Hydroxamic Acid Derivatives as Anti-melanogenic Agents: The Importance of a Basic Skeleton and Hydroxamic Acid Moiety

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The production of melanin is mainly regulated by melanogenic enzyme tyrosinase. Tyrosinase[1] is bifunctional enzyme, which catalyzes the hydroxylation of L-tyrosine to L-dopa and enhances the oxidation of L-dopa to dopaquinone. Therefore, inhibitors of tyrosinase should be useful as therapeutic agents for the treatment of melanin hyperpigmentation. Many metal ion chelators, for example, kojic acid,[2] flavonol,[3] benzaldoxime,[4] *N*-nitrosohydroxyl amine,[5] have been developed as tyrosinase inhibitors. Their inhibiting activities come from binding with copper in active site of tyrosinase. Hydroxamic acids[6] were well known as metal ion chelators. However, studies on hydroxamic acids as tyrosinase inhibitors and depigmenting agents were rare.[7] Recently we reported hydroxamic acid derivative **1**[7b] containing adamantane moiety strongly inhibits melanin synthesis (Fig. 1). However, compound **2** which is precursor of compound **1** showed no inhibitory activity. Moreover, salicylhydroxamic acid exhibited no inhibitory activity in tested concentration. These result revealed that hydroxamic acid moiety as well as the rest part play an important role for the anti-melanogenic activity.

To gain more insight into an anti-melanogenic activity of hydroxamic acid, several hydroxamic acid derivatives were synthesized and evaluated their inhibitory effects on tyrosinase and depigmenting effects in a murine melanocyte cell line were evaluated.

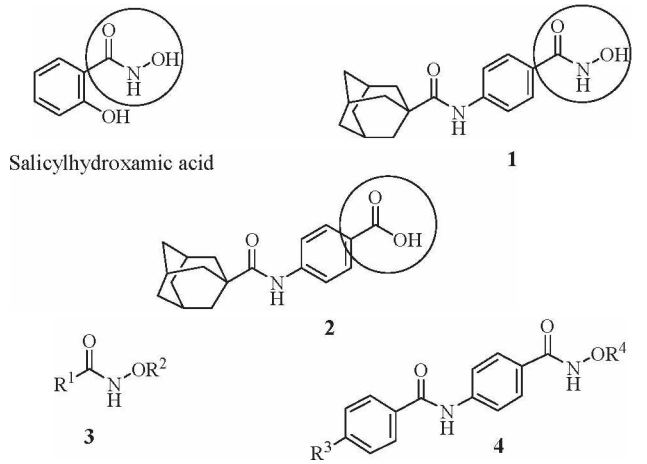


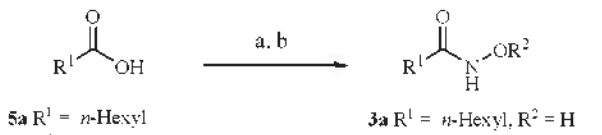
Figure 1. Structure of hydroxamic acid derivatives

Results and Discussion

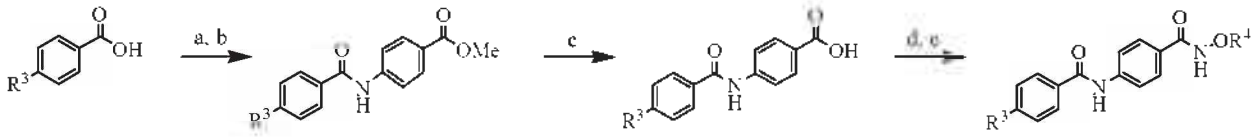
The synthetic pathways of hydroxamic acid derivatives are shown in scheme 1 and 2.

The acids **5a-5d** were reacted with ethylchloroformate and *N*-methylmorpholine in THF as solvent to convert the carboxylic acids to an anhydrides.[8] The anhydrides were immediately reacted NH_2OH·HCl or NH_2OMe·HCl to produce the corresponding hydroxamic acid derivatives **3a-3d** or methyl protected hydroxamic acids **3e** and **3f** (Scheme 1). 4-Substituted benzoic acids (**5c**, **5e**, **5f**, **5g** and **5h**) were refluxed in thionyl chloride to afford acid chlorides. These acid chlorides were reacted immediately with methyl 4-aminobenzoate in pyridine to produce corresponding amide derivatives (**6a-6e**). The ester groups were hydrolyzed under standard condition (NaOH, ethanol) to produce corresponding acids (**7a-7e**). The acids were reacted with ethylchloroformate and *N*-methylmorpholine in THF to convert the carboxylic acids to anhydrides. The anhydrides were reacted immediately with NH_2OH·HCl or NH_2OMe·HCl to produce the corresponding hydroxamic acid derivatives (**4a-4e**) or methyl protected hydroxamic acids **4f** and **4g** (Scheme 2).

