Bioorganic & Medicinal Chemistry xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of natural product-like polyprenylated phenols and quinones: Evaluation of their neuroprotective activities

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ARTICLE INFO

Keywords:
Fungal metabolites
Neogrifolin
Derivatization
MAO-B
SH-SY5Y cells

ABSTRACT

Twenty-seven natural product-like polyprenylated phenols and quinones were synthesized and their neuroprotective activity was tested using human monoamine oxidase B (MAO-B) and SH-SY5Y cells. Eight compounds inhibited MAO-B (IC_{50} values $< 25\,\mu M$) and the inhibition mode and molecular docking of two (**8c** and **16c**) were investigated. Compounds inhibiting MAO-B activity were additionally tested for their ability to protect SH-SY5Y cells from peroxide injury. Three derivatives (**3c**, **8c** and **16c**) exhibited both MAO-B inhibitory and neuroprotective activity. A structure activity-relationship study showed that a phenolic hydroxyl group and a longer side chain are important for both activities.

1. Introduction

The prenyl group is a natural functional group biosynthesized by mevalonate or non-mevalonate pathways. Natural compounds with prenyl subunits exhibit various bioactivities and are essential for the melanogenesis activity of diketopiperazine derivatives reported by us previously.[1] The natural polyprenylated phenols grifolin and neogrifolin are secondary metabolites found in ascomycetes of *Grifola* spp. and *Albatrellus* spp.[2] Grifolic acid, ovinol and ovinal were isolated from *Albatrellus* spp., have an aldehyde, carboxylic acid or hydroxyl group (Fig. 1),[3] and exhibit antimicrobial, antioxidative, and protective effects against brain injury.[4]

Ubiquinones are polyprenylated quinones such as vitamin E and are biosynthesized from polyhydroxy phenols. Several terpenoid-quinones exhibit biochemical activities in the human body; for example, ubiquinone 10 (Coenzyme Q10, Fig. 1) shows neuroprotective activity by inhibiting amyloid β protein aggregation.[5]

Monoamine oxidase B (MAO-B) plays a critical role in neurological disease, especially Parkinson's disease. The MAO-B inhibitors selegiline and resagiline are approved treatments for Parkinson's disease worldwide and recently have been used to treat Alzheimer's disease (AD). MAO-B expression is increased in the hippocampus and cerebral cortex of AD patients. Oxidative deamination by MAO produces hydrogen peroxide (H_2O_2) and injures neurons[6] and thus polyprenylated aromatic compounds hold promise as novel lead compounds for treating cranial nerve diseases such as Parkinson's and AD. Though various natural polyprenylated phenols were isolated and evaluated their bioactivity the structure activity relationship focused on the number of prenyl group or their substituted group were not investigated.

In this study, the structure activity-relationship of the neuroprotective effects of polyprenylated phenol and quinone derivatives were investigated. We describe the synthesis of neogrifolin and ubiquinone derivatives containing a number of prenyl groups and tested their neuroprotective activities using MAO-B and SH-SY5Y cells.

2. Results and discussion

2.1. Synthesis of neogrifolin derivatives

The synthesis of neogrifolin derivatives involved a combination of (1) alkylation (2) formylation (3) oxidation and (4) demethylation. The alkylation of orcinol (**1**), the precursor of neogrifolin, with $BF_3{\cdot}Et_2O$ and alkyl alcohol[7] gave neogrifolin and the derivatives **2a-2c**.[8]

Formylation was conducted using $POCl_3$/DMF to yield aldehydes **3a-3c**.[9] To discover the structure activity-relationship, di-prenylated, di-geranylated and di-farnesilated derivatives **3d-3f** were synthesized by a combination of alkylation and formylation of **1**. Kraus-Pinnic oxidation was performed on **3a-3c** to provide the grifolic acid-type derivatives **4a-4c**[10] in low yields (Scheme 1). Activity due to the hydroxyl group was investigated by methylating compounds **2a-c** with CH_3I to give the methoxy derivatives **5a-5c**[2,11] (Scheme 1).

We synthesized trihydroxy derivatives using inexpensive

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https://doi.org/10.1016/j.bmc.2019.115156
Received 19 July 2019; Received in revised form 4 October 2019; Accepted 5 October 2019

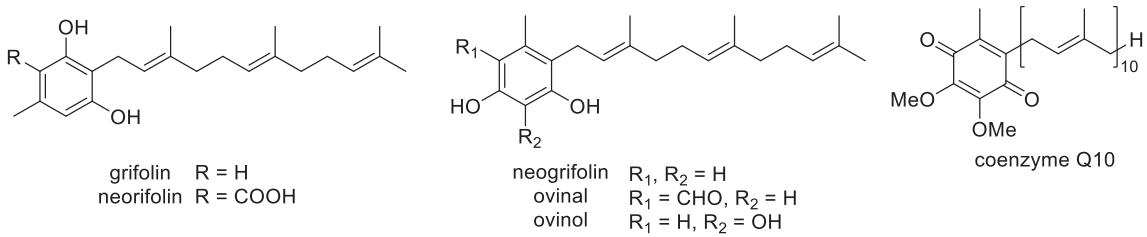
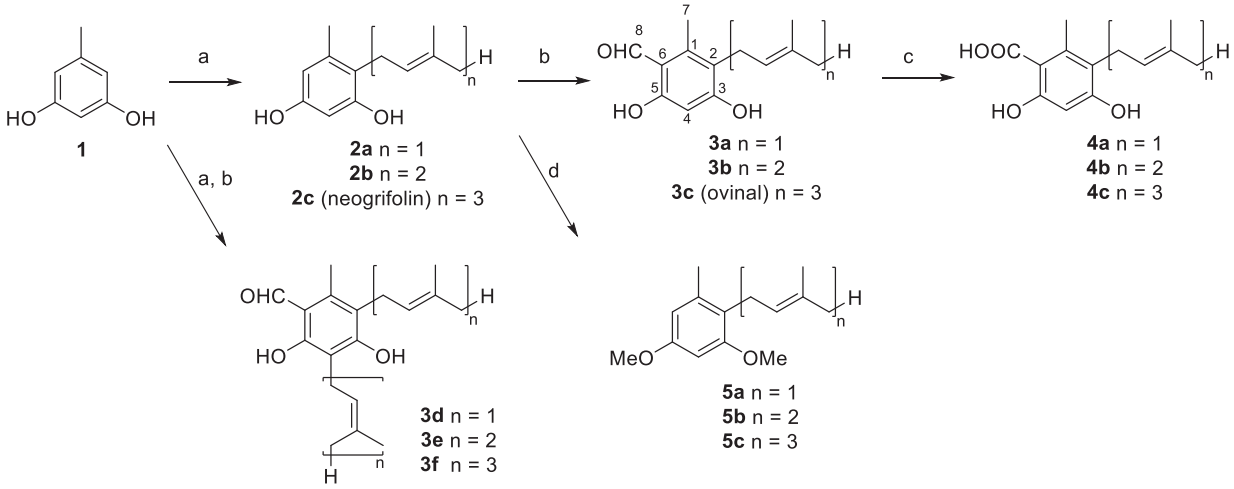


Fig. 1. Structures of grifolin derivatives and coenzyme Q10.



Scheme 1. Synthesis of neogrifolin derivatives: (a) alkyl alcohol, $BF_3{\cdot}Et_2O$; (b) $POCl_3$, DMF; (c) $NaClO_2$, Na_2PO_4; (d) CH_3I, K_2CO_3.

polymethoxy toluene (**6**) as the starting material. Alkylation was performed as described above to provide the polymethoxy neogrifolin derivatives **7a-7c**.[12] However, demethylation of trimethoxy derivative **7a** did not give expected the trihydroxy derivative **8a** but rather tetrahydropyran **9**. Similarly, although alkylation of tetramethoxy toluene **10** yielded the proposed tetramethoxy neogrifolin derivatives **11a-11c**,[13] demethylation of **11a** did not give tetrahydroxy derivative **12a** but rather **13** (Scheme 2).

