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ANTIOXIDANT EFFECTS OF THE HYDROXY GROUPS IN THE SIMPLE PHENOLIC CARBAZOLES

Yuhzo Hieda,[a] Noriyuki Hatae,[b] Makoto Anraku,[c] Nobuyasu Matsuura,[d] Kazuhide Uemura,[e] Satoshi Hibino,[a] Tominari Choshi,[a]* Hisao Tomida,[a] Osamu Hori,[f] and Haruto Fujioka[a]*

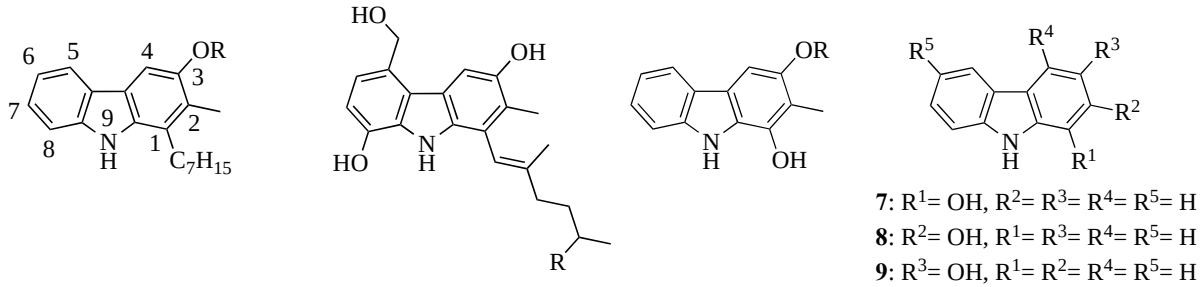
[a]Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan [b]School of Pharmaceutical Sciences, Health Science University of Hokkaido, Ishikari, Tobetsu, Hokkaido 061-0293, Japan [c]Faculty of Pharmaceutical Sciences, Sojo University, Kumamoto 860-0082, Japan [d]Department of Life Science, Okayama University of Science, Kita-ku, Okayama 700-0005, Japan [e]Department of Biomedical Sciences, College of Life and Health Sciences, Chubu University, Kasugai, Aichi 487-8501, Japan [f]Department of Neuroanatomy, Kanazawa University, Graduate School of Medical Sciences, Takaramachi, Kanazawa 920-8640, Japan. E-mail: choshi@fupharm.fukuyama-u.ac.jp and fujioka@fupharm.fukuyama-u.ac.jp

Abstract – Antioxidant activities of the simple phenolic carbazoles **5**-**11** were evaluated by 2,2-diphenyl-1-picrylhydrazyl and 2,2'-azinobis-(3-ethylbenzthiazoline-6-sulfonate)$^+$ radical scavenging assays. The simple phenolic carbazoles **5**-**7**, **9**, and **11** exhibited stronger antioxidant activities than α-tocopherol, and similar antioxidant activities as phenolic carbazole alkaloids carazostatin (**1**), and carbazomadurins A (**3**) and B (**4**). Bond dissociation energies and highest occupied molecule orbital energy levels of a series of phenolic carbazoles including phenolic carbazole alkaloids were calculated. The reducing ability of the phenolic carbazole core could be important role for the antioxidant activity of carbazole alkaloids **1**, **3**, and **4**.

Reactive oxygen species (ROS) are highly reactive small substances with an important role in the initiation of various diseases such as carcinogenesis, drug-associated toxicity, inflammation, and atherogenesis as well as aging in aerobic organisms. Natural antioxidants, including ascorbic acid, α-tocopherol (VE), ubiquinol, uric acid, polyphenols and their analogs have been intensive investigation

for clinical applications.[1] Edaravone (3-methyl-*N*-phenylpyrazolin-5-one) scavenges free radicals and protects the brain against ischemic lesions after stroke, thus improving the clinical outcomes for patients with acute ischemic damage.[2] Synthetic and/or medicinal chemists are interested in obtaining novel antioxidant substances as an important approach to treating oxidative stress-related diseases.[1,2]

Carbazole alkaloids are a well-known class of natural products possessing a benzo[*b*]indole ring system.[3] These heterocyclic natural products have a wide variety of bioactivities, such as antibacterial, antibiotic,[4] antimalarial, antitumor,[5,6] cardiotonic,[7] anti-inflammatory,[8] free radical scavenging and neuronal cell-protecting[9-13] activities. Due to their interesting biologic effects, carbazole alkaloids and their related compounds constitute an important class of natural products.