The inhibitory activities of our synthetic hydroxamic acid derivatives on mushroom tyrosinase was initially investigated and compared with those of kojic acid and hydroquinone which are well known tyrosinase inhibitors. Acetohydroxamic acid[9] showed no inhibitory activity against tyrosinase. When methyl group was replaced by normal hexyl and cyclohexyl groups, mild activities were shown (IC_{50} = 39.99 μM and IC_{50} = 17.89 μM). Surprisingly, when methyl group was replaced by phenyl group, the resulting compound **3c** showed potent inhibition activity (IC_{50} = 0.28 μM). Naphthyl derivative **3d** showed more potent inhibitory activity (IC_{50} = 0.10 μM). However, when the NHOH group of **3c** and **3d** were methyla-



Scheme 1. Reaction conditions; (a) ethylchloroformate, *N*-methylmorpholine, THF; (b) NH_2OH·HCl or NH_2OMe·HCl, Et_3N, DMF



5c R^3 = H
5e R^3 = Methyl
5f R^3 = Ethyl
5g R^3 = *n*-Propyl
5h R^3 = *n*-Butyl

6a R^3 = H
6b R^3 = Methyl
6c R^3 = Ethyl
6d R^3 = *n*-Propyl
6e R^3 = *n*-Butyl

7a R^3 = H
7b R^3 = Methyl
7c R^3 = Ethyl
7d R^3 = *n*-Propyl
7e R^3 = *n*-Butyl

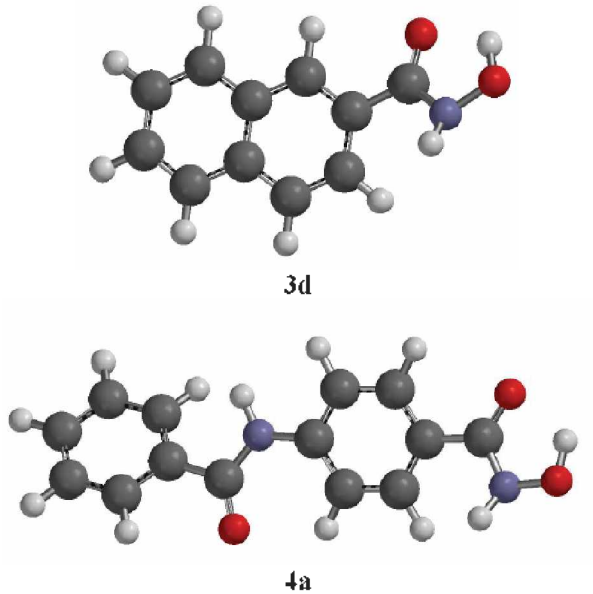
4a R^3 = H, R^4 = H
4b R^3 = Methyl, R^4 = H
4c R^3 = Ethyl, R^4 = H
4d R^3 = *n*-Propyl, R^4 = H
4e R^3 = *n*-Butyl, R^4 = H
4f R^3 = *n*-Propyl, R^4 = Me
4g R^3 = *n*-Butyl, R^4 = Me

Scheme 2. Reaction conditions; (a) $SOCl_2$, reflux; (b) methyl 4-aminobenzoate, pyridine; (c) NaOH, EtOH; (d) ethylchloroformate, *N*-methylmorpholine, THF; (e) NH_2OH·HCl or NH_2OMe·HCl, Et_3N, DMF

ted on the hydroxyl group, their inhibitory activities were completely lost. These results indicated that planar hydrophobic group and hydroxamic acid moiety are necessary for the inhibition of tyrosinase. In a next set of experiments, we changed planar naphthyl group of **3d** into more bulky and a little flexible structure (Fig. 2).