Therefore, demethylation of **6** to **14** and **10** to **15** was attempted. Alkylation of **14** gave the expected trihydroxy derivatives **8a-8c** but the alkylation of **15** did not yield tetramethoxy derivatives but rather the unexpected compounds **16a-16c**. The ^{13}C NMR spectra of **16a-16c** showed two downshifted carbons (around 180 ppm) and HMBC correlations between H-2 to C-5 and H-7 to C-2 were observed for **16a**. These spectroscopic data showed the presence of 2,3-dihydroxy-1,4-quinones. Though synthesis of the ubiquinone derivatives from phenol derivatives typically requires two steps (alkylation and oxidation)[14] this result showed could synthesis them only one step.

This is the first report of the synthesis of the neogrifolin derivative natural compounds ovinal (**3c**) and ovinol (**12c**) in two or three steps. The structures of the known compounds were confirmed by comparison of their spectroscopic data with published data. The structures of the new compounds (**3d-3f**, **4b-4c**, **7b**, **8a-8b**, **13**, **16a-16c**) and known compounds which their spectral data was not defined (**3a**, **5a** and **9**) were established by analysis of their NMR and MS spectroscopic data.

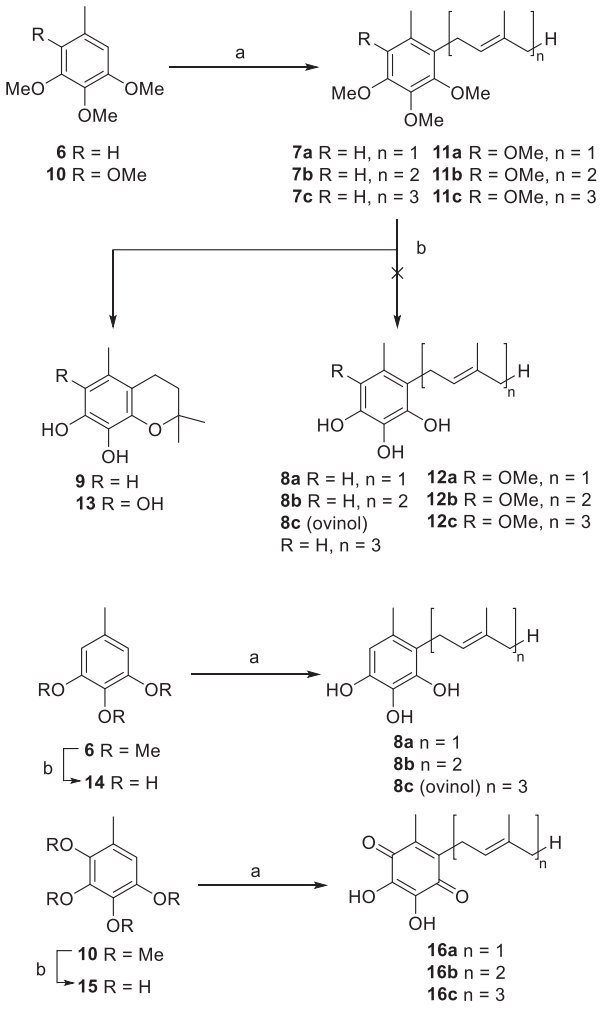
2.2. Biological evaluation of the synthesized compounds

2.2.1. MAO-B inhibitory activity

The synthesized compounds were evaluated for their MAO-B inhibitory activity using kynuramine, a substrate of MAO-B, and measuring the amount of quinolinol produced. Of the synthesized derivatives, nine exhibited inhibitory activity and four (**3c**, **8c**, **16b** and **16c**) had IC_{50} values greater than 5 μM (Table 1). In contrast, all derivatives with a methoxy group showed no inhibitory activity. Of the derivatives with two alkyl side chains (**3d-3f**), only the di-prenylated derivative showed activity. These results provided insights into the structure activity-relationships of these compounds. Hydroxy groups at C-3 and C-5 are essential for inhibitory activity due to the comparison of IC_{50} values of polyhydroxy derivatives (**2c**, **8b** and **8c**, IC_{50} = 1.3–10.5 μM) and their polymethoxy derivatives (**5b**, **7b** and **7c**, IC_{50} = N.D.). In addition, in derivatives with mono-alkyl chains, the number of prenyl units affected inhibitory activity, with longer (two or three) prenyl sidechains (**2c**, **3c**, **4c**, **8c**, **16b** and **16c**, IC_{50} 1.3–26.5 μM) exhibiting stronger activity than with a prenyl sidechain (**2a**, **3a**, **4a**, **8a**, and **16a**, IC_{50} = N.D.). This relationship did not hold for derivatives with two alkylated side chains (**3d-3f**), perhaps due to the poor solubility of **3e** and **3f** in DMSO. Comparison of **2b** (IC_{50} = N.D.) with **8b** (IC_{50} = 10.5 μM) and **2c** (IC_{50} = 9.2 μM) with **8c** (IC_{50} = 1.3 μM) showed that an additional hydroxy group at C-4 enhances activity. Derivatives with stronger activity (**3c**, **8c**, **16b** and **16c**) typically had an additional formyl, hydroxy or carbonyl group which might act as hydrogen bond acceptors or donors with MAO-B. Therefore, these results discovered the importance of the number of prenyl group and hydrogen bond acceptors to show MAO-B inhibitory activity.

2.2.2. Kinetics

The kinetics of MAO-B inhibition was performed using **8c** and **16c** and reported protocols. Lineweaver-Burk plots of the inhibitory activities of **8c** and **16c** towards MAO-B indicated they are mixed (noncompetitive) inhibitors (Fig. 2). On the other hands, some inhibitor with inhibition mode defined as “tight-binding inhibition” was well-known. Their Lineweaver-Burk plots showed mixed or noncompetitive behavior, but ligands are bound to the enzyme active site. In this case, the standard steady-state kinetic model used to describe the mechanism of inhibition is no longer valid.[15] Plotting the IC_{50} values for each compound at different substrate concentrations found that **8c** and **16c** show a linear correlation between IC_{50} value and substrate concentration, in full agreement with tight-binding competitive inhibition (Fig. 3).[15]



Scheme 2. Synthesis of polymethoxy, polyhydroxy and 1,4-quinone derivatives: (a) alkyl alcohol, $BF_3{\cdot}Et_2O$; (b) BBr_3/CH_2Cl_2.

2.2.3. Docking study

A molecular docking study was performed to investigate the mode of binding of synthesized compounds **8c** and **16c**. Affinity was evaluated by calculating the stability of the ligands when docked with the binding pocket of the published MAO-B crystal structure (PDB 4A79)[16] using Auto Dock 4.2.[17] The molecular interactions of **8c** in the binding pocket include hydrogen bonding with Leu 171 and π- alkyl interactions with Leu 164, Ile 316, Ile 199, Phe 103, Tyr 326, Trp 119, Pro 104 and Leu 171 (Fig. 4). The binding affinity (−12.74 kJ/mol) was greater than that of **3c** and **1** (−11.59 and −5.11 kJ/mol). Similar to **8c**, the binding mode of **16c** was predicted to involve a hydrogen bond between 4-OH and Cys 173 and π-alkyl interactions (Fig. S1). The binding affinity of **16c** to MAO-B was also high (−12.54 kJ/mol).

These binding simulations afforded two important findings. First, a longer sidechain supplies accepters for π-alkyl interactions, with the arborized methyl group interacting with various amino acids. Second the catechol substructure (trihydroxy and quinone derivatives) might act as a hydrogen bond acceptor and stabilize the conformation. These results explained the strong inhibitory activity of **8c** and **16c**.

2.2.4. Neuroprotective effect towards SH-SY5Y cells

Synthesized compounds with long alkyl chains (geranyl or farnesyl) showed MAO-B inhibitory activity and thus the ability of these compounds to protect SH-SY5Y cells from H_2O_2 toxicity was estimated.[18] Compounds showing MAO-B inhibitory activity were selected as test compounds and the results are shown in Fig. 5. Treatment with H_2O_2 alone decreased cell viability to 46.7%. **3c**, **8c** and **16c** at 10 μM resulted in over 20% recovery from H_2O_2 without cytotoxicity and showed concentration dependency (Fig. 6). On the other hand, **2c** showed cytotoxicity at 5 and 10 μM (< 70% of cell viability). These results show that the formyl and polyhydroxy groups on the phenol and the number of prenyl groups are important.