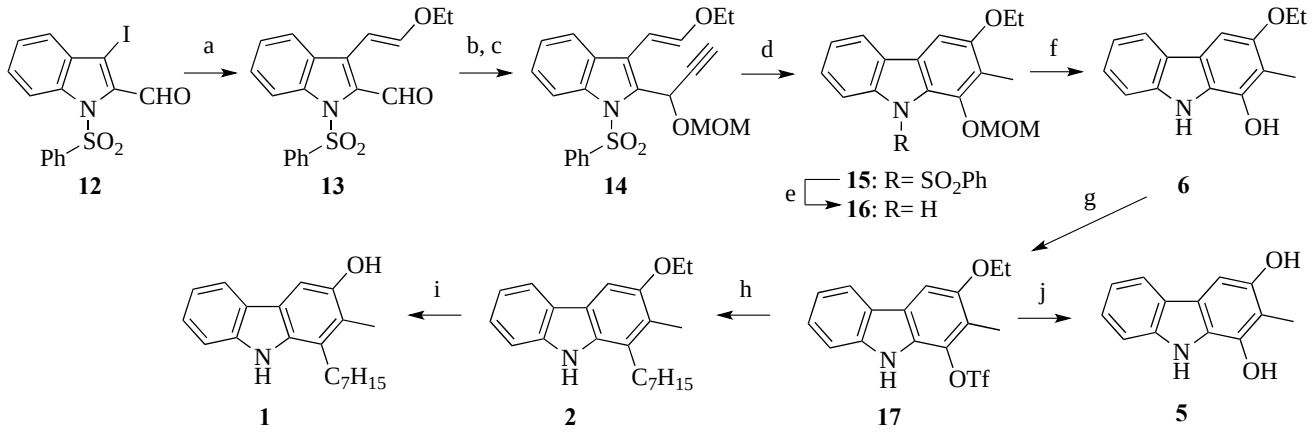
1: carazostatin (R= H)
2: *O*-ethylcarazostatin (R= Et)
3: carbazomadurin A (R=Me)
4: carbazomadurin B (R= Et)
5: R= H
6: R= Et
7: R^1= OH, R^2= R^3= R^4= R^5= H
8: R^2= OH, R^1= R^3= R^4= R^5= H
9: R^3= OH, R^1= R^2= R^4= R^5= H
10: R^4= OH, R^1= R^2= R^3= R^5= H
11: R^1= R^5= OH, R^2= R^3= R^4= H

Figure 1. Phenolic carbazole alkaloids and simple hydroxycarbazoles

In 1989, the 3-hydroxycarbazole alkaloid carazostatin (**1**) was isolated from *Streptomyces chromofuscus* as a free radical-scavenging substance.[9a] This alkaloid exhibits strong inhibitory activity against free radical–induced lipid peroxidation and stronger antioxidant activity in liposomal membranes than VE.[9b] Furthermore, the antioxidant activity of **1** and 2-hydoxycarbazole (**8**) was assessed in the oxidation of methyl linolate induced by aza radical initiator.[10] Few years later, 3,8-dihydroxycarbazoles carbazomadurins A (**3**) and B (**4**) were isolated from *Actinomadula madurae* 2808-SV-1.[11] The antioxidative activity of these alkaloids was evaluated based on their inhibition of L-glutamate toxicity in N18-RE-195 cells. In addition, the first example of carbazole-3,4-quinone alkaloid carquinostatin A was isolated in 1993 from *Streptomyces exfoliates* 2419-SVT2.[12a] This natural product is a potent neuronal cell-protecting substance and exhibits free radical scavenging activity.[12b] On the other hand, 3-hydroxycarbazole lipocarbazoles A1-A4, closely related to carazostatin, were found in *Tsukamurella pseudospumae Acta* 1857.[13] The antioxidant activity of lipocarbazole A3 was reported to be more active than ascorbic acid in a 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay.[13]

These 3-hydroxycarbazole, 3,8-dihydroxycarbazole and carbazole-3,4-quinone alkaloids were independently evaluated in a bioassay system during isolation, but have not yet been evaluated comprehensively. We recently reported that 3-hydroxycarbazole carazostatin (**1**), 3,8-dihydroxycarbazole

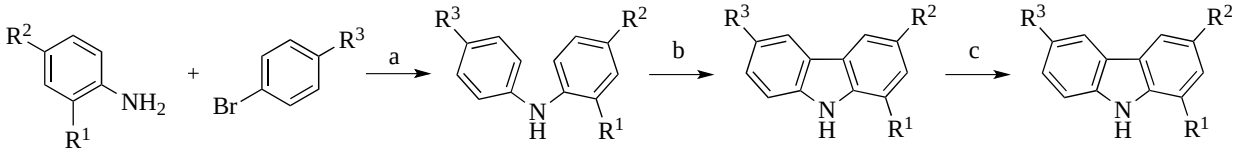
alkaloids carbazomadurins A (**3**) and B (**4**), and related carbazoles, except carbazole-3,4-quinone alkaloid carquinostatin A, exhibit strong antioxidant effects based on a comprehensive evaluation in several assay systems using propyl galate (PG), VE and edaravone as standards.[14] Recently, the radical scavenging activities by antioxidants were rationalized based on their chemical properties using quantum chemical calculations. The scavenging activities of free radicals by lipocarbazoles were well evaluated by the O-H and N-H bond dissociation enthalpies.[15] The glutathione peroxidase-like antioxidant activities of aliphatic selenides were consistent with their highest occupied molecule orbital (HOMO) energy levels (E_{HOMO}).[16] In the present paper, we describe the relationship between the calculated structure and antioxidant activity of simple oxygenated carbazoles **5**-**11** in comparison with carazostatin (**1**) and carbazomadurins A (**3**) and B (**4**) (Figure 1).



