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Adamantyl *N*-benzylbenzamide: New series of depigmentation agents with tyrosinase inhibitory activity

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ABSTRACT

A new series of polyhydroxylated *N*-benzylbenzamide derivatives containing an adamantyl moiety has been synthesized, and the depigmenting and tyrosinase inhibitory activities of the molecules were evaluated. The lipophilic character of the adamantyl moiety appeared to confer greater depigmentation power on the benzamide derivatives as compared to those lacking adamantyl substitution. Molecular modeling was applied in order to elucidate the interactions between ligands and tyrosinase that led to inhibition.

The role of melanin is to protect the skin from the harmful effects of ultraviolet light and scavenging free radicals. In addition, the quantity of melanin in keratinocytes is an important determinant of skin color in humans. Excess production of melanins from melanocytes can lead to hyperpigmentation, which can manifest as melasma, freckles, and dark-spots.[1,2]

Melanin synthesis is accelerated by external stimuli such as ultraviolet light and inflammation, and therefore melanin formation can be controlled by reducing harmful stimuli and blocking signal transmission. However, there is a third means of control through the suppression of tyrosinase, a key enzyme in melanin biosynthesis.[3–5]

Tyrosinase inhibition is the main strategy for treating hyperpigmentation, and is widely applied to not only the treatment of dermatological disorders but also to the preservation of food color by the reduction of browning.[6,7] Thus, there is considerable interest in the development of new tyrosinase inhibitors with improved potency for use as depigmenting agents. However, it has proven difficult to develop tyrosinase inhibitors that have sufficient clinical efficacy as well as in vitro efficacy. Indeed, most known depigmenting agents currently in use have unsatisfactory efficacy in humans, in addition to low stability, and skin irritation (Fig. 1).[7,8]

In order to obtain a significantly more effective agent, we sought to develop a small molecule possessing both anti-melanogenic activity and tyrosinase inhibition, which we anticipate will possess substantial clinical efficacy in skin depigmentation.

There are many reports on polyhydroxy tyrosinase inhibitors from various natural and synthetic sources, such as flavonoids, aurones, stilbenes, benzyl benzoates, *N*-benzylbenzamides, chalcones, biaryls, etc.[4,9–14] Among natural sources, the extract of *Broussonetia kazinoki* contains a 1,3-diphenylpropane skeleton which gives rise to kazinols and broussonins, which have a 1,3-diaryl skeleton with polyhydroxyl and prenyl substituents.[15]

In our ongoing research into depigmenting agents, we took notice of polyhydroxy compounds containing an adamantane moiety and became interested in the influence of this group on melanin formation.[16–18] Consequently, we used a kazinol mimic as our synthetic starting point and proceeded by exchanging the C3-alkyl chain for an alkylamide and introducing dihydroxyl and adamantyl moieties in place of a prenyl group.

The adamantyl substituted benzamide derivatives were synthesized via the route outlined in Scheme 1. First, alkylation of hydroxybenzoic acid **1** under acidic conditions gave adamantyl derivatives **2** in good yield. Then intermediates **2** were subjected to *N*-hydroxysuccinimide (HOSu)/DCC coupling conditions, followed by reaction with 2,4-dihydroxybenzylamine HCl salt to afford the desired *N*-benzylbenzamides **3**. A detailed procedure for the synthesis of 5-adamantan-1-yl-*N*-(2,4-dihydroxy-benzyl)-2,4-dihydroxy-benzamide (**3a**) is presented in Ref. 19 in order to illustrate an application of Scheme 1.

The benzamide analogues were tested for their ability to inhibit melanogenesis in a murine melanoma cell line (B16) and evaluated for mushroom tyrosinase inhibition activity.

The benzylbenzamides **3d–f** lacking an adamantyl group on the A ring displayed submicromolar tyrosinase inhibition, which

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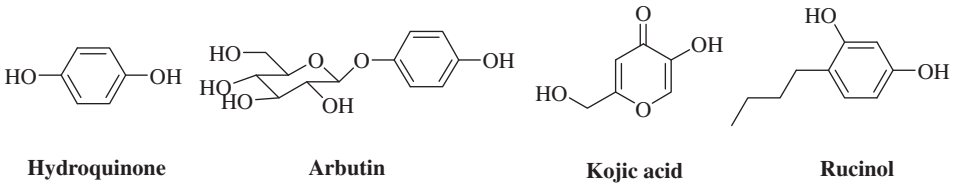


Figure 1. Structure of known depigmenting agents.