3. Conclusion

Polyprenyl aromatic compounds were synthesized with the structural features of neogrifolin. Three derivatives (**3c**, **8c** and **16c**) exhibited both MAO-B inhibitory and SH-SY5Y neuroprotective activity and are thus potent and multi-target inhibitors exhibiting neuroprotective activity. Furthermore, similar SAR results (structures with long prenyl sidechain, catechol and formyl groups on the aromatic ring are important scaffolds exhibiting neuroprotective activity) were obtained using the two tests. Therefore, our results showed that the discovery of novel pharmacophores for lead compounds targeting cranial nerve diseases.

4. Experimenal section

4.1. General experimental procedures

^1H and ^{13}C NMR spectra were measured with a Varian 400-MR spectrometer (Agilent, Tokyo, Japan), using tetramethylsilane as the internal standard. Low- and high-resolution FABMS spectra were measured with a JEOL JMS-700 spectrometer (JEOL). Column chromatography was performed using Wakogel C-200 (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) and ODS-A (YMC, Kyoto, Japan). All reagents and solvents were purchased from commercial sources. Farnesol (TCI T0608) contains slightly *cis* isomer.

Table 1
MAO-B inhibitory activities of the synthesized compounds.

	Inhibition rate (%)[a]	IC_{50} (μM)		Inhibition rate (%)[a]	IC_{50} (μM)		Inhibition rate (%)[a]	IC_{50} (μM)
2a	4.2 ± 2.4		**4a**	16.3 ± 6.1		**11a**	7.2 ± 2.5	
2b	30.7 ± 0.7		**4b**	31.2 ± 1.7		**11b**	38.0 ± 1.2	
2c	96.4 ± 0.1	9.2	**4c**	49.2 ± 8.6	26.5	**11c**	15.2 ± 2.4	
3a	36.3 ± 1.4		**5a**	5.4 ± 2.5		**8a**	32.7 ± 2.4	
3b	77.4 ± 2.5	19.7	**5b**	N. D.[c]		**8b**	88.7 ± 5.6	10.5
3c	91.2 ± 0.3	2.3	**5c**	10.8 ± 7.6		**8c**	97.8 ± 0.1	1.3
3d	84.7 ± 0.3	5.5	**7a**	18.6 ± 3.3		**16a**	38.3 ± 1.3	
3e	48.1 ± 0.8	N. D.[b]	**7b**	5.9 ± 3.1		**16b**	92.2 ± 0.1	1.4
3f	48.8 ± 1.2	N. D.[b]	**7c**	34.9 ± 4.1		**16c**	93.1 ± 0.4	1.3

[a] Results are shown as mean ± SD (n = 3) at 25 μM.
[b] Not determined due to poor solubility over 25 μM.
[c] Not determined due to the inhibition rate was under 0%. Pargyline was used as positive control (IC_{50} = 0.22 μM).

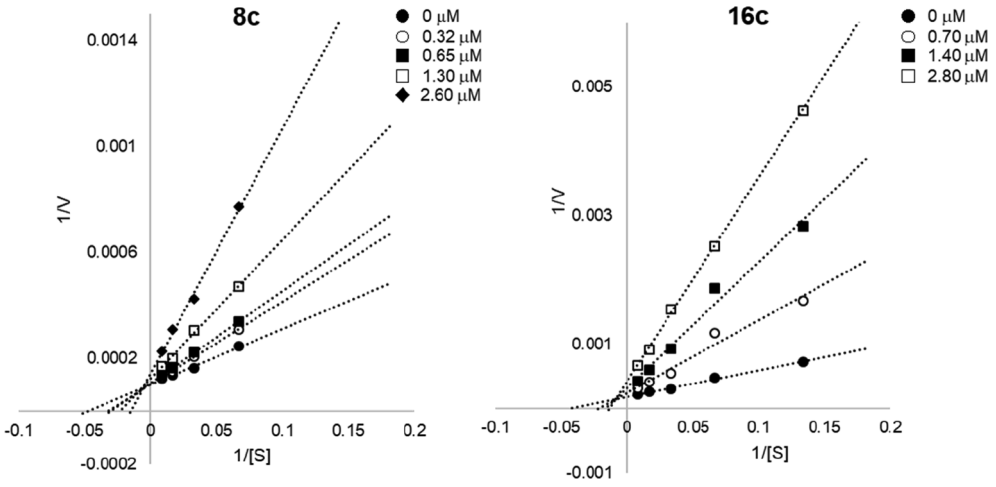


Fig. 2. Lineweaver–Burk plots for MAO-B inhibition by **8c** and **16c**.

4.2. Synthesis

4.2.1. General procedure A: Alkylation

$BF_3{\cdot}Et_2O$ was slowly added dropwise, to a stirred solution of polyhydroxy or polymethoxy phenols and alkyl alchol in dioxane at 0 °C. After the addition was completed, the stirring was continued for 3 h at room temperature. The mixture was poured water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The crude was chromatographed on silica gel.

4.2.2. General procedure B: formylation

Phosphorus oxychloride ($POCl_3$) was added dropwise into DMF below 0 °C. Alkylated orcinol in of DMF was added slowly and then ice bath was removed. The stirring was continued for overnight at room temperature. Water was added end extracted by EtOAc. The organic layer was over dried by Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The crude was chromatographed on silica gel with *n*-Hex/EtOAc.

4.2.3. General procedure C: oxidation

NaH_2PO_4 dissolved in H_2O was added to DMSO-THF 1:1 solution of aldehyde and then $NaClO_2$ in H_2O was added and stirred 12 h at room temperature. The mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The crude was chromatographed on octadecylsilyl (ODS) silica gel with MeOH/H_2O.

4.2.4. General procedure D: methylation

A stirring mixture of alkylated derivatives, anhydrous K_2CO_3, and methyl iodide in acetone was refluxed for 6 h. The crude mixture was chromatographed on silica gel with *n*-Hex/EtOAc.

4.2.5. General procedure E: demethylation

Boron tribromide (17% in CH_2Cl_2, 4 eq.) was added to the solution of 3,4,5-trimethoxytoluene or 2,3,4,5-tetramethoxytoluene (1 eq.) in CH_2Cl_2 at 0 °C. The ice bath was removed, and the mixture was stirred for 3 h. The reaction mixture was evaporated under reduced pressure and the residue was used for the next reaction without further purification.

4.2.6. 5-Methyl-4-(3-methylbut-2-en-1-yl)benzene-1,3-diol (**2a**)

Alkylation of orcinol (300.0 mg, 2.4 mmol) with 3-methyl-2-buten-1-ol (373 μL, 2.4 mmol) and $BF_3{\cdot}Et_2O$ (150 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 5:1) yielded **2a** as colorless oil (95.0 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, J = 2.6 Hz, H-6), 6.21 (d, J = 2.6 Hz, H-4), 5.13 (m, H-2′), 3.28 (brd, J = 7.0 Hz, H-1′), 2.23 (s, H-7), 1.80 (s, H-5′) 1.73 (s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (C-3), 154.3 (C-5), 138.6 (C-1), 134.0 (C-3′), 122.3 (C-2′), 118.1 (C-2), 109.8 (C-6), 101.1 (C-4), 25.9 (C-4′), 25.3 (C-1′), 20.2 (C-7), 18.0 (C-5′); HREIMS *m/z*: 192.1150 $[M]^+$ (calcd. for $C_{12}H_{16}O_2$, 192.1150). The structure was confirmed by comparison of spectroscopic data with the published data.[7]

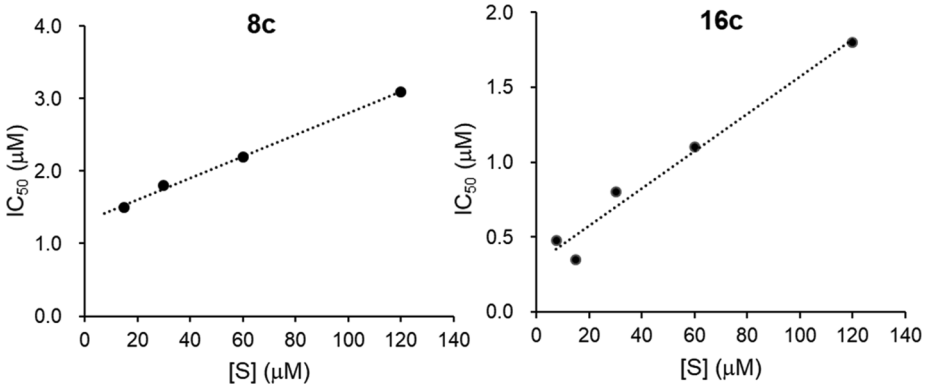


Fig. 3. Effects of substrate (S) concentration on the IC_{50} values of **8c** and **16c**.

