showed activity (MDA-MB-231: IC_{50} 1.96 μM) which was stronger than that of CDDP.

Table 1. Growth-inhibitory Activity of Indole-4,7-quinones against NCI-H460 and MDA-MB-231 cells

Compd.	IC_{50} value (μM)	
	NCI-H460	MDA-MB-231
CDDP	0.483	11.6
1a	16.60	17.4
1b	2.93	3.51
6	10.10	7.38
8	9.85	1.96
15	8.43	3.98

In conclusion, the synthesis of 6-methylindole-4,7-quinone (**1b**) has been established by the construction of the functionalized indole ring based on the allene-mediated electrocyclic reaction using the pyrrole [*b*]-bond. The structure of natural indolequinone (**1a**)[3] was not identical with either synthetic **1a**[4] or **1b** in all respects. The exact structure of natural **1a** is now unclear. Furthernore, the antitumor activities of five indole-4,7-quinones (**1a**, **1b**, **6**, **8**, and **15**) were examined in two human cell lines. It was found that *N*-phenylsulfonyl-5-methylindole-4,7-quinone (**8**) shows strong inhibitory activity against human cancer cell line MDM-MB-231.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Horiba FT-720 spectrophotometer. ^{1}H-NMR spectra were taken by JNM AL-300 spectrometers using $SiMe_4$ as an internal standard. MS spectra and HRMS were recorded on Shimadzu QP-5050 and JEOL JMS-700 spectrometers (EI). Silica gel (60-100 mesh, Merck Art 7734) was used for the column chromatography.

3-Ethenyl-*N*-tosylpyrrole-2-carbaldehyde (12)

A mixture of the 3-bromopyrrole (**11**) (216 mg, 0.66 mmol), vinyl *n*-tributyltin (0.38 mL, 1.31 mmol), Ph_3As (6 mg, 0.02 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (20 mg, 0.02 mmol) in DMF (5 mL) was heated at 80°C for 3 h under Ar atmosphere. After being cooled to an ambient temperature, an aqueous 30% KF solution (8 mL) was added to the reactant, and then the mixture was stirred at rt for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc-hexane (1:9 v/v) as an eluent to give

the oily 3-ethenylpyrrole (**12**) (170 mg, 94%). IR (KBr) ν : 1670, 1370 cm^{-1}. MS *m*/*z* : 275 (M^+); ^{1}H-NMR ($CDCl_3$) δ : 2.41 (3H, s), 5.44 (1H, dd, *J*=1.1, 11 Hz), 5.75 (1H, dd, *J*=1.1, 17 Hz), 6.60 (1H, d, *J*=3.3 Hz), 7.27 (1H, dd, *J*=11, 17 Hz), 7.31 (2H, d, *J*=8.4 Hz), 7.52 (1H, d, *J*=3.3 Hz), 7.75 (2H, d, *J*=8.4 Hz), 10.2 (1H, s). HRMS (EI) calcd for $C_{14}H_{13}NO_3S$ 275.0616, found 275.0630.

3-Ethenyl-2-(1-hydroxyprop-2-yn-1-yl)-*N*-tosylpyrrole (13)

An ice-cooled solution of ethynylmagnesium bromide (0.5 M in THF, 5 mL, 2.55 mmol) was added to a solution of 3-ethenylpyrrole (**12**) (235 mg, 0.85 mmol) in THF (15 mL). After being stirred at rt for 1 h, the mixture was treated with aqueous NH_4Cl solution (saturated) and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc-hexane (1:9, v/v) as an eluent to give the oily propargyl alcohol (**13**) (225 mg, 88%). IR (KBr) ν : 3290, 1370 cm^{-1}. MS *m*/*z* : 301 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 2.39 (3H, s), 2.49 (1H, d, *J*=2.2 Hz), 5.24 (1H, dd, *J*=1.1, 11 Hz), 5.51 (1H, dd, *J*=1.1, 17 Hz), 6.03 (1H, d, *J*=2.2 Hz), 6.47 (1H, d, *J*=3.3 Hz), 6.97 (1H, dd, *J*=11, 17 Hz), 7.22 (1H, d, *J*=3.3 Hz), 7.28 (2H, d, *J*=8.4 Hz), 7.73 (2H, d, *J*=8.4 Hz). HRMS (EI) calcd for $C_{16}H_{15}NO_3S$ 301.0773, found 301.0761.