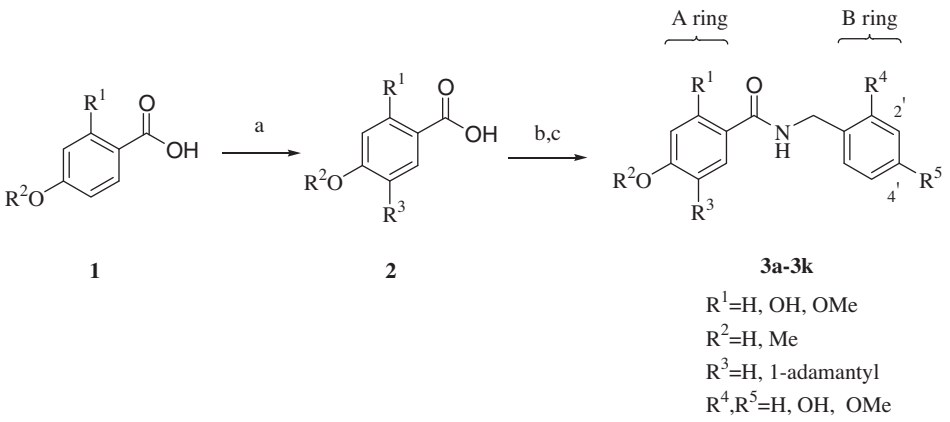
makes them over 30 times more potent than kojic acid. Remarkably, masking the free OH with CH_3 on ring A, as in compounds **3e** and **3f**, did not diminish their inhibitory activities (Table 1). In the presence of the sterically hindered adamantyl group on ring A, compounds **3a–c** exhibited lightly lower, but still potent, tyrosinase inhibitions. Furthermore, compounds **3g** and **3h** lacking the 2-OH substituent on ring A, showed activities similar to those of compounds **3a–f**. Despite the presence of the substituted 2,4-resorcinol structure on ring A, which resembles the potent tyrosinase inhibitor rucinol, the adamantyl substitution did not influence the tyrosinase inhibition activity. Therefore, based on these SAR studies, the pharmacophore for this benzylbenzamide series appeared to be contained in ring B. When substituents on ring B were changed from 2′,4′-dihydroxy to 2′,4′-dimethoxy, 2′-hydroxy, and 4′-hydroxy, respectively, compounds **3i–k**, lost their tyrosinase inhibitory activities (<5% at 1 μM), indicating that the position and numbers of free hydroxyl groups on ring B are critical for inhibitory activity in this benzylbenzamide series.

In order to understand the binding modes of compounds **3a** and **3d** with mushroom tyrosinase, docking studies were performed using Surflex-Dock[20] v.2.51 in the SYBYL-X 1.2 program (TRIPOS, L.P. St. Louis, MO, USA). The crystal structure of the oxy form of tyrosinase was obtained from the Protein Data Bank (PDB code 1wx2).[21] The caddie protein (ORF378) and water molecules were removed. Hydrogen atoms were added to the enzyme using SYBYL. The docked conformations with the highest docking scores were selected for further analysis of binding modes. The binding modes of compounds **3a** and **3d** were quite similar to that of the superimposed L-tyrosine from Tyr98 of the caddie protein (ORF378) as shown in Figure 2.

For both docked ligands, interactions between the oxygen atoms of the ligands and Cu(B) were found to interact within 2.6 Å. Moreover, both docked conformations formed an H-bonding interaction with peroxide in the active site. In the binding pocket, H-bonding interactions were also formed between each docked ligands and residues Asn191, and Ala202. Table 2 shows that compound **3d** has a stronger contribution from polar interactions than compound **3a**. Compound **3a**, conversely, has a greater contribution from hydrophobic interactions as compared with compound **3d**, making compound **3a** less soluble. The docking scores agreed well with the observed in vitro data in error bound analysis. In addition, a π–π interaction between each ligand and His194 was found, and the position of the aromatic ring was nearly identical to that of superimposed L-tyrosine. However, the binding mode of compound **3i** was significantly different from the others, as shown in Figure 2. It completely lost the important interaction between the methoxy groups of the ligand and Cu(B), and the H-bonding interaction with peroxide in the active site. The docking analysis indicated that it was bound just outside of the binding pocket, on the surface of the protein. This binding mode explains the loss of tyrosinase inhibition activity in compound **3i**.