Scheme 1. Synthesis of carazostatin (**1**) and related carbazoles **2**, **5** and **6**
Reagents and conditions: (a) 2-ethoxyvinylstannane, $PdCl_2(PPh_3)_2$, Et_4NCl, DMF, 80 °C, 2 h, 84%; (b) ethynylmagnesium bromide, THF, 0 °C, 1 h, 82%; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 50 °C, 12 h, 97%; (d) *t*-BuOK, *t*-BuOH, THF, 90 °C, **15**: 41%, **16**: 43%; (e) 3M NaOH, MeOH, THF, 80 °C, 18 h, 98%; (f) TMSCI, NaI, MeCN, -20 °C, 5 min, 63%; (g) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 2 h, 85%; (h) 1-heptene, 9-BBN, 3M NaOH, $PdCl_2$(dppf), THF, 80 °C, 1 h, 85%; (i) BBr_3, CH_2Cl_2, -78 °C, 4 h, 90%; (j) (1) BBr_3, CH_2Cl_2, -78 °C, 4 h; (2) $LiAlH_4$, THF, 0 °C, 60% (2 steps)

To evaluate the antioxidant activities of 3-hydroxycarbazole alkaloid, carazostatin (**1**) was prepared by an allene-mediated electrocyclic reaction involving the indole 2,3-bond according to the previously reported procedure (Scheme 1).[17] Treatment of the indole-2-propargyl ether **14**, derived from 3-iodoindole-2-carbaldehyde **12** in three steps, with *t*-BuOK afforded tri-substituted carbazole **15**. Cleavage of the phenylsulfonyl group of **15** with NaOH, followed by treatment of TMS-I afforded the 1-hydroxy-3-ethoxycarbazole **6**. Treatment of **6** with Tf_2O gave the *O*-triflate **17**, which was subjected to a Pd-catalyzed cross-coupling reaction with 9-hexyl-9-BBN to give the 1-hexylcarbazole **2**. Subsequent treatment of **2** with BBr_3 provided carazostatin (**1**). In addition, 1,3-dihydroxycarbazole **5** was prepared in two steps from **17**. Carazostatin (**1**), 1-hexyl-3-ethoxycarbazole **2**, 1,3-dihydroxycarbazole **5**, and 1-hydroxy-3-ethoxycarbazole **6** were used to evaluate antioxidant activities. 3,8-Dihydroxycarbazole

alkaloids carbazomadurins A (**3**) and B (**4**) were prepared according to our reported procedure and used in radical scavenging assays.[18]



18a: R^1= OMe, R^2= H **19a**: R^3= H **20a**: R^1= OMe, R^2= R^3= H **21a**: R^1= OMe, R^2= R^3= H **7**: R^1= OH, R^2= R^3= H
18b: R^1= H, R^2= OMe **19b**: R^3= OMe **20b**: R^1= R^3= H, R^2= OMe **21b**: R^1= R^3= H, R^2= OMe **9**: R^2= OH, R^1= R^3= H
20c: R^1= R^3= OMe, R^2= H **21c**: R^1= R^3= OMe, R^2= H **11**: R^1= R^3= OH, R^2= H

Scheme 2. Synthesis of simple hydroxycarbazoles **7**, **9** and **11**
Reagents and conditions: (a) $Pd(OAc)_2$ (0.04 equiv.), BINAP (0.04 equiv.), K_2CO_3 (1.4 equiv.), toluene, 12 h, 150 °C, **20a**: 98%, **20b**: 83%, **20c**: 79%; (b) $Pd(OAc)_2$ (1.2 equiv.), AcOH, 130 °C, 15 h, **21a**: 61%, **21b**: 31%, **21c**: 29%; (c) BBr_3, CH_2Cl_2, -78 °C to rt, 5 h, **7**: 65%, **9**: 60%, **11**: 49%