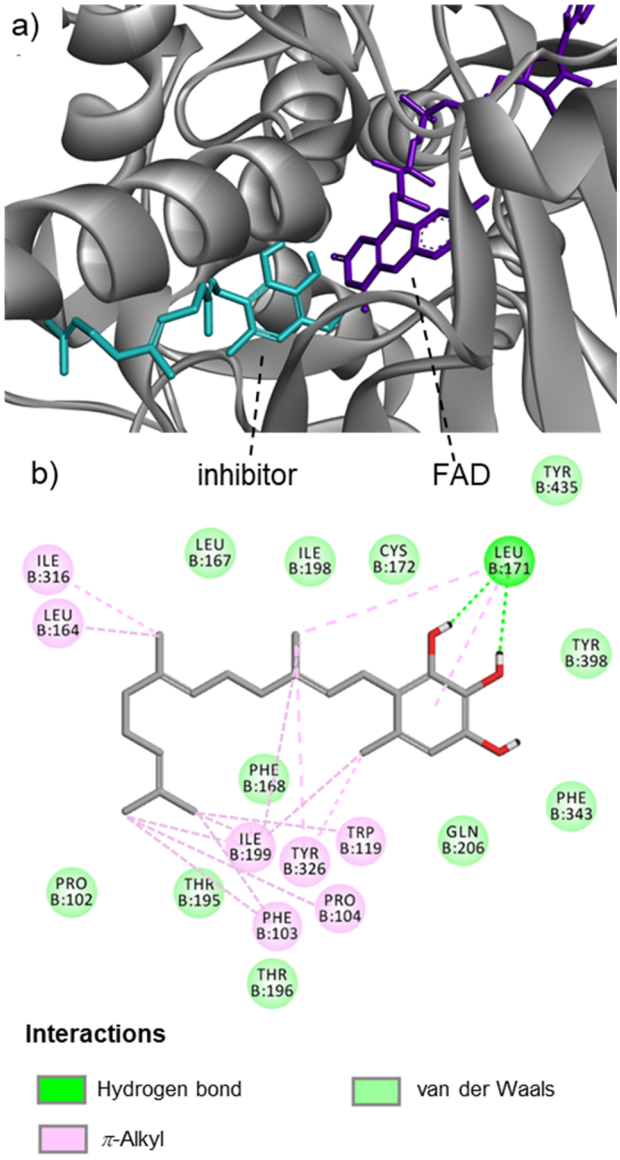


Fig. 4. Molecular docking of **8c** and MAO-B. (a) Predicted binding conformations. (b) The key residues and their interactions with **8c**.

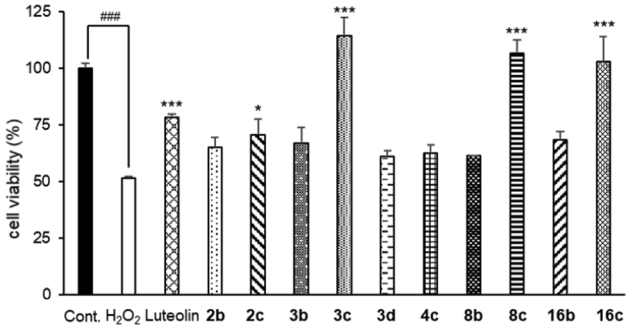


Fig. 5. Protective effect of the tested compounds against H_2O_2 toxicity towards SH-SY5Y cells (n = 3, *, ***: $P < 0.05$, 0.001 vs·H_2O_2, ###: $P < 0.001$ vs. cont.). Synthesized compounds were tested at 10 μM·H_2O_2 was tested at 500 μM. Luteolin was used as positive control.

4.2.7. (E)-4-(3,7-dimethylocta-2,6-dien-1-yl)-5-Methylbenzene-1,3-diol (2b)

Alkylation of orcinol (300 mg, 2.4 mmol) with geraniol (373 μL, 2.4 mmol) and $BF_3{\cdot}Et_2O$ (150 μL) followed to general procedure A.

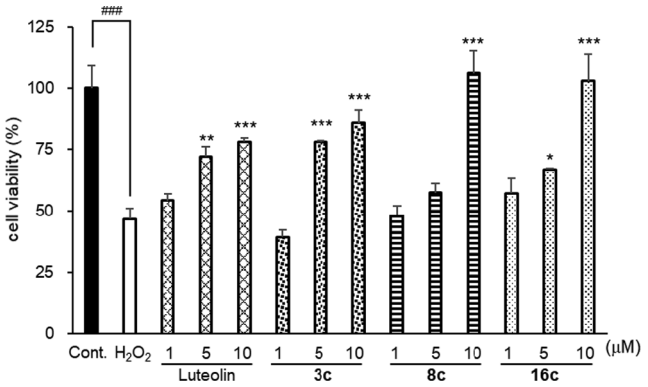


Fig. 6. Protective effect of farnesyl derivatives against H_2O_2 toxicity towards SH-SY5Y cells (n = 3, *, **, ***: $P < 0.05$, 0.01, 0.001 vs·H_2O_2, ###: $P < 0.001$ vs. cont.)·H_2O_2 was tested at 500 μM. Luteolin was used as positive control.

Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 5:1) yielded **2b** as colorless oil (98.9 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, J = 2.6 Hz, H-6), 6.21 (d, J = 2.6 Hz, H-4), 5.14 (m, H-2′), 5.04 (m, H-6′), 3.28 (brd, J = 6.7 Hz, H-1′), 2.23 (s, H-7), 2.00–2.11 (overlapped, H-4′ and H-5′), 1.79 (s, H-9′), 1.65 (s, H-8′), 1.57 (s, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (C-3), 154.2 (C-5), 138.5 (C-1), 137.7 (C-3′), 131.9 (C-7′), 123.8 (C-6′), 122.0 (C-2′), 117.9 (C-2), 109.6 (C-6), 101.0 (C-4), 39.7 (C-4′), 26.4 (C-5′), 25.7(C-8′), 25.1 (C-1′), 20.1 (C-7), 17.7 (C-10′), 16.1 (C-9′); HREIMS *m/z*: 260.1778 $[M]^+$ (calcd. for $C_{17}H_{24}O_2$, 260.1776). The structure was confirmed by comparison of spectroscopic data with the published data.[7]

4.2.8. Neogrifolin (2c)

Alkylation of orcinol (2.0 g, 16.1 mmol) with farnesol (4.0 mL, 16.1 mmol) and $BF_3{\cdot}Et_2O$ (660 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 5:1) yielded **2c** as colorless oil (1.3 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, J = 3.0 Hz, H-6), 6.21 (d, J = 3.0 Hz, H-4), 5.13 (m, H-2′), 5.06 (overlapped, H-6′ and H-10′), 3.28 (brd, J = 6.8 Hz, H-1′), 2.23 (s, H-7), 1.95–2.10 (overlapped, H-4′ H-5′, H-8′ and H-9′), 1.80 (s, H-13′), 1.67 (s, H-12′), 1.59 (s, H-15′), 1.57 (s, H-14′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (C-3), 154.2 (C-5), 138.5 (C-1), 137.4 (C-3′), 135.6 (C-7′), 131.3 (C-11′), 124.4 (C-10′), 123.7 (C-6′), 122.1 (C-2′), 118.0 (C-2), 109.7 (C-6), 101.0 (C-4), 39.9 (C-4′), 39.7 (C-8′), 26.7 (C-9′), 26.4 (C-5′), 25.7 (C-12′), 25.1 (C-1′), 20.1 (C-7), 17.7 (C-15′), 16.2 (C-13′), 16.0 (C-14′); HREIMS *m/z*: 328.2398 $[M]^+$ (calcd. for $C_{22}H_{32}O_2$, 328.2402). The structure was confirmed by comparison of spectroscopic data with the published data.[2]