Depigmenting activities for compounds **3d–f** showed moderate to good melanogenesis inhibition (IC_{50} = 10–30 μM), which are similar to that of rucinol (IC_{50} = ~20 μM). Compared with the results of the tyrosinase inhibition study, the melanogenesis inhibition capacity of these compounds appeared to be relatively weak in the cell-based environments. To improve depigmenting activity of the compounds, we sought to change their physicochemical properties, particularly hydrophobicity, which seemed to be crucial to biological activity in the cell.

Our previous research indicated that the adamantyl group of the diphenolic compound has some influence on melanin formation.[17] Therefore, we selected this highly lipophilic group as a means in increase hydrophobicity in ring A instead of *t*-butyl or the naturally abundant prenyl group. Introduction of a 5-adamantyl group to compounds **3d–f** changed the lipophilicity parameter ($\Delta C\log P$ = 4–5), and as a result, the melanogenesis inhibition of compounds **3a–c** increased in a manner corresponding to the increase of $C\log P$.[22] Compounds **3b** and **3c** exhibited potent depigmenting activities with IC_{50} = 1.8 and 1.1 μM, respectively, making these compounds about 200 times more potent than kojic acid. Although compound **3a** showed 90% inhibition at 3 μM, its cytotoxicity was also quite high (62% viability at 10 μM, 86% viability at 1 μM), and unfortunately its inhibitory activity was less than



Scheme 1. General reagents and conditions: (a) 1-Adamantanol, c-H_2SO_4/AcOH, CH_2Cl_2, rt; (b) HOSu, DCC, dioxane, rt; (c) Amine (salt), $NaHCO_3$, H_2O/50–60 °C, 2–4 h.

Table 1
Tyrosinase inhibitory and anti-melanogenic activity of polyphenolic benzamides **3a–k**

Compounds	R^1	R^2	R^3	R^4	R^5	Tyrosinase inhibition[a] (IC_{50}, μM)	Melanogenesis inhibition[a] (IC_{50}, μM)	Cytotoxicity [viability (%@ 10 μM,72 h)]
3a	OH	H	Ad[b]	OH	OH	1.1	<5%[c]	62 ± 0.02{86 ± 6.3}[d]
3b	OH	Me	Ad	OH	OH	0.8	1.8	100 ± 18
3c	OMe	Me	Ad	OH	OH	0.9	1.1	95 ± 7
3d	OH	H	H	OH	OH	0.9	26.7	100 ± 2
3e	OH	Me	H	OH	OH	0.3	27.6	93 ± 5.3
3f	OMe	Me	H	OH	OH	0.4	14.2	100 ± 2
3g	H	H	Ad	OH	OH	0.9	<5%[c]	41 ± 0.04{99 ± 2.1}[d]
3h	H	Me	Ad	OH	OH	1.4	<5%[c]	44 ± 0.2{100 ± 3.2}[d]
3i	OH	H	Ad	OMe	OMe	<5%[c]	—[e]	—
3j	OH	H	Ad	OH	H	<5%[c]	—	—
3k	OH	H	Ad	H	OH	<5%[c]	—	—
Kojic acid						32	500	100 ± 3.4

[a] Value is the mean of at least two measurements.
[b] 1-Adamantyl.
[c] % inhibition at 1 μM.
[d] Figures in parentheses refer to viability % at 1 μM.
[e] Not tested.