Simple hydroxycarbazoles **7**, **9** and **11** were prepared by the reported procedures[19] as follows (Scheme 2). Buchwald-Hartwig amination of bromobenzene (**19a**) with *o*-anisidine (**18a**) or *p*-anisidine (**18b**) gave the diphenylamine **20a** and **20b**, respectively. Similarly, amination of 4-bromoanisole (**19b**) with *o*-anisidine (**18a**) afforded the diphenylamine **20c**. Diphenylamines **20a**, **20b** and **20c** were subjected to a palladium(II)-catalyzed oxidative cyclization to produce corresponding methoxycarbazoles **21a**,[20] **21b**[21] and **21c**,[22] which were treated with BBr_3 to provide three hydroxycarbazoles **7**, **9** and **11**, respectively. 1-Hydroxycarbazole (**7**),[20] 3-hydroxycarbazole (**9**)[23] and 1,6-dihydroxycarbazole (**11**) were used in our assays. Commercially available 2-hydroxycarbazole (**8**) and 4-hydroxycarbazole (**10**) were used.[24]
The structures of all synthesized compounds (Figure 1), except commercially available **8** and **10**, were elucidated on the basis of ^1H and ^{13}C NMR spectra. Antioxidant activities against DPPH,[25] and 2,2'azinobis-(3-ethylbenzthiazoline-6-sulfonate) cations ($ABTS^+$)[26] were measured.

Evaluation of DPPH radical scavenging activity is a rapid and convenient method for screening the antioxidant activity. In the DPPH radical scavenging assay (Table 1),[25] hydroxycarbazoles **1**, **3**, **4**, **5**, **6**, **7**, **9** and **11** exhibited higher radical-scavenging activities than VE (15.4) and edaravone (19.7). Among them, simple 1-hydroxycarbazole (**7**) (10.4) and 3-hydroxycarbazole (**9**) (9.4) displayed the same potent scavenging activity as carbazomadurins A (**3**) (9.9) and B (**4**) (9.8)[14] as reported previously. Compared to carazostatin (**1**), 3-hydroxycarbazole (**9**) exhibited the more potent radical scavenging activity. In addition, simple 1,6-dihydroxycarbazole (**11**) (8.0), the core structure of 3,8-dihydroxycarbazole carbazomadurins A (**3**) and (B) (**4**), exhibited the strongest radical scavenging activity of all tested compounds compared with PG (6.1). Furthermore, 1,3-dihydroxycarbazole **5** (13.7) and 1-hydroxy-3-ethoxycarbazole **6** (13.2) exhibited better radical scavenging activity than VE or edaravone. *O*-Ethylcarazostatin (**2**) and

Table 1. Radical scavenging activities of carbazole alkaloids and hydroxycarbazoles

Compounds	Radical scavenging activiies IC_{50} (mM)	
	DPPH radical	$ABTS^+$ radical
PG[a]	6.1 ± 0.2	187.5 ± 7.0
VE[b]	15.4 ± 0.3	211.1 ± 4.6
Edaravone	19.7 ± 0.2	213.7 ± 4.0
1	12.0 ± 0.3	158.9 ± 4.6
2	> 50	196.1 ± 1.4
3	9.9 ± 0.1	111.7 ± 3.5
4	9.8 ± 0.4	115.9 ± 2.0
5	13.7 ± 0.1	115.7 ± 1.4
6	13.2 ± 0.7	129.5 ± 2.2
7	10.4 ± 0.2	117.8 ± 3.1
8	71.4 ± 0.6	598.5 ± 8.7
9	9.4 ± 0.6	184.9 ± 5.5
10	22.4 ± 0.3	116.3 ± 1.2
11	8.0 ± 0.1	101.6 ± 1.2

Data are expressed as the mean ±S.E. of three experiments.
[a] PG = propyl gallate, [b] VE = α-tocopherol

2-hydroxycarbazole (**8**), however, exhibited weak antioxidant activities in this assay because they could not be transformed to a suitable iminoquinone form.

The $ABTS^+$ radical assay is a conventional and excellent model for assessing the antioxidant activities of hydrogen-donation and chain-breaking antioxidants. In this assay, $ABTS^+$ radicals were produced by reacting ABTS with potassium persulfate in sodium phosphate buffer solution.[26] As shown in Table 1, all oxygenated carbazoles **1**, **3**-**7**, and **9**-**11**, except *O*-ethylcarazostatin (**2**) and 2-hydroxycarbazole (**8**), exhibited better $ABTS^+$ radical scavenging activities than the strong antioxidants PG (188) with better IC_{50} values.

Among them, seven hydroxycarbazoles **3** (112), **4** (116), **5** (116), **6** (121), **7** (118), **10** (116), and **11** (102) exhibited stronger $ABTS^+$ radical scavenging activities than PG. Simple 1,3-dihydroxycarbazole **5**, 1-hydroxycarbazole (**7**), and 4-hydroxycarbazole (**10**) possessed strong antioxidant activities similar to 3,6-dihydroxycarbazole alkaloids carbazomadurins A (**3**) and B (**4**). Based on this assay, the simple 1,6-dihydroxycarbazole (**11**) (102), the core structure of carbazomadurins A (**3**) and B (**4**), had the strongest antioxidant activity of all tested compounds. Although *O*-ethylcarazostatin (**2**) displayed weak DPPH radical scavenging activity, the $ABTS^+$ radical scavenging activity of **2** (196) was between that of VE (211) and PG (188). The simple 2-hydroxycarbazole (**8**) exhibited the lowest $ABTS^+$ radical scavenging activity in this assay.