Interestingly, 4-(phenylcarboxamido)-*N*-hydroxybenzamide **4a** containing two phenyl groups connected with amide linkage showed decreasing activity (IC_{50} = 2.29 μM). When methyl group was attached to the *para* position of phenylcarboxamido group, the resulting compound **4b** showed decreasing activity (IC_{50} = 4.38 μM). Decreases in the activities were detected along with an increasing chain length such as ethyl, *n*-propyl and *n*-butyl (Table 1, **4c-4e**). In tyrosinase assay, planar structure is important factor for the inhibitory activity of hydroxamic acid. Without planar structures such as phenyl and naphthyl, hydroxamic acid moiety may not bind tightly to the active site or other essential part of tyrosinase. However, more bulky groups than naphthyl also interrupted binding of hydoxamic acid to tyrosinase.

After testing tyrosinase inhibitory activity, we evaluated the inhibitory potency against the melanin formation. The synthesized derivatives were assayed for their cytotoxicities and inhibitory effects in a murine melanocytes cell line (Melan-a). The results obtained from these experiments revealed that acetohydroxamic acid showed no anti-melanogenic acitivity (IC_{50} = > 50 μM). In agreement with the results on tyrosinase activity, compounds **3e**, **3f**, **4f** and **4g** containing NHOMe group showed no inhibitory activities. All other compounds presented inhibitory activities. However, anti-melanogenic activities in a murine melanocytes cell line are a little different from inhibitory potentials of tyrosinase. Compound **3d** containing naphthyl group, which exhibited the highest activity in tyrosinase inhibition, showed moderate activity (IC_{50} = 26.16 μM). More bulky and a little flexible hydroxamic acid, 4-(phenylcarboxamido)-*N*-hydroxybenzamide **4a**, showed more



3d

4a

Figure 2. Energy minimized structure of **3d** and **4a**. Calculations were carried out using a Spartan 04 Windows. Global minimum-energy structures were obtained by molecular-mechanics computation and further refined by DFT computation (B3LYP at the 6-31G* level).

Table 1. Anti-melanogenic activities of hydroxamic acid derivatives

Compounds	Tyrosinase IC_{50}[a]	Melanin Inhibition IC_{50}[a]	% Survival of melan-a cell
Acetohydroxamic acid	> 200 μM	> 50 μM	93.77 (50 μM)
3a	39.99 μM	15.72 μM	105.27 (30 μM)
3b	17.89 μM	42.31 μM	98.22 (50 μM)
3c	0.28 μM	45.51 μM	96.63 (50 μM)
3d	0.10 μM	26.16 μM	98.34 (30 μM)
3e	> 200 μM	> 50 μM	97.23 (50 μM)
3f	> 200 μM	> 50 μM	94.25 (50 μM)
4a	2.29 μM	4.53 μM	96.30 (30 μM)
4b	4.38 μM	4.01 μM	100.21 (30 μM)
4c	7.31 μM	2.93 μM	92.10 (30 μM)
4d	12.51 μM	1.24 μM	97.38 (30 μM)
4e	27.41 μM	1.69 μM	95.31 (30 μM)
4f	> 200 μM	> 50 μM	103.64 (50 μM)
4g	> 200 μM	> 50 μM	99.23 (50 μM)
Kojic acid	25.85 μM	1.10 mM	97.12 (3.0 mM)
Hydroquinone	9.81 μM	3.97 μM	87.27 (10 μM)

[a]Values were determined from logarithmic concentration-inhibition curves and are given as means of three experiments.

potent activity (IC_{50} = 4.54 μM). In contrast to the result of tyrosinase, increasing inhibitory activities were detected along with increasing chain length such as methyl, ethyl and *n*-propyl. Interestingly *n*-butyl group did not show any significant increase in the inhibitory activity. Among all derivatives, compound **4d** showed stronger inhibitory activity (IC_{50} = 1.24 μM). These differences can be explained by two hypotheses. One is the difference of amino acid sequence between mushroom tyrosinase and murine tyrosinase.[10] The other is different physical properties of hydroxamic acid derivatives for cell penetration.[11] In case of cell based assay, synthetic derivatives must penetrate into the cell membrane to show inhibitory activity.

In conclusion, new hydroxamic acid derivatives **3a-3f** and **4a-4g**, containing various hydrophobic characters, were synthesized and evaluated as potent inhibitors on tyrosinase activity and melanin formation in melan-a cells. The hydroxamic acid moiety and basic skeleton having proper hydrophobic character are very important for anti-melanogenic activity. Among all compounds tested, compound **4d** showed stronger inhibitory activity (IC_{50} = 1.24 μM) in cell based assay. Its activity was more potent than that of hydroquinone (IC_{50} = 3.97 μM) which is known as a most powerful anti-melanogenic agent.