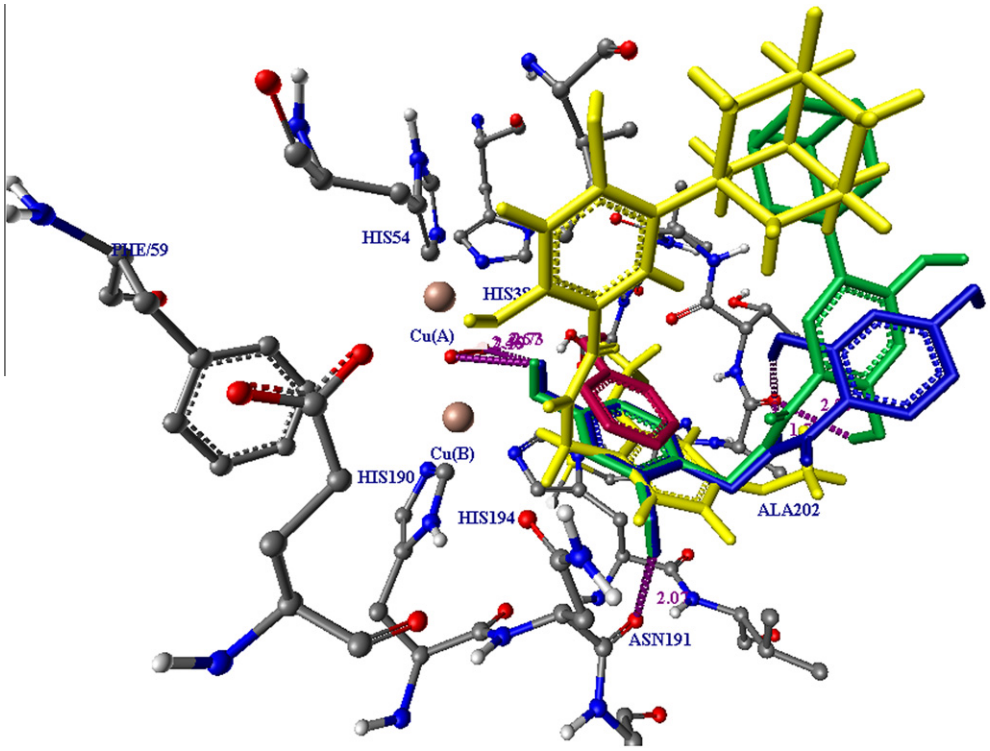


Figure 2. Docking positions of compounds **3a** (green), **3d** (blue), and **3i** (yellow) with superimposed L-tyrosine (purple) from Tyr98 of the caddie protein (ORF378).

Table 2
Docking scores and the contributions of polar interactions

Compounds	Surflex-Dock score[a]	Polar contribution
3a	6.98	2.25
3d	5.81	3.15
3i	4.02	1.02

[a] Surflex-Dock score represents the binding affinity in units of $-\log K_d$.

5% at a 1 μM concentration. In compounds **3a**, **3g** and **3h**, the 5-adamantyl group appeared to influence cell viability, and the absence of the 2-OH on ring A seemed to negatively affect the anti-melanogenesis activity when the 2,4-OH on B ring is present.

Altogether, greater lipophilicity of the molecule improved its depigmenting effect in these compounds, but also seemed to cause a decrease in cell viability.

In summary, we prepared a series of potent anti-melanogenic agents while preserving tyrosinase inhibitory activity by modulating the physicochemical properties of the molecules. We determined that modulation of molecular lipophilicity by modification via hydrophobic functional groups is important for enhanced depigmenting activity without a concomitant increase in cytotoxicity, and the selection of the position and numbers of OH is critical for tyrosinase inhibitory activity. Among these analogues, compound **3c** was selected for in vivo efficacy evaluation and we are investigating further modification of this scaffold as depigmenting agent for practical use.