For scavenging activity of the free radicals by hydroxycarbazoles, the O-H and N-H groups provided efficient DPPH scavenging activity.[27-29] Both O-H and N-H bond dissociation energies, examined by density functional theory at ωB97X-D/6-31+G(d), were calculated for all of the tested compounds (Table

2). Among all of the carbazoles, except compound **2**, the bond dissociation energies of the O-H groups were lower than those of the N-H group.

Table 2. Bond dissociaction (BD) energy values and HOMO energy levels of carbazole alkaloids and hydroxycarbazoles

Compounds	BD energy (kcal/mol)[a]			E_{HOMO} (eV)[d]
	N-H radical	O-H radical (1)[b]	O-H radical (2)[c]	
1	90.7	81.3	-	-7.11
2	86.2	-	-	-7.03
3	94.2	82.7	80.1	-7.00
4	94.2	82.7	80.0	-7.00
5	92.2	79.7	80.3	-7.12
6	92.4	80.1	-	-7.05
7	96.3	80.8	-	-7.38
8	95.5	85.5	-	-7.49
9	91.2	82.8	-	-7.28
10	94.8	85.2	-	-7.41
11	92.1	80.3	82.7	-7.13

[a] BD energies are indicated bond dissociation energies, which were calculated by a density functional theory (DFT) at the ωB97X-D/6-31+G(d).
[b] O-H radicals (1) mean the hydroxy group with lower substitution number than another one.
[c] O-H radicals (2) mean the hydroxy group with higher substitution number than another one.
[d] E_{HOMO} (HOMO energy levels) were calculated by DFT at the ωB97X-D/6-31+G(d).

In conclusion, the simple phenolic carbazoles **5**-**11** were subjected to the evaluation of antioxidant activities by DPPH radical and $ABTS^+$ radical scavenging assays in comparison with potent antioxidant alkaloids carazostatin (**1**), and carbazomadurins A (**3**) and B (**4**). Among them, the simple phenolic carbazoles **5**-**7**, **9**, and **11** exhibited stronger antioxidant activities than α-tocopherol, and similar antioxidant activities as phenolic carbazole alkaloids **1**, **3**, and **4**. As a result, three simple phenolic carbazoles **7**, **9**, and **11** exhibited the strong antioxidant activities similar to the potent antioxidant alkaloids **3** and **4**. 1-Hydroxycarbazole (**7**), 3-hydroxycarbazole (**9**) and 1,6-dihydroxycarbazole (**11**) are the minimum core structures of alkaloids **1**, **3** and **4**, respectively. Consequently, the existence of one or two hydroxy groups at least at the 1-, 3-, 6-, or 8-positions of the carbazole ring is essential to the iminoquinone form. By contrast, it is considered that the weak antioxidant activities of *O*-ethylcarazostatin (**2**) and 2-hydroxycarbazole (**8**) cannot be transformed to a suitable iminoquinone form through a radical scavenging process. Furthermore, the antioxidant activity by hydroxy groups in simple phenolic carbazoles **7**-**10** could be correlated with their E_{HOMO} levels, but not their bond dissociation energies. Based on these results, the reducing ability of the phenolic carbazole core could be important role for the ability of carbazole alkaloids **1**, **3**, and **4**.

EXPERIMENTAL

All non-aqueous reactions were carried out under nitrogen in dried glassware, unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin layer chromatography was performed with silica gel $60PF_{254}$ (Merck). Silica gel column chromatography was performed with silica gel 60N (63-210 μm, Kanto Chemical Co., Inc.). All melting points were determined with a Yanagimoto micro melting point apparatus. The ultraviolet (UV) spectra were measured by a Shimadzu UV-2550 spectrophotometer. The proton nuclear magnetic resonance (^{1}H NMR) spectroscopic data were recorded with a JEOL AL-300 at 300 MHz and a JEOL JMN-LA500 at 500 MHz. Chemical shifts are reported relative to Me_4Si (δ = 0.00 ppm). The NMR spectroscopic data were recorded using $CDCl_3$, unless otherwise noted. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). The carbon nuclear magnetic resonance (^{13}C NMR) spectroscopic data were recorded with a JEOL AL-300 at 75 MHz and JEOL JMN-LA500 at 125 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ = 77.0 ppm) and DMSO-d_6 (δ = 39.7 ppm). Infrared spectra were recorded using the attenuated total reflectance (ATR) method with a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and high resolution mass spectra were recorded with JEOL JMS-700 spectrometers by using a direct inlet system.