4.2.9. 4,6-Dihydroxy-2-methyl-3-(3-methylbut-2-en-1-yl)benzaldehyde (3a)

Formylation of **2a** (540.0 mg 2.8 mmol) with $POCl_3$ (456 μL, 4.9 mmol) followed to general procedure B. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 5:1) yielded **3a** as colorless oil (122.8 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.5 (s, 5-OH), 10.2 (s, H-8), 6.23 (brs, H-4), 5.81 (brs, 3-OH), 5.06 (m, H-2′), 3.34 (brd, J = 6.7 Hz, H-1′), 2.49 (s, H-7), 1.80 (s, H-5′) 1.73 (s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7 (C-8), 164.4 (C-5), 162.2 (C-3), 142.0 (C-1), 134.0 (C-3′), 121.5 (C-2′), 119.2 (C-2), 113.9 (C-6), 101.4 (C-4), 25.7 (C-4′), 24.7 (C-1′), 17.9 (C-5′), 13.8 (C-7); HREIMS *m/z*: 220.1095 $[M]^+$ (calcd. for $C_{13}H_{16}O_3$, 220.1099).

4.2.10. (E)-3-(3,7-dimethylocta-2,6-dien-1-yl)-4,6-Dihydroxy-2-methylbenzaldehyde (3b)

Formylation of **2b** (160.0 mg 0.50 mmol) with $POCl_3$ (103 μL, 1.1 mmol) followed to general procedure B. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 5:1)

yielded **3b** as colorless oil (84.6 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 5-OH), 10.16 (s, H-8), 6.34 (brs, 4-OH), 6.24 (brs, H-4), 5.03–5.07 (overlapped, H-2′ and H-6′), 3.33 (brd, J = 6.4 Hz, H-1′), 2.48 (s, H-7), 2.01–2.09 (overlapped, H-4′ and H-5′), 1.79 (s, H-9′), 1.66 (s, H-8′), 1.58 (s, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7 (C-8), 164.4 (C-3), 162.5 (C-5), 142.1 (C-1), 137.5 (C-3′), 131.8 (C-7′), 123.9 (C-6′), 121.5 (C-2′), 119.5 (C-2), 113.8 (C-6), 101.3 (C-4), 39.6 (C-4′), 26.4 (C-5′), 25.7(C-8′), 24.6 (C-1′), 17.7 (C-10′), 16.3 (C-9′), 13.8 (C-7); HREIMS *m/z*: 288.1723 $[M]^+$ (calcd. for $C_{18}H_{24}O_3$, 288.1725). The structure was confirmed by comparison of spectroscopic data with the published data.[8]

4.2.11. Ovinal (3c)

Formylation of **2c** (417.7 mg, 1.3 mmol) with $POCl_3$ (236 μL, 2.5 mmol) followed to general procedure B. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 5:1) yielded **3c** as colorless oil (357.6 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 5-OH), 10.17 (s, H-8), 6.24 (s, H-4), 6.18 (brs, 3-OH), 5.04–5.09 (overlapped, H-2′, H-6′ and H-10′), 3.34 (brd, J = 6.6 Hz, H-1′), 2.48 (s, H-7), 1.95–2.10 (overlapped, H-4′ H-5′, H-8′ and H-9′), 1.80 (s, H-13′), 1.67 (s, H-12′), 1.59 (s, H-15′), 1.59 (s, H-14′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (C-8), 164.5 (C-3), 162.6 (C-5), 142.2 (C-1), 137.7 (C-3′), 135.7 (C-7′), 131.5 (C-11′), 124.4 (C-10′), 123.8 (C-6′), 122.6 (C-2′), 119.6 (C-2), 114.0 (C-6), 101.5 (C-4), 39.8 (C-4′), 39.8 (C-8′), 26.8 (C-9′), 26.5 (C-5′), 25.9 (C-12′), 24.7 (C-1′), 17.8 (C-15′), 16.4 (C-13′), 16.2 (C-14′), 14.0 (C-7); HREIMS *m/z*: 356.2354 $[M]^+$ (calcd. for $C_{23}H_{32}O_3$, 356.2351). The structure was confirmed by comparison of spectroscopic data with the published data.[3]

4.2.12. 2,4-Dihydroxy-6-methyl-3,5-bis(3-methylbut-2-en-1-yl) benzaldehyde (3d)

Formylation of orcinol (1.0 g, 7.0 mmol) with $POCl_3$ (1.58 mL, 14.1 mmol) followed to general procedure B. Crystallization from aqueous layer and purification from organic layer yielded 2,4-dihydroxy-6-methylbenzaldehyde (706.8 mg, 66%). This aldehyde (230.0 mg, 1.5 mmol) was subjected to alkylation with 2-methyl-3buten-2-ol (780 μL, 7.4 mmol) and $BF_3{\cdot}Et_2O$ (100 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 20:1) yielded **3d** as colorless oil (54.8 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.9 (s, 5-OH), 10.2 (s, H-8), 6.33 (s, 3-OH), 5.23 (m, H-2″), 5.04 (m, H-2′), 3.42 (brd, J = 7.1 Hz, H-1″), 3.32 (brd, J = 6.6 Hz, H-1′), 2.45 (s, H-7), 1.83, 1.78 (each s, H-5′ and H-5″) 1.76, 1.71 (each s, H-4′ and H-4″); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7 (C-8), 161.7 (C-5), 161.2 (C-3), 139.3 (C-1), 136.0 (C-3″), 133.0 (C-3′), 122.0 (C-2″), 121.2 (C-2′), 119.5 (C-2), 113.3 (C-6), 111.2 (C-4), 25.9, 25.7 (C-4′and C-4″), 24.8, 21.5 (C-1′ and C-1″), 18.0, 17.9 (C-5′ and C-5″), 13.5 (C-7); HREIMS *m/z*: 288.1728 $[M]^+$ (calcd. for $C_{18}H_{24}O_3$, 288.1725).

4.2.13. 3,5-Bis((E)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxy-6-methylbenzaldehyde (3e)

3b (380.0 mg, 1.2 mmol) was subjected to alkylation with geraniol (236 μL, 1.3 mmol) and $BF_3{\cdot}Et_2O$ (100 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 20:1) and ODS silica gel with MeOH/H_2O yielded **3e** as colorless oil (3.6 mg, 0.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.8 (s, 5-OH), 10.2 (s, H-8), 6.37 (s, 3-OH), 5.24 (m, H-2″), 5.02–5.06 (overlapped, H-2′, H-6′ and H-6″), 3.42 (brd, J = 7.1 Hz, H-1″), 3.32 (brd, J = 6.6 Hz, H-1′), 2.45 (s, H-7), 1.98–2.15 (overlapped, H-4′, H-4″, H-5′ and H-5″) 1.82, 1.77 (each, s, H-9′ and H-9″), 1.68, 1.66 (each s, H-8′ and H-8″), 1.59, 1.58 (each s, H-10′ and H-10″); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (C-8), 161.7 (C-3), 161.4 (C-5), 139.8 (C-1), 139.4, 136.4 (C-3′ and C-3″), 132.1, 131.6 (C-7′ and C-7″), 124.0, 123.7 (C-6′ and C-6″), 122.1, 121.1 (C-2′ and C-2″), 119.7 (C-2), 113.3 (C-6), 111.4 (C-4), 39.7 (2C, C-4′ and C-4″), 26.5, 26.3 (C-5′ and C-5″), 25.7 (2C, C-8′and C-8″), 24.6, 21.5 (C-1′ and C-1″), 17.7 (2C, C-10′ and C-10″), 16.2 (2C, C-9′ and C-9″), 13.5 (C-7); HREIMS *m/z*: 424.2969 $[M]^+$ (calcd. for $C_{28}H_{40}O_3$, 424.2977).