Experimental Section

***N*-Hydroxyhexanamide (3a).** To a solution of hexanoic acid **5a** (1.0 g, 8.6 mmol) and *N*-methylmorpholine (960 mg, 9.5 mmol) in THF (15 ml) at 0 °C were added ethylchloroformate (1.0 g, 9.5 mmol) dropwise and the mixture was stirred for 30 min. The solid was filtered off and the filtrate was added to the solution of hydroxylamine hydrochloride (894 mg, 12.9 mmol) and Et_3N (1.3 g, 12.9 mmol) in DMF (20 ml) for 10 min. The reaction mixture was stirred for 30 min at 25 °C. DMF was evaporated *in vacuo*. The residue was extracted with ethyl acetate (80 mL), washed with water. The solvent was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by silica gel column chromatography to *N*-hydroxyhexanamide **3a** (936 mg) in 83 % yields.

^{1}H NMR (300MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.68 (s, 1H), 1.95 (t, 2H, *J* = 7.2 Hz), 1.47 (m, 2H), 1.25 (m, 4H), 0.87 (t, 3H, *J* = 7.2 Hz). IR ν_{max} (KBr) 3253, 2954, 1622 cm^{-1}. FABMS, *m/e* 132 $[M+1]^+$.

***N*-Hydroxycyclohexanecarboxamide (3b).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.64 (s, 1H), 1.94 (m, 1H), 1.02-1.80 (m, 10H). IR ν_{max} (KBr) 3190, 2921, 1625 cm^{-1}. FABMS, *m/e* 144 $[M+1]^+$.

***N*-Hydroxybenzamide (3c).** ^{1}H NMR (300MHz, DMSO-d_6) δ 11.23 (s, 1H), 9.05 (s, 1H), 7.74 (m, 2H), 7.45 (m, 3H). IR ν_{max} (KBr) 3187, 3034, 1625 cm^{-1}. FABMS, *m/e* 138 $[M+1]^-$.

***N*-Hydroxy-2-naphthamide (3d).** ^{1}H NMR (300MHz, DMSO-d_6) δ 11.37 (s, 1H), 9.14 (s, 1H), 8.36 (s, 1H), 8.00 (m, 3H), 7.82 (d, 1H, *J* = 8.4 Hz), 7.60 (m, 2H). IR ν_{max} (KBr) 3188, 3034, 1625 cm^{-1}. FABMS, *m/e* 188 $[M+1]^+$.

***N*-Methoxybenzamide (3e).** ^{1}H NMR (300MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.76 (m, 2H), 7.49 (m, 3H), 3.71 (s, 3H). IR ν_{max} (KBr) 3184, 3033, 1625 cm^{-1}. FABMS, *m/e* 152 $[M+1]^-$.

***N*-Methoxy-2-naphthamide (3f).** ^{1}H NMR (300MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.34 (s, 1H), 8.01 (m, 3H), 7.78 (d, 1H, *J* = 8.4 Hz), 7.62 (m, 2H), 3.73 (s, 3H). IR ν_{max} (KBr) 3142, 3006, 1623 cm^{-1}. FABMS, *m/e* 202 $[M+1]^+$.

Preparation of methyl 4-(phenylcarbamoyl)benzoate (6a). Benzoic acid **5c** (6.1 g, 0.05 mol) was dissolved in 100 mL of $SOCl_2$ at 0 °C and refluxed for 1 h. The $SOCl_2$ was removed *in vacuo*, and crude acid chloride was dissolved in CH_2Cl_2 (50 mL). To a solution of methyl 4-aminobenzoate (7.5 g, 0.05 mol) in pyridine (100 mL) was added prepared acid chloride solution. The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was extracted with ethyl acetate (250 mL), washed with water. The organic layer was dried with anhydrous $MgSO_4$ and concentrated to give a crude product. The resultant was purified by crystallization from dichloromethane-hexane to give a methyl 4-(phenylcarbamoyl)benzoate **6a** (10.3 g) in 81% yields.

^{1}H NMR (300MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.94 (d, 2H, *J* = 8.7 Hz), 7.85 (m, 2H), 7.72 (d, 2H, *J* = 8.7 Hz), 7.54 (m, 3H), 3.46 (s, 3H). FABMS, *m/e* 256 $[M+1]^+$.