Synthesis of carbazoles

1,3-Dihydroxy-2-methylcarbazole (5): To a stirred solution of *O*-triflate-carbazole **17**[17] (100 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) was added BBr_3 (85 μL, 0.87 mmol) at -78 °C. After stirring at an ambient temperature for 12 h, the reaction mixture was poured into an ice water. The mixture was extracted with EtOAc. The EtOAc phase was washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was used for the next step without further purification. To a solution of the residue in THF (2 mL) was added $LiAlH_4$ (33.0 mg, 0.87 mmol) at -78 °C. After stirring at rt for 5 h, the reaction mixture was quenched with EtOAc and water. The mixture was filtered off using Celite pad, and then the Celite pad washed with EtOAc. The filtrate was extracted with EtOAc. The EtOAc phase was washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g; EtOAc/hexane, 1/4 v/v) to give the 1,3-dihydroxycarbazole (**5**) (37 mg, 0.17 mmol, 60%) as a dark solid, mp 196-198 °C (EtOAc-hexane). IR (ATR): 3456, 3221 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.16 (s, 3H), 6.97 (s, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 8.76 (br. s, 1H), 8.79 (br. s, 1H), 10.33 (br. s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 9.91, 96.35, 110.18, 111.45, 118.15, 120.01, 120.93, 123.16, 124.73, 124.95, 139.74, 140.64, 149.76. MS (EI): *m/z* 213[M]$^+$. HRMS (EI): calcd. for $C_{13}H_{11}NO_2$ 213.0790; found 213.0754.

General procedure for the synthesis of *N*-phenylanilines

2-Methoxy-*N*-phenylaniline (20a): To a stirred solution of *o*-anisidine (**18a**) (1 g, 8.12 mmol) in dry toluene (10 mL) was added to a solution of bromobenzene (**19a**) (1.27 g, 8.12 mmol), $Pd(OAc)_2$ (73 mg, 0.32 mmol), *rac*-BINAP (202 mg, 0.32 mmol) and K_2CO_3 (1.57 g, 11.37 mmol) at rt, and then the mixture was heated at 140 °C for 12 h. After cooling to an ambient temperature, the mixture was quenched with water. The resulting mixture was extracted with EtOAc. The EtOAc phase was washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g; EtOAc/hexane, 1/19 v/v) to give the 2-methoxy-*N*-phenylaniline (**20a**) (1.60 g, 8.03 mmol, 99%) as a colorless oil. IR (ATR): 3406 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.15 (br. s, 1H), 6.82-6.97 (m, 4H), 7.14-7.17 (m, 2H), 7.25-7.32 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.59, 110.50, 114.65, 118.55, 119.86, 120.78, 121.11, 129.24, 132.96, 142.69, 148.25. MS (EI): *m/z* 199 $[M]^+$. HRMS (EI): calcd. for $C_{13}H_{13}NO$: 199.0997; found 197.0951.

4-Methoxy-*N*-phenylaniline (20b): The same procedure as above was carried out using *p*-anisidine (**18b**) (500 mg, 4.06 mmol), bromobenzene (**19a**) (637 mg, 4.06 mmol), $Pd(OAc)_2$ (36 mg, 0.16 mmol), *rac*-BINAP (101 mg, 0.16 mmol) and K_2CO_3 (786 mg, 5.68 mmol) to give the 4-methoxy-*N*-phenylaniline (**20b**) (670 mg, 3.36 mmol, 83%) as a white solid, mp 105-107 °C (Et_2O-hexane) (Lit.,[30] mp 104-106 °C). IR (ATR): 3386 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 5.54 (br. s, 1H), 6.86-6.97 (m, 5H), 7.10-7.15 (m, 2H), 7.24-7.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.56, 114.64, 115.61, 119.54, 122.18, 129.28, 135.70, 145.14, 155.25. MS (EI): *m/z* 199 $[M]^+$. HRMS (EI): calcd. for $C_{13}H_{13}NO$: 199.0997; found 197.0971.

2-Methoxy-*N*-(4-methoxyphenyl)aniline (20c): The same procedure as above was carried out using *p*-anisidine (**18b**) (500 mg, 4.06 mmol), *o*-bromoanisole (**19b**) (759 mg, 4.06 mmol), $Pd(OAc)_2$ (36 mg, 0.16 mmol), *rac*-BINAP (101 mg, 0.16 mmol) and K_2CO_3 (786 mg, 5.68 mmol) to give the 2-methoxy-*N*-(4-methoxyphenyl)aniline (**20c**) (720 mg, 3.21 mmol, 79%) as a white solid, mp 70-71 °C (Et_2O-hexane) (Lit.,[31] mp 70-71 °C). IR (ATR): 3379 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.91 (s, 3H), 5.98 (br. s, 1H), 6.75-6.91 (m, 5H), 7.05 (dd, *J* = 1.8, 9.0 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.52(×2), 110.16, 112.55, 114.50, 118.50, 120.88, 122.71, 135.00, 135.37, 147.33, 155.25. MS (EI): *m/z* 229 $[M]^+$. HRMS (EI): caclcd. for $C_{14}H_{15}NO_2$: 229.1103; found 229.1112.