4.2.14. 2,4-Dihydroxy-6-methyl-3,5-bis((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzaldehyde (3f)

2,4-dihydroxy-6-methylbenzaldehyde (1.0 g 6.6 mmol) was subjected to alkylation with farnesol (3.0 mL, 12 mmol) and $BF_3{\cdot}Et_2O$ (600 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 20:1) and ODS silica gel with MeOH/H_2O yielded **3f** as colorless oil (10.1 mg, 0.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.9 (s, 5-OH), 10.2 (s, H-8), 6.34 (s, 3-OH), 5.24 (m, H-2″), 5.03–5.09 (overlapped, H-2′, H-6′, H-6″, H-10′ and H-10″), 3.43 (brd, J = 7.1 Hz, H-1″), 3.32 (brd, J = 6.6 Hz, H-1′), 2.45 (s, H-7), 1.92–2.13 (overlapped, H-4′, H-4″, H-5′, H-5″, H-8′, H-8″, H-9′ and H-9″) 1.82, 1.77 (each, s, H-13′ and H-13″), 1.68 (overlapped, H-12′ and H-12″), 1.58 (overlapped, H-14′, H-14″, H-15′ and H-15″); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (C-8), 161.7 (C-5), 161.3 (C-3), 139.7 (C-1), 139.4, 136.4 (C-3′ and C-3″), 135.8, 135.6 (C-7′ and C-7″), 131.3, (2C, C-11′ and C-11″), 124.7, 124.3 (C-10′ and C-10″), 123.9, 123.5 (C-6′ and C-6″), 122.1, 121.1 (C-2′ and C-2″), 119.7 (C-2), 113.3 (C-6), 111.1 (C-4), 39.7 (4C, C-4′, C-4″, C-8′ and C-8″), 26.7 (2C, C-9′ and C-9″), 26.3 (2C, C-5′ and C-5″), 25.7 (2C, C-12′and C-12″), 24.6, 21.5 (C-1′ and C-1″), 17.7 (2C, C-15′ and C-15″), 16.3 (2C), 16.2, 16.0 (C-13′, C-13″, C-14′ and C-14″), 13.5 (C-7); HREIMS *m/z*: 560.4222 $[M]^+$ (calcd. for $C_{38}H_{56}O_3$, 560.4229).

4.2.15. 4,6-Dihydroxy-2-methyl-3-(3-methylbut-2-en-1-yl)benzoic acid (4a)

Oxidation of **3a** (20.0 mg, 0.091 mmol) with NaH_2PO_4 (55.0 mg) and $NaClO_2$ (55.0 mg) followed to general procedure C. After purification **4a** was yielded as white solid (14.1 mg 66%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.20 (brs, H-4), 5.00 (m, H-2′), 3.30 (overlapped with CD_3OD, H-1′), 2.43 (s, H-7), 1.75 (s, H-5′) 1.67 (s, H-4′); ^{13}C NMR (100 MHz, CD_3OD) δ 173.7 (C-8), 161.9 (C-5), 160.1 (C-3), 140.7 (C-1), 130.1 (C-3′), 123.1 (C-2′), 120.2 (C-2), 105.5 (C-6), 99.7 (C-4), 24.5 (C-4′), 24.3 (C-1′), 17.2 (C-5′), 16.5 (C-7); HREIMS *m/z*: 236.1042 $[M]^+$ (calcd. for $C_{13}H_{16}O_4$, 236.1049). The structure was confirmed by comparison of spectroscopic data with the published data.[9]

4.2.16. (E)-3-(3,7-dimethylocta-2,6-dien-1-yl)-4,6-Dihydroxy-2-methylbenzoic acid (4b)

Oxidation of **3b** (79.0 mg, 0.27 mmol) with NaH_2PO_4 (106.0 mg) and $NaClO_2$ (65.0 mg) followed to general procedure C. After purification **4b** was yielded as white solid (13.4 mg 16%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.20 (s, H-4), 5.04, 5.01 (each m, H-2′and H-6′), 3.30 (overlapped, H-1′), 2.43 (s, H-7), 2.06, 1.97 (overlapped, H-4′ and H-5′) 1.74 (s, H-9′), 1.62 (s, H-8′), 1.56 (s, H-10′); ^{13}C NMR (100 MHz, CD_3OD) δ 173.8 (C-8), 161.8 (C-5), 160.0 (C-3), 140.8 (C-1), 133.7 (C-3′), 130.6 (C-7′), 124.0, (C-6′), 123.4 (C-2′), 120.2 (C-2), 105.7 (C-6), 99.6 (C-4), 39.7 (C-4′), 26.2 (C-5′), 24.4 (C-8′), 24.1 (C-1′), 17.2 (C-10′), 16.3 (C-9′), 14.8 (C-7); HREIMS *m/z*: 304.1673 $[M]^+$ (calcd. for $C_{18}H_{24}O_4$, 304.1673).

4.2.17. 4,6-Dihydroxy-2-methyl-3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoic acid (4c)

Oxidation of **3c** (357.0 mg, 1.0 mmol) with NaH_2PO_4 (390.0 mg) and $NaClO_2$ (225.0 mg) followed to general procedure C. After purification **4c** was yielded as white solid (32.2 mg 9%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.20 (s, H-4), 4.98–5.06 (overlapped, H-2′, H-6′ and H-10′), 3.30 (overlapped, H-1′), 2.43 (s, H-7), 1.88–2.14 (overlapped, H-4′, H-5′, H-8′ and H-9′) 1.75 (s, H-13′), 1.63 (s, H-12′), 1.57, 1.55 (each, s, H-14′ and H-15′); ^{13}C NMR (100 MHz, CD_3OD) δ 173.8 (C-8), 162.0 (C-5), 160.2 (C-3), 140.9 (C-1), 134.4 (C-3′), 133.6 (C-7′), 130.5 (C-11′), 124.1, (C-10′), 124.0 (C-6′), 123.4 (C-2′), 120.2 (C-2), 105.4 (C-6), 99.7 (C-4), 39.7, 39.4 (C-4′ and C-8′), 26.2 (C-9′), 25.9 (C-5′), 24.5 (C-12′), 24.2 (C-1′), 17.3 (C-15′), 16.3, 14.9 (C-13′ and C-14′),

14.7 (C-7); HREIMS *m/z*: 372.2296 $[M]^+$ (calcd. for $C_{23}H_{32}O_4$, 372.2301).

4.2.18. 1,5-Dimethoxy-3-methyl-2-(3-methylbut-2-en-1-yl)benzene (5a)

Methylation of **2a** (100.0 mg 0.52 mmol) with anhydrous K_2CO_3 (360.0 mg, 2.6 mmol) and methyl iodide (160 μL, 2.6 mmol) followed to general procedure D. The di-methylated derivative **5a** was yielded as colorless oil (69.1 mg 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (overlapped, H-4 and H-6), 5.07 (m, H-2′), 3.83, 3.80 (each s, 3-OMe and 5-OMe), 3.30 (brd, J = 6.9 Hz, H-1′), 2.28 (s, H-7), 1.78 (s, H-5′), 1.68 (s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (C-3 and C-5), 138.0 (C-1), 130.8 (C-3′), 123.0 (C-2′), 121.0 (C-2), 106.5 (C-6), 96.2 (C-4), 55.6, 55.2 (3-OMe and 5-OMe), 25.8 (C-4′), 24.8 (C-1′), 20.0 (C-7), 17.8 (C-5′); HREIMS *m/z*: 220.1461 $[M]^+$ (calcd. for $C_{14}H_{20}O_2$, 220.1463).