3-Ethenyl-2-[1-(methoxymethyloxy)prop-2-yn-1-yl]-*N*-tosylpyrrole (10)

A stirred solution of the propargyl alcohol (**13**) (69 mg, 0.23 mmol), MOMCl (0.10 mL, 1.34 mmol), and *i*-Pr_2NEt (0.32 mL, 0.34 mmol) in CH_2Cl_2 (10 mL) was heated at 50 ºC for 16 h. The solution was treated with water, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (1:9 v/v) as an eluent to give the oily *O*-MOM-ether (**10**) (76 mg, 96%). IR (neat) ν : 1370 cm^{-1}. MS *m*/*z* : 345 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 2.39 (3H, s), 2.51 (1H, d, *J*=2.2 Hz), 3.35 (3H, s), 4.55 (1H, d, *J*=6.9 Hz), 4.88 (1H, d, *J*=6.9 Hz), 5.19 (1H, dd, *J*=1.1, 11 Hz), 5.50 (1H, dd, *J*=1.1, 17 Hz), 6.22 (1H, d, *J*=3.3 Hz), 6.51 (1H, d, *J*=3.3 Hz), 7.05 (1H, dd, *J*=11, 17 Hz), 7.26-7.29 (3H, m), 7.71 (2H, d, *J*=8.4 Hz). HRMS (EI) calcd for $C_{18}H_{19}NO_4S$ 345.1035, found 345.1022.

7-(Methoxymethyloxy)-6-methyl-*N*-tosylindole (9)

A solution of the *O*-MOM-ether (**10**) (100 mg, 0.29 mmol) in THF (5 mL) was added to a stirred solution of *t*-BuOK (97 mg, 0.87 mmol) in *t*-BuOH (10 ml) at ambient temperature for 1 h. The mixture was quenched with an aqueous NH_4Cl (saturated) solution, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (1:9 v/v) as an eluent to give the oily *N*-tosylindole (**9**) (43 mg, 43%). IR (neat) ν : 1355 cm^{-1}. MS *m*/*z* : 345 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 2.33 (3H, s), 2.39 (3H, s), 3.60 (3H, s), 5.16 (2H, s), 6.57-6.58 (1H, m), 6.99-7.02 (1H, m), 7.12-7.19 (3H, m), 7.65-7.71 (3H, m). HRMS (EI) calcd for $C_{18}H_{19}NO_4S$ 345.1035, found 345.1015.

7-Hydroxy-6-methyl-*N*-tosylindole (14)

A solution of *N*-tosylindole (**9**) (143 mg, 0.41 mmol), ethylene glycol (0.4 mL), and 6 M HCl (1 mL) in THF (4 mL) was stirred at 60ºC for 1 h. After being cooled to an ambient temperature, the mixture was basified with an aqueous K_2CO_3 (saturated) solution, and then the resulting mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the oily 7-hydroxyindole (**14**) (104 mg, 83%). mp 104-107 ºC (EtOH). IR (KBr) ν : 3350, 1340 cm^{-1}. MS *m*/*z* : 301 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 2.33 (3H, s), 2.36 (3H, s), 6.59 (1H, d, *J*=3.6 Hz), 6.91 (1H, d, *J*=7.7 Hz), 7.03 (1H, d, *J*=7.7 Hz), 7.20-7.22 (2H, m), 7.37 (1H, d, *J*=3.6 Hz), 7.65-7.68 (2H, m), 8.85 (1H, s). HRMS (EI) calcd for $C_{16}H_{15}NO_3S$ 301.0773, found 301.0786.

6-Methyl-*N*-tosylindole-4,7-quinone (15)

A stirred solution of the 7-hydroxyindole (**14**) (19 mg, 0.06 mmol) and salcomine (4 mg, 0.01 mmol) in DMF (8 mL) was bubbled with oxygen at rt for 1 h. The reaction mixture was diluted with water, and then the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (1:9 v/v) as an eluent to give the quinone (**15**) (19 mg, 95%). mp 158-160 ºC (EtOAc-hexane). IR (KBr) ν : 1660, 1375 cm^{-1}. MS *m*/*z* : 315 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 2.03 (3H, d, *J*=1.4 Hz), 2.44 (3H, s), 6.45 (1H, d, *J*=1.4 Hz), 6.70 (1H, d, *J*=3.3 Hz), 7.37 (2H, d, *J*=8.4 Hz), 7.77 (1H, d, *J*=3.3 Hz), 8.04 (2H, d, *J*=8.4 Hz). HRMS (EI) calcd for $C_{16}H_{13}NO_4S$ 315.0565, found 315.0548.