General procedure for the synthesis of carbazoles

1-Methoxycarbazole (21a): To a stirred solution of 2-methoxy-*N*-phenylaniline (**20a**) (200 mg, 1.00 mmol) in acetic acid (5 mL) was added to a solution of $Pd(OAc)_2$ (270 mg, 1.21 mmol) at rt, and then the mixture was heated at 130 °C for 12 h. After cooling the reaction to an ambient temperature, the mixture was quenched with water. The resulting mixture was extracted with EtOAc. The EtOAc phase was washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue

was purified by column chromatography (silica gel, 20 g; EtOAc/hexane, 3/97 v/v) to give the 1-methoxycarbazole (**21a**) (120 mg, 0.61 mmol, 61%) as a white solid, mp 71-72 ºC (Et_2O-hexane) (Lit.,[20] mp 70-72 ºC). IR (ATR): 3413 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H), 6.90 (d, *J* = 7.9 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.21-7.27 (m, 1H), 7.39-7.46 (m, 2H), 7.70 (d, *J* = 7.9 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 8.28 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.46, 105.89, 110.89, 112.83, 119.32, 119.70, 120.51, 123.61, 124.29, 125.64, 129.75, 139.14, 145.63. MS (EI): *m/z* 197 $[M]^+$. HRMS (EI): caclcd. for $C_{13}H_{11}NO$: 197.0841; found 199.0817.

3-Methoxycarbazole (21b): The same procedure as above was carried out using 4-methoxy-*N*-phenylaniline (**20b**) (300 mg, 1.51 mmol), $Pd(OAc)_2$ (405 mg, 1.81 mmol) to give the 3-methoxycarbazole (**21b**) (93 mg, 0.47 mmol, 31%) as a white solid, mp 151-153 ºC (EtOAc-hexane) (Lit.,[21] mp 146-148 ºC). IR (ATR): 3421 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.07 (dd, *J* = 2.5, 7.9 Hz, 1H), 7.18-7.24 (m, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.56 (d, *J* = 2.5 Hz, 1H), 7.92 (br. s, 1H), 8.03 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.07, 103.18, 110.72, 111.27, 115.05, 119.04, 120.24, 123.35, 123.79, 125.78, 134.36, 140.27, 153.89. MS (EI): *m/z* 197 $[M]^+$. HRMS (EI): calcd. for $C_{13}H_{11}NO$: 197.0841; found 199.0860.

1,6-Dimethoxycarbazole (21c): The same procedure as above was carried out using 4-methoxy-*N*-(2-methoxyphenyl)aniline (**20c**) ((300 mg, 1.31 mmol), $Pd(OAc)_2$ (352 mg, 1.57 mmol) to give the 1,6-dimethoxycarbazole (**21c**) (147 mg, 0.65 mmol, 49%) as a white solid, mp 120-121 ºC (EtOAc-hexane) (Lit.,[23] mp 118-120 ºC). IR (ATR): 3410 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.01 (s, 3H), 6.89 (d, *J* = 7.9 Hz, 1H), 7.06 (dd, *J* = 2.5, 7.9 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 8.12 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 103.18, 105.74, 111.62, 112.75, 115.08, 119.32, 124.05, 124.27, 130.61, 134.11, 145.75, 153.81. MS (EI): *m/z* 227 $[M]^+$. HRMS (EI): calcd. for $C_{14}H_{13}NO_2$: 227.0946; found 227.0980.

General procedure for the synthesis of hydroxycarbazoles

1-Hydroxycarbazole (7): To a solution of 1-methoxycarbazole (**21a**) (85 mg, 0.43 mmol) in CH_2Cl_2 (2 mL) was added BBr_3 (169 μL, 1.72 mmol) at -78 ºC. After stirring at rt for 5 h, the reaction mixture was poured into ice water. The mixture was extracted with EtOAc. The EtOAc phase was washed with water and brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g; EtOAc/hexane, 1/4 v/v) to give the 1-hydroxycarbazole (**7**) (51 mg, 0.28 mmol, 65%) as a white solid, mp 165-167 ºC ($CHCl_3$) (Lit.,[20] mp 163-165 ºC). IR (ATR): 3429, 3197 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.99 (br. s, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 7.21-7.26 (m, 1H), 7.40-7.48 (m, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 8.24 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.63, 110.94, 113.25, 119.44, 119.68, 120.59, 123.57, 125.34, 125.93, 128.95, 139.41, 141.00. MS (EI): *m/z* 183 $[M]^+$. HRMS (EI): calcd. for $C_{12}H_9NO$: 183.0684;

found 183.0706.