4.2.19. (E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-1,5-Dimethoxy-3-methylbenzene (5b)

Methylation of **2b** (57.2 mg, 0.22 mmol) with anhydrous K_2CO_3 (151.0 mg, 1.1 mmol) and methyl iodide (155 μL, 2.5 mmol) followed to general procedure D. The di-methylated derivative **5b** was yielded as colorless oil (49.5 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, H-4 and H-6), 5.02–5.07 (overlapped, H-2′ and H-6′), 3.79, 3.78 (each s, 3-OMe and 5-OMe), 3.28 (brd, J = 6.7 Hz, H-1′), 2.25 (s, H-7), 1.94–2.06 (overlapped, H-4′ and H-5′), 1.75 (s, H-9′), 1.65 (s, H-8′), 1.57 (s, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 158.2 (C-3 and C-5), 138.2 (C-1), 164.4 (C-3), 134.4 (C-3′), 131.2 (C-7′), 124.4 (C-6′), 123.0 (C-2′), 121.1 (C-2), 106.5 (C-6), 96.2 (C-4), 55.6, 55.2 (3-OMe and 5-OMe), 39.8 (C-4′), 26.7 (C-5′), 25.7(C-8′), 24.6 (C-1′), 20.0 (C-7), 17.6 (C-10′), 16.1 (C-9′); HREIMS *m/z*: 288.2091 $[M]^+$ (calcd. for $C_{19}H_{28}O_2$, 288.2089). The structure was confirmed by comparison of spectroscopic data with the published data.[10]

4.2.20. 1,5-Dimethoxy-3-methyl-2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (5c)

Methylation of **2c** (100.0 mg 0.30 mmol) with anhydrous K_2CO_3 (207.0 mg, 1.5 mmol) and methyl iodide (93 μL, 1.5 mmol) followed to general procedure D. The di-methylated derivative **5c** was yielded as colorless oil (30.4 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33, 6.32 (each s, H-4 and H-6), 5.04–5.10 (overlapped, H-2′, H-6′ and H-10′), 3.79 3.78 (each s, 3-OMe and 5-OMe), 3.28 (brd, J = 6.7 Hz, H-1′), 2.25 (s, H-7), 1.93–2.09 (overlapped, H-4′ H-5′, H-8′ and H-9′), 1.75 (s, H-13′), 1.67 (s, H-12′), 1.59 (s, H-15′), 1.57 (s, H-14′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 158.2 (C-3 and C-5), 138.2 (C-1), 134.8 (C-3′), 134.4 (C-7′), 131.2 (C-11′), 124.4 (C-10′), 124.2 (C-6′), 123.0 (C-2′), 121.1 (C-2), 106.5 (C-6), 96.2 (C-4), 55.6, 55.2 (3-OMe and 5-OMe), 39.8 (C-4′), 39.7 (C-8′), 26.7 (C-9′), 26.6 (C-5′), 25.8 (C-12′), 24.6 (C-1′), 20.0 (C-7), 17.8 (C-15′), 16.1 (C-13′), 16.0 (C-14′); HREIMS *m/z*: 356.2723 $[M]^+$ (calcd. for $C_{24}H_{36}O_2$, 356.2715). The structure was confirmed by comparison of spectroscopic data with the published data.[2]

4.2.21. 1,2,3-Trimethoxy-5-methyl-4-(3-methylbut-2-en-1-yl)benzene (7a)

Alkylation of 3,4,5-trimethoxytoluene (1.0 g, 5.5 mmol) with 3-methyl-2-buten-1-ol (549 μL, 5.5 mmol) and $BF_3{\cdot}Et_2O$ (330 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 10:1) yielded **7a** as colorless oil (482.9 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, H-6), 5.04 (m, H-2′), 3.85, 3.84, 3.82 (each s, 3-OMe, 4-OMe and 5-OMe), 3.28 (brd, J = 6.9 Hz, H-1′), 2.23 (s, H-7), 1.77 (s, H-5′), 1.68 (s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 151.2 (C-3 and C-5), 140.5 (C-4), 132.0 (C-1), 131.2 (C-3′), 126.4 (C-2), 123.3 (C-2′), 109.6 (C-6), 61.1, 60.9, 56.1 (3-OMe, 4-OMe and 5-OMe), 25.9 (C-4′), 25.8 (C-1′), 19.8 (C-7), 17.8 (C-5′); HREIMS *m/z*: 250.1567 $[M]^+$ (calcd. for $C_{15}H_{22}O_3$, 250.1569). The structure was confirmed by comparison of spectroscopic data with the published data.[11]

4.2.22. (E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-3,4,5-Trimethoxy-1-methylbenzene (7b)

Alkylation of 3,4,5-trimethoxytoluene (1.0 g, 5.5 mmol) with geraniol (963 μL, 5.5 mmol) and $BF_3{\cdot}Et_2O$ (330 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 10:1) yielded **7b** as colorless oil (539.6 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, H-6), 5.02–5.07 (overlapped, H-2′ and H-6′), 3.85 (s, 4-OMe), 3.83 (s, 3-OMe and 5-OMe), 3.29 (brd, J = 7.0 Hz, H-1′), 2.23 (s, H-7), 1.98–2.07 (overlapped, H-4′ and H-5′), 1.76 (s, H-9′), 1.65 (s, H-8′), 1.57 (s, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 (C-5), 151.0 (C-3), 140.3 (C-4), 134.8 (C-3′), 132.0 (C-1), 131.3 (C-7′), 126.3 (C-2), 124.3 (C-6′), 123.1 (C-2′), 109.4 (C-6), 61.0 (5-OMe), 60.8 (3-OMe), 55.9 (4-OMe), 39.7 (C-4′), 26.6 (C-5′), 25.7(C-8′), 25.5 (C-1′), 19.7 (C-7), 17.7 (C-10′), 16.1 (C-9′); HREIMS *m/z*: 318.2195 $[M]^+$ (calcd. for $C_{20}H_{30}O_3$, 318.2195).

4.2.23. 1,2,3-Trimethoxy-5-methyl-4-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (7c)

Alkylation of 3,4,5-trimethoxytoluene (1.0 g, 5.5 mmol) with farnesol (1372 μL, 5.5 mmol) and $BF_3{\cdot}Et_2O$ (330 μL) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 10:1) yielded **7c** as colorless oil (759.4 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, H-6), 5.03–5.10 (overlapped, H-2′, H-6′ and H-10′), 3.85 3.83, 3.83 (each s, 3-OMe, 4-OMe and 5-OMe), 3.29 (brd, J = 7.1 Hz, H-1′), 2.23 (s, H-7), 1.95–2.08 (overlapped, H-4′ H-5′, H-8′ and H-9′), 1.77 (s, H-13′), 1.67 (s, H-12′), 1.59 (s, H-15′), 1.57 (s, H-14′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 151.0 (C-3 and C-5), 140.3 (C-4), 135.1 (C-7′), 134.8 (C-3′), 132.0 (C-1), 131.3 (C-11′), 126.3 (C-2), 125.0 (C-10′), 124.3 (C-6′), 123.1 (C-2′), 109.4 (C-6), 61.0, 60.8, 55.9 (3-OMe, 4-OMe and 5-OMe), 40.0 (C-4′), 39.7 (C-8′), 26.7 (C-9′), 26.6 (C-5′), 25.7 (C-12′), 25.5 (C-1′), 19.7 (C-7), 17.6 (C-15′), 16.2 (C-13′), 16.0 (C-14′); HREIMS *m/z*: 386.2818 $[M]^+$ (calcd. for $C_{25}H_{38}O_3$, 386.2821). The structure was confirmed by comparison of spectroscopic data with the published data.[11]

4.2.24. 1,2,3,4-Tetramethoxy-5-methyl-6-(3-methylbut-2-en-1-yl)benzene (11a)

Alkylation of 2,3,4,5-tetrahydroxyoluene (300.0 mg, 1.41 mmol) with 3-methyl-2-buten-1-ol (141 μL, 1.41 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 50:1) yielded **11a** as colorless oil (97.5 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (m, H-2′), 3.91, 3.90, 3.79, 3.78 (each s, 3-OMe, 4-OMe, 5-OMe and 6-OMe), 3.31 (brd, J = 6.7 Hz, H-1′), 2.15 (s, H-7), 1.77 (s, H-5′), 1.69 (s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.6 (C-3 and C-6), 144.9, 144.7 (C-4 and C-5), 131.4 (C-3′), 129.2 (C-2), 125.3 (C-2′), 122.8 (C-1), 61.1, 61.1, 61.1, 60.7 (3-OMe, 4-OMe, 5-OMe and 6-OMe), 25.9 (C-4′), 25.8 (C-1′), 17.9 (C-5′), 11.7 (C-7′); HREIMS *m/z*: 280.1677 $[M]^+$ (calcd. for $C_{16}H_{24}O_4$, 280.1675). The structure was confirmed by comparison of spectroscopic data with the published data.[12]