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19. Selected compounds were prepared as follows.
    5-Adamantan-1-yl-*N*-(2,4-dihydroxy-benzyl)-2,4-dihydroxy-benzamide (**3a**): 5-Adamantan-1-yl-2,4-dihydroxybenzoic acid (0.606 g, 2.1 mmol), *N*-hydroxy-succinimide (0.24 g, 2.1 mmol), and *N*,*N*′-dicyclohexyl-carbodiimide (0.433 g, 2.1 mmol) were dissolved in 1,4-dioxane (5 mL) under nitrogen atmosphere. The solution was stirred at ambient temperature for 12 h. The precipitate was filtered off and the filtrate added to a solution of 2,4-dihydroxybenzylamine HCl salt (0.406 g, 2.3 mmol) and $NaHCO_3$ (0.177 g, 2.3 mmol) in H_2O (2 mL). The reaction mixture was heated to 60 °C under nitrogen and stirred for 2 h. After cooling to room temperature, 10% HCl solution was added and the mixture extracted with EtOAc. The combined organic layers were washed with brine, dried under anhydrous $MgSO_4$, and filtered, and the filtrate was evaporated in vacuo. The crude product was purified by column chromatography (hexanes–EtOAc = 2:1) to yield compound **3a** as a white solid (0.24 g, 30%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.41 (s, 1H), 9.91 (s, 1H), 9.40 (s, 1H), 9.09 (s, 1H), 8.83 (m, 1H), 7.47 (s, 1H), 6.89 (d, 1H, J = 8.1 Hz), 6.26 (s, 2H), 6.16 (d, 1H, J = 8.1 Hz), 4.29 (m, 2H), 2.02 (s, 9H), 1.70 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 160.8, 159.3, 157.3, 155.7, 129.4, 127.6, 125.8, 115.6, 106.3, 105.9, 103.6, 102.4, 40.2, 37.2, 36.5, 35.8, 28.3: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{24}H_{26}NO_5$ 408.1811 found 408.1810.
    5-Adamantan-1-yl-*N*-(2,4-dihydroxy-benzyl)-2-hydroxy-4-methoxy-benzamide (**3b**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.73 (s, 1H), 9.40 (s, 1H), 9.11 (s, 1H), 8.95 (m, 1H), 7.52 (s, 1H), 6.90 (d, 1H, J = 8.4 Hz), 6.43 (s, 1H), 6.28 (s, 1H), 6.17 (d, 1H, J = 8.4 Hz), 4.31 (d, 2H, J = 5.4 Hz), 3.79 (s, 3H), 2.00 (s, 9H), 1.71 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 162.5, 160.1, 157.3, 155.7, 129.3, 128.9, 125.3, 115.5, 106.8, 105.9, 102.4, 100.3, 55.2, 40.4, 37.2, 36.5, 36.1, 28.3: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{25}H_{28}NO_5$ 422.1967 found 422.1966.
    5-Adamantan-1-yl-*N*-(2,4-dihydroxy-benzyl)-2,4-dimethoxy-benzamide (**3c**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 9.13 (s, 1H), 8.51 (m, 1H), 7.78 (m, 1H), 6.92 (d, 1H, J = 8.1 Hz), 6.66 (s, 1H), 6.27 (s, 1H), 6.16 (d, 1H, J = 8.1 Hz), 4.30 (d, 2H, J = 5.4 Hz), 3.93 (s, 3H), 3.88 (s, 3H), 1.98 (s, 9H), 1.71 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.7, 161.8, 157.5, 156.9, 156.1, 129.9, 129.7, 128.9, 116.0, 112.3, 105.9, 102.6, 96.8, 56.1, 55.4, 40.3, 38.4, 36.4, 35.8, 28.3: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{26}H_{30}NO_5$ 436.2124 found 436.2119.
    N-(2,4-Dihydroxy-benzyl)-2,4-dihydroxy-benzamide (**3d**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.71 (s, 1H), 10.00 (s, 1H), 9.39 (s, 1H), 9.08 (s, 1H), 8.75 (m, 1H), 7.73 (d, 1H, J = 8.4 Hz), 6.89 (d, 1H, J = 8.7 Hz), 6.24 (m, 3H), 6.15 (d, 1H, J = 8.7 Hz), 4.29 (d, 2H, J = 5.4 Hz): ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.8, 162.0, 161.9, 157.3, 155.7, 129.3, 115.4, 106.9, 105.9, 102.6, 102.3, 37.3: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{14}H_{12}NO_5$ 274.0715 found 274.0713.
    N-(2,4-Dihydroxy-benzyl)-2-hydroxy-4-methoxy-benzamide (**3e**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.91 (s, 1H), 9.40 (s, 1H), 9.12 (s, 1H), 8.86 (m, 1H), 7.85 (d, 1H, J = 8.7 Hz), 6.90 (d, 1H, J = 8.7 Hz), 6.44 (m, 2H), 6.28 (s, 1H), 6.16 (d, 1H, J = 8.1 Hz), 4.31 (d, 2H, J = 5.1 Hz), 3.76 (s,3H): ^{13}C NMR (125 MHz,DMSO-d_6) δ 168.7, 163.3, 162.2, 157.3, 155.7, 129.3, 129.1, 115.2, 108.1, 105.9, 105.7, 102.3, 101.1, 55.2, 37.3: HRMS(FAB$^-$) [M−H]$^-$ calcd for $C_{15}H_{14}NO_5$ 288.0872 found 288.0871.