3-Hydroxycarbazole (9): The same procedure as above was carried out using 3-methoxycarbazole (**21b**) (90 mg, 0.46 mmol), BBr_3 (179 µL, 1.83 mmol) to give the 3-hydroxycarbazole (**9**) (50 mg, 0.27 mmol, 60%) as a brown solid, mp 234-236 °C (EtOAc-hexane) (Lit.,[23] mp 260-261 °C). IR (ATR): 3398, 3151 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.87 (dd, *J* = 2.6, 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 7.25-7.32 (m, 2H), 7.37-7.40 (m, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 8.90 (br. s, 1H), 10.85 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 104.83, 110.81, 111.28, 114.99, 117.70, 120.06, 122.27, 123.03, 125.18, 133.74, 140.39, 150.37. MS (EI): *m/z* 183 $[M]^+$. HRMS (EI): calcd. for $C_{12}H_9NO$: 183.0684; found 183.0666.

1,6-Dihydroxycarbazole (11): The same procedure as above was carried out using 1,6-dimethoxycarbazole (**21c**) (147 mg, 0.65 mmol), BBr_3 (253 µL, 2.59 mmol) to give the 1,6-dihydroxycarbazole (**11**) (63 mg, 0.28 mmol, 49%) as a dark soliid, mp 200-202 °C (EtOAc-hexane). IR (ATR): 3413, 3278 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 6.74 (d, *J* = 7.5 Hz, 1H): 6.81-6.88 (m, 2H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 8.84 (br. s, 1H), 9.62 (br. s, 1H), 10.61 (br. s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 105.47, 110.56, 112.12, 112.67, 115.59, 119.57, 124.22, 124.55, 130.75, 134.45, 143.48, 150.50. MS (EI): *m/z* 199 $[M]^+$. HRMS (EI): calcd. for $C_{12}H_9NO_2$: 199.0633; found 199.0627.

Radical scavenging assays

DPPH (047-04051) and ABTS (018-10311) were purchased from Wako Pure Chemical Industries, Ltd. All the data were statistically analyzed with student's test, and the data, whose association was calculated less than 0.01 of *p* score, took significantly difference each other. Inhibition concentrations at which 50% of the radicals were scavenged (IC_{50} values) were calculated to evaluate the antioxidant activity.

DPPH radical scavenging assay:[25] Stock solutions were prepared for DPPH (200 µM) and the test samples (100 µM) in MeOH. All solutions were kept cool and in the dark until use. For each sample different aliquots of the stock solutions were taken and the volume was adjusted to 3 mL in MeOH. The reaction was started by adding 1 mL of 200 µM DPPH stock solution (final DPPH concentration 50 µM). After shaking for 30 min at ambient temperature in the dark, the absorbance was measured at 517 nm in MeOH using a Shimadzu UV-2550 spectrophotometer. DPPH radical scavenging capacity was expressed as µM, the results were expressed as means ± S.E. (n = 3 or higher, and the results of one of at least three similar experiments are shown). DPPH radical scavenging (capacity) (%) = $(A_{control} - A_{sample})/ A_{control}$ x 100%, where $A_{control}$ is the absorbance of the control (DPPH radical without test sample) and A_{sample} is the absorbance of the test sample (DPPH radical with test sample). The control contain all reagents except the scavenger.

$ABTS^+$ radical scavenging assay:[26] The procedure to prepare the $ABTS^+$ radical stock solution was modified slightly.[26] Sufficient amounts of the diammonium salts of ABTS and $K_2S_2O_8$ were dissolved in

5.00 mL H_2O to achieve concentrations of 7.00 and 1.40 mM, respectively. This solution was kept in the dark for at least 16 h to form $ABTS^+$ radical, then diluted to 100 mL with MeOH so that the solution had an absorbance or $A_{control}$ of ~0.80 at 734 nm using a Shimadzu UV-2550 spectrophotometer. Various concentrations of carbazoles were added to $ABTS^+$ radical solution at ambient temperature to reach a stable absorbance ($A_{control}$). Then, the percentage of $ABTS^+$ radical scavenged was calculated as follows. $ABTS^+$ radical scavenging (capacity) (%) = $A_{control} - A_{sample})/ A_{control}$ x 100%, where $A_{control}$ is the absorbance of the control ($ABTS^+$ radical without test sample) and A_{sample} is the absorbance of the test sample ($ABTS^+$ radical with test sample). The control contain all reagents except the scavenger. The concentration-percentage of scavenged $ABTS^+$ radical relationships for each reagent, which were derived from their IC_{50} values, were fitted to a four-parameter logistic equation using a non-linear curve-fitting program (KaleidaGraph; Synergy Software, Reading, PA). Where appropriate, the results were expressed as means ± S.E. (n = 3 or higher, and the results of one of at least three similar experiments are shown).

Bond dissociation (BD) energy and HOMO energy[35]

Carbazoles and their corresponding radicals were calculated by density functional theory (DFT) at ωB97X-D/6-31+G(d). The bond dissociation energies (BD energies) were calculated as the following energies: BD energies = Energy of antioxidant radical + Energy of H radical - Energy of antioxidant.

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