Preparation of 4-(phenylcarbamoyl)benzoic acid (7a). Methyl 4-(phenylcarbamoyl)benzoate **6a** (7.6 g, 0.03 mol) was dissolved in KOH (0.5 M, 300 ml) solution and heated to 50 °C. After obtaining clear solution, the clear solution was acidified with HCl (1M) solution and resulting precipitate was gathered by filteration to give 4-(phenylcarbamoyl)benzoic acid **7a** (8.3 g) in 87 % yields.

^{1}H NMR (300MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.92 (d, 2H, *J* = 8.7 Hz), 7.83 (m, 2H), 7.71 (d, 2H, *J* = 8.7 Hz), 7.52 (m, 3H). FABMS, *m/e* 242 $[M+1]^+$.

Prepation of 4-(phenylcarboxamido)-*N*-hydroxybenzamide (4a). To a solution of 4-(phenylcarbamoyl)benzoic acid **7a** (1000 mg, 4.1 mmol) and *N*-methylmorpholine (456 mg, 4.5 mmol) in THF (10 ml) at 0 °C were added ethylchloroformate (488 mg, 4.5 mmol) dropwise and the mixture was stirred for 30 min. The solid was filtered off and the filtrate was added to the solution of hydroxylamine hydrochloride (427 mg, 6.1 mmol) and Et_3N (617 mg, 6.1 mmol) in DMF (10 ml) for 10 min. The reaction mixture was stirred for 30 min at 25 °C. DMF was evaporated *in vacuo*. The residue was extracted with ethyl acetate (50 mL), washed with water. The solvent was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by silica gel column chromatography to afford 4-(phenylcarboxamido)-*N*-hydroxybenzamide **4a** (840 mg) in 81 % yields. ^{1}H NMR (300MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.44 (s, 1H), 9.01 (s, 1H), 7.79 (d, 2H, *J* = 8.4 Hz), 7.86 (d, 2H, *J* = 8.7 Hz), 7.74 (d, 2H, *J* = 8.7 Hz), 7.54 (m, 3H). IR ν_{max} (KBr) 3187, 3034, 1650, 1623 cm^{-1}. FABMS, *m/e* 257 $[M+1]^+$.

4-((4-Methylphenyl)carboxamido)-*N*-hydroxybenzamide (4b). ^{1}H NMR (300MHz, DMSO-d_6) δ 11.15 (s, 1H), 10.37 (s, 1H), 8.99(s, 1H), 7.87 (m, 4H), 7.73 (d, 2H, *J* = 8.7 Hz), 7.34 (d, 2H, *J* = 8.7 Hz), 2.39 (s, 3H). IR ν_{max} (KBr) 3255, 3033, 1654, 1620 cm^{-1}. FABMS, *m/e* 271 $[M+1]^+$.

4-((4-Ethylphenyl)carboxamido)-*N*-hydroxybenzamide (4c). ^{1}H NMR (300MHz, DMSO-d_6) δ 11.15 (s, 1H), 10.37 (s, 1H), 8.99 (s, 1H), 7.88 (m, 4H), 7.74 (d, 2H, *J* = 8.7 Hz), 7.36 (d, 2H, *J* = 8.7 Hz), 2.70 (q, 2H, *J* = 7.5 Hz), 1.21 (t, 3H, *J* =

7.5 Hz). IR ν_{max} (KBr) 3188, 3050, 1654, 1621 cm^{-1}. FABMS, *m/e* 285 $[M+1]^-$.

4-((4-*n*-Propylphenyl)carboxamido)-*N*-hydroxybenzamide (4d). ^{1}H NMR (300MHz, DMSO-d_6) δ 11.15 (s, 1H), 10.37 (s, 1H), 8.98 (s, 1H), 7.83 (m, 4H), 7.73 (d, 2H, J = 8.7 Hz), 7.37 (d, 2H, J = 8.7 Hz), 2.66 (t, 2H, J = 7.5 Hz), 1.66 (m, 2H), 0.93 (t, 3H, J = 7.5 Hz). IR ν_{max} (KBr) 3200, 3039, 2911, 1655, 1621 cm^{-1}. FABMS, *m/e* 299 $[M+1]^+$.