6-Methylindole-4,7-quinone (1b)

The mixture of the quinone (**15**) (129 mg, 0.41 mmol) and an aqueous $NaHCO_3$ (8 mL) solution (saturated) in MeOH (10 mL) was heated at 60ºC for 30 min. After being cooled to ambient temperature, water was added to the mixture, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 25 g) using EtOAc-hexane (1:9 v/v) as an eluent to give the 6-methylindolequinone (**1b**) (53 mg, 80%). mp 169-172 ºC (EtOAc-hexane). IR (KBr) ν : 3241, 1670, 1643, 1602, 1492, 1411, 1375 cm^{-1}. MS *m*/*z* : 161 (M^+). ^{1}H-NMR (DMSO-d_6) δ : 2.00 (3H, s), 6.48 (2H, s), 7.21 (1H, s), 12.7 (1H, br s); ^{13}C-NMR (DMSO-d_6) δ : 15.1, 106.9, 125.4, 126.5, 130.8, 133.6, 145.2, 177.2, 183.3. HRMS (EI) calcd for $C_9H_7NO_2$ 161.0477, found 161.0473.

7-(Methoxymethyloxy)-6-methylindole (16)

A solution of the *O*-MOM-ether (**10**) (69 mg, 0.20 mmol) in THF (5 mL) was added to a stirred solution of *t*-BuOK (67 mg, 0.60 mmol) in *t*-BuOH (10 mL) at 90ºC for 3 h. After being cooled to ambient temperature, the mixture was quenched with an aqueous NH_4Cl (saturated) solution, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using

EtOAc-hexane (1:9 v/v) as an eluent to give the oily 6-methylindole (**16**) (15 mg, 39%). MS *m*/*z* : 191 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 2.36 (3H, s), 3.72 (3H, s), 5.20 (2H, s), 6.49-6.51 (1H, m), 6.90 (1H, d, *J*=8.4 Hz), 7.13-7.15 (1H, m), 7.27 (1H, d, *J*=8.4 Hz), 9.52 (1H, br s). HRMS (EI) calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0959.

7-(Methoxymethyloxy)-6-methyl-*N*-methylindole (17)

A solution of the 6-methylindole (**16**) (27 mg, 0.14 mmol) in DMF (5 mL) was adde to a stirred suspension of 60%NaH (7 mg, 0.15 mmol) in DMF (1 mL) under cooled ice-water. After being stirred at room temperature for 30 min, methyl iodide (62 μL, 1.0 mmol) was added to the reaction mixture, and then was stirred at room temperature for 16 h. The mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (1:19 v/v) as an eluent to give the oily *N*-methylindole (**17**) (27 mg, 94%). MS *m*/*z* : 205 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 2.42 (3H, s), 3.59 (3H, s), 4.02 (3H, s), 5.08 (2H, s), 6.39 (1H, d, *J*=2.9 Hz), 6.87 (1H, d, *J*=7.7 Hz), 6.89 (1H, d, *J*=2.9 Hz), 7.27 (1H, d, *J*=7.7 Hz). HRMS (EI) calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1092.

In vitro growth inhibition assay

Human non-small cell lung cancer cell line NCI-H460 and breast cancer cell line MDA-MB-231 (American Type Culture Collection, VA 20108, USA) were cultured in RPMI1640 medium (Asahi Techno Glass Corporation, Chiba, Japan), containing 10% fetal bovine serum (lot No. 49300604, Moregate Bio Tech, Australia). Some supplements were added into the medium appropriately. Appropriate numbers of cells were inoculated into 96-well microplates. Following overnight culture, serially diluted compounds were added into the wells. After a 3-day culture, cells were stained with 0.05% methyleneblue dissolved in 10 mM Tris buffer (pH8.5) for 30 min, and then thoroughly washed with distilled water. The stained dye was extracted with 3% HCl, and OD660 was measured with microplate reader Benchmark Plus (Bio-Rad, USA) to determine cell growth inhibition. Cysplatin (CDDP, Nippon Kayaku Co., Ltd., Tokyo, Japan) was used as a standard cytotoxic anti-cancer compound.

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