    N-(2,4-Dihydroxy-benzyl)-2,4-dimethoxy-benzamide (**3f**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.13 (s, 1H), 8.52 (m, 1H), 7.87 (d, 1H, J = 8.4 Hz), 6.93 (d, 1H, J = 8.7 Hz), 6.63 (m, 2H), 6.28(s, 1H), 6.16 (d, 1H, J = 8.1 Hz), 4.30 (d, 2H, J = 5.7 Hz), 3.90 (s, 3H), 3.81 (s, 3H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 162.9, 158.6, 157.5, 156.1, 132.5, 129.8, 115.9, 114.1, 105.9, 105.7, 102.6, 98.5, 56.0, 55.4, 38.4: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{16}H_{16}NO_5$ 302.1028 found 302.1028.
    3-Adamantan-1-yl-*N*-(2,4-dihydroxy-benzyl)-4-hydroxy-benzamide (**3g**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.87 (s, 1H), 9.64 (s, 1H), 9.09 (s, 1H), 8.73 (m, 1H), 7.58 (m, 2H), 6.89 (d, 1H, J = 8.1 Hz), 6.77 (d, 1H, J = 7.8 Hz), 6.18 (m, 2H), 4.25 (m, 2H), 2.07 (s, 9H), 1.72 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.2, 159.0, 157.4, 155.9, 135.0, 129.9, 126.2, 126.0, 124.2, 116.2, 115.8, 106.0, 102.7, 38.0, 36.5, 36.2, 28.2: HRMS(FAB$^-$) [M−H]$^-$ calcd for $C_{24}H_{26}NO_4$ 392.1862 found 392.1857.
    3-Adamantan-1-yl-*N*-(2,4-dihydroxy-benzyl)-4-methoxy-benzamide (**3h**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.09 (s, 1H), 8.81 (t, 1H, J = 5.4 Hz), 7.73 (m, 2H), 7.02 (d, 1H, J = 8.4 Hz), 6.90 (d, 1H, J = 8.1 Hz), 6.18 (m, 2H), 4.26 (d, 2H, J = 5.7 Hz), 3.84 (s, 3H), 2.05 (s, 9H), 1.73 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.8, 160.8, 157.4, 155.8, 137.0, 129.8, 126.5, 125.6, 116.1, 111.4, 106.0, 102.7, 55.3, 39.9, 38.0, 36.5, 36.4, 28.2: HRMS(FAB$^-$) [M−H]$^-$ calcd for $C_{25}H_{28}NO_4$ 406.2018 found 406.2019.
    5-Adamantan-1-yl-*N*-(2,4-dimethoxy-benzyl)-2,4-dihydroxy-benzamide (**3i**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H), 9.92 (s, 1H), 8.86 (m, 1H), 7.48 (s, 1H), 7.07 (d, 1H, J = 8.1 Hz), 6.56 (m, 1H), 6.48 (m, 1H), 6.18 (m, 2H), 6.27 (s, 1H), 4.35 (d, 2H, J = 5.4 Hz), 3.80 (s, 3H), 3.73 (s, 3H), 2.03 (s, 9H), 1.71 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 160.8, 159.5, 157.5, 128.4, 127.6, 125.7, 118.9, 106.3, 104.4, 103.7, 98.2, 55.3, 55.1, 40.2, 36.7, 36.6, 35.8, 28.3: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{26}H_{30}NO_5$ 436.2124 found 436.2129.
    5-Adamantan-1-yl-2,4-dihydroxy-*N*-(2-hydroxy-benzyl)-benzamide (**3j**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.42 (s, 1H), 9.93 (s, 1H), 9.56 (s, 1H), 8.86 (m, 1H), 7.50 (s, 1H), 7.10 (m, 2H), 6.79 (m, 2H), 6.28 (s, 1H), 4.40 (d, 2H, J = 5.1 Hz), 2.03 (s, 9H), 1.71 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.3, 160.9, 159.4, 154.7, 128.1, 127.7, 125.8, 125.1, 118.7, 114.9, 106.2, 103.7, 40.2, 37.4, 36.6, 35.8, 28.3: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{24}H_{26}NO_4$ 392.1862 found 392.1859.
    5-Adamantan-1-yl-2,4-dihydroxy-*N*-(4-hydroxy-benzyl)-benzamide (**3k**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.68 (s, 1H), 9.94 (s, 1H), 9.26 (s, 1H), 8.98 (m, 1H), 7.42 (s, 1H), 7.11 (d, 2H, J = 8.1 Hz), 6.70 (d, 2H, J = 8.1 Hz), 6.24 (s, 1H), 4.33 (m, 2H), 2.02 (s, 9H), 1.70 (s, 6H): ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4, 160.9, 160.0, 156.2, 129.6, 128.6, 127.6, 125.3, 114.9, 105.9, 103.7, 41.6, 40.2, 36.6, 35.9, 28.3: HRMS (FAB$^-$) [M−H]$^-$ calcd for $C_{24}H_{26}NO_4$ 392.1862 found 392.1863.
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22. *C*log *P* values were calculated by Chem Draw 12.0v. *C*log *P* for compounds **3a**–**f**: 5.68, 6.42, 5.89, 1.50, 1.13, 1.60.