4-((4-*n*-Butylphenyl)carboxamido)-*N*-hydroxybenzamide (4e). ^{1}H NMR (300MHz, DMSO-d_6) δ 11.15 (s, 1H), 10.38 (s, 1H), 9.00 (s, 1H), 7.89 (m, 4H), 7.76 (d, 2H, J = 8.7 Hz), 7.37 (d, 2H, J = 8.7 Hz), 2.66 (t, 2H, J = 7.5 Hz), 1.58 (m, 2H), 1.32 (m, 2H), 0.90 (t, 3H, J = 7.5 Hz). IR ν_{max} (KBr) 3187, 3034, 2910, 1650, 1623 cm^{-1}. FABMS, *m/e* 313 $[M+1]^+$.

4-((4-*n*-Propylphenyl)carboxamido)-*N*-methoxybenzamide (4f). ^{1}H NMR (300MHz, DMSO-d_6) δ 11.60 (s, 1H), 10.28 (s, 1H), 7.84 (m, 4H), 7.72 (d, 2H, J = 8.7 Hz), 7.34 (d, 2H, J = 8.7 Hz), 3.63 (s, 3H), 2.65 (t, 2H, J = 7.5 Hz), 1.64 (m, 2H), 0.93 (t, 3H, J = 7.2 Hz). IR ν_{max} (KBr) 3201, 3035, 2910, 1652, 1624 cm^{-1}. FABMS, *m/e* 313 $[M+1]^+$.

4-((4-*n*-Butylphenyl)carboxamido)-*N*-methoxybenzamide (4g). ^{1}H NMR (300MHz, DMSO-d_6) δ 11.60 (s, 1H), 10.28 (s, 1H), 7.85 (m, 4H), 7.75 (d, 2H, J = 8.7 Hz), 7.36 (d, 2H, J = 8.7 Hz), 3.62 (s, 3H), 2.65 (t, 2H, J = 7.5 Hz), 1.58 (m, 2H), 1.31 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz). IR ν_{max} (KBr) 3190, 3031, 2914, 1654, 1620 cm^{-1}. FABMS, *m/e* 327 $[M+1]^-$.

Mushroom tyrosinase assay. Mushroom tyrosinase, L-tyrosine were purchased from Sigma Chemical. The reaction mixture for mushroom tyrosinase activity consisted of 150 μl of 0.1 M phosphate buffer (pH 6.5), 3 μl of sample solution, 8 μl of mushroom tyrosinase (2,100 unit/ml, 0.05 M phosphate buffer at pH 6.5), and 36 μl of 1.5 mM L-tyrosine. Tyrosinase activity was determined by reading the optical density at 490 nm on a microplate reader (Bio-Rad 3550, Richnmond, CA, U.S.A.) after incubation for 20 min at 37 °C. The inhibitory activity of the sample was expressed as the concentration that inhibits 50% of the enzyme activity (IC_{50}).

Cell culture. Murine melan-a melanocytes were originally derived from C57BL/6 J (black, a/a) mice, a kind gift from Prof. Dorothy C. Bennett (St. George's Hospital, London, U.K.). Melan-a cells were cultured in RPMI 1640 medium containing 10 % heat-inactivated FBS, 100 units/ml of penicillin, 100 μg/ml of streptomycin, and 200 nM of phorbol 12-myristate 13-acetate (TPA) at 37 °C in 10 % CO_2. The culture medium was changed twice every week, and the cells were subcultured once a week.

Measurements of cell viability. To evaluate the effects of hydroxamic acid derivatives on cell viability, the percentages of viable melan-a cells were determined using a modified crystal violet assay.[12] After removing the medium from each well, the cells were washed with PBS and stained with 0.1 % crystal violet in 10 % ethanol for 5 min at room temperature. The cells were then rinsed four times with distilled water, and crystal violet retained by adherent cells was extracted with 95 % ethanol at room temperature for 10 min. Crystal violet absorption was measured at 590 nm (Molecular Devices Co., Sunnyvale, CA, U.S.A.).

Measurements of melanin content. The melanin content was measured using the method reported by Hosoi et al. with a slight modification.[13] The cells (2×10^5 cells/ml) were seeded into 24-well plates and the test compounds were added in triplicate. The medium was changed daily and after 4 d of culture, the cells were lysed with 1 ml of 1 N NaOH. Then 200 μL of each crude cell extract was transferred into 96-well plates. The relative melanin content was measured at 400 nm with a microplate reader (Molecular Devices).

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