4.2.25. (E)-1-(3,7-dimethylocta-2,6-dien-1-yl)-2,3,4,5-Tetramethoxy-6-methylbenzene (11b)

Alkylation of 2,3,4,5-tetrahydroxyoluene (300.0 mg, 1.41 mmol) with geraniol (246 μL, 1.41 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 50:1) yielded **11b** as colorless oil (45.7 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93–5.22 (overlapped, H-2′ and H-6′), 3.91, 3.90, 3.79, 3.79 (each s, 3-OMe, 4-OMe, 5-OMe and 6-OMe), 3.32 (brd, J = 6.7 Hz, H-1′), 2.14 (s, H-7), 1.99–2.08 (overlapped, H-4′ and H-5′), 1.76 (s, H-9′), 1.64 (s, H-8′), 1.58 (s, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.7 (C-3 and C-6), 144.9, 144.7 (C-4 and C-5), 135.0 (C-7′), 131.3 (C-3′), 129.3 (C-2), 125.4 (C-2′), 124.3 (C-6′), 122.9 (C-1), 61.1, 61.1, 61.1, 60.7 (3-OMe, 4-OMe, 5-OMe and 6-OMe), 39.7 (C-4′), 26.6 (C-5′), 25.7 (C-8′), 25.7 (C-1′), 17.7 (C-10′), 16.2 (C-9′), 11.7 (C-7); HREIMS *m/z*: 348.2301 $[M]^+$ (calcd. for $C_{21}H_{32}O_4$, 348.2301). The

structure was confirmed by comparison of spectroscopic data with the published data.[12]

4.2.26. 1,2,3,4-Tetramethoxy-5-methyl-6-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (11c)

Alkylation of 2,3,4,5-tetrahydroxyoluene (200.0 mg, 0.94 mmol) with farnesol (470 μL, 1.89 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography (*n*-Hex/EtOAc, 50:1) yielded **11c** as colorless oil (15.5 mg, 4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61–5.79 (overlapped, H-2′, H-6′ and H-10′), 3.91 3.90, 3.78, 3.78 (each s, 3-OMe, 4-OMe, 5-OMe and 6-OMe), 3.29 (brd, J = 7.1 Hz, H-1′), 2.23 (s, H-7), 1.95–2.08 (overlapped, H-4′ H-5′, H-8′ and H-9′), 1.77 (s, H-13′), 1.67 (s, H-12′), 1.59 (s, H-15′), 1.57 (s, H-14′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.7 (C-3 and C-6), 144.9, 144.7 (C-4 and C-5), 135.1 (C-7′), 135.0 (C-3′), 131.5 (C-11′), 129.3 (C-2), 126.3 (C-2′), 124.3 (C-6′), 124.1 (C-10′), 122.9 (C-1), 61.1, 61.1, 61.1, 60.7 (3-OMe, 4-OMe, 5-OMe and 6-OMe), 39.8 (C-4′), 39.7 (C-8′), 26.7 (C-9′), 26.6 (C-5′), 25.8 (C-12′), 25.7 (C-1′), 17.7 (C-15′), 16.2 (C-13′), 16.0 (C-14′), 11.7 (C-7); HREIMS m/z: 416.2931 $[M]^+$ (calcd. for $C_{26}H_{40}O_4$, 416.2927). The structure was confirmed by comparison of spectroscopic data with the published data.[12]

4.2.27. 2,2,5-Trimethylchromane-7,8-diol (9)

Demethylation of **7a** (100.0 mg, 0.71 mmol) followed to general procedure E yielded **9** as colorless oil (11.4 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, H-6), 5.21 (overlapped, 4-OH and 5-OH), 2.56 (t, J = 6.8 Hz, H-1′), 2.12 (s, H-7), 1.82 (t, J = 6.8 Hz, H-2′), 1.34 (s, H-4′ and H-5′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 141.1 (C-3 and C-5), 129.8 (C-4), 127.3 (C-1), 111.6 (C-2), 108.3 (C-6), 74.8 (C-3′), 32.9 (C-1′), 26.7 (C-4′ and C-5′), 19.8 (C-2′), 18.6 (C-7); HREIMS m/z: 208.1102 $[M]^+$ (calcd. for $C_{12}H_{16}O_3$, 208.1099).

4.2.28. 2,2,5-trimethylchromane-6,7,8-triol (13)

Demethylation of **11a** (50.0 mg, 0.18 mmol) followed to general procedure E yielded **13** as colorless oil (15.3 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (overlapped, 4-OH 5-OH and 6-OH), 2.56 (t, J = 6.8 Hz, H-1′), 2.07 (s, H-7), 1.82 (t, J = 6.8 Hz, H-2′), 1.31 (s, H-4′ and H-5′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 134.5, 130.2 (C-3, C-4 and C-5), 129.3 (C-1), 112.4 (C-2), 111.4 (C-6), 74.2 (C-3′), 33.3 (C-1′), 26.5 (C-4′ and C-5′), 19.9 (C-2′), 10.4 (C-7); HREIMS m/z: 224.1052 $[M]^+$ (calcd. for $C_{12}H_{16}O_4$, 224.1052).

4.2.29. 5-Methyl-4-(3-methylbut-2-en-1-yl)benzene-1,2,3-triol (8a)

Alkylation of **14** (100.0 mg, 0.71 mmol) with 3-methyl-2-buten-1-ol (71 μL, 0.71 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography ($CHCl_3$/MeOH, 50:1) yielded **8a**as colorless oil (17.0 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, H-6), 5.05 (m, H-2′), 4.87 (overlapped, 3-OH, 4-OH and 5-OH), 3.23 (brd, J = 6.8 Hz, H-1′), 2.08 (s, H-7), 1.74 (s, H-5′), 1.65 (s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (C-3), 144.4 (C-5), 131.9 (C-3′), 130.8 (C-4), 128.4 (C-1), 125.0 (C-2′), 119.6 (C-2), 109.5 (C-6), 26.1 (C-4′), 25.9 (C-1′), 19.4 (C-7), 17.9 (C-5′); HREIMS m/z: 208.1101 $[M]^+$ (calcd. for $C_{12}H_{16}O_3$, 208.1099).

4.2.30. (E)-4-(3,7-dimethylocta-2,6-dien-1-yl)-5-Methylbenzene-1,2,3-triol (8b)

Alkylation of **14** (100.0 mg, 0.71 mmol) with geraniol (124 μL, 0.71 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography ($CHCl_3$/MeOH, 50:1) and ODS silica gel column chromatography (MeOH/H_2O 8:2) yielded **8b**as colorless oil (55.5 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, H-6), 5.28 (overlapped, 3-OH, 4-OH and 5-OH), 5.17 (m, H-2′), 5.04 (m, H-6′), 3.30 (brd, J = 6.9 Hz, H-1′), 2.18 (s, H-7), 2.00–2.14 (overlapped, H-4′ and H-5′), 1.79 (s, H-9′), 1.67 (s, H-8′), 1.59 (s, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6 (C-3), 141.5 (C-5), 137.8 (C-3′), 132.0 (C-7′), 130.0 (C-4), 127.8 (C-1), 123.8 (C-6′), 122.2 (C-2′), 118.1 (C-2), 109.3 (C-6), 39.6 (C-4′), 26.4 (C-5′), 25.7 (C-8′), 25.7 (C-1′), 19.4 (C-7), 17.7 (C-10′), 16.1 (C-9′); HREIMS m/z: 276.1728 $[M]^+$ (calcd. for $C_{17}H_{24}O_3$, 276.1725).

4.2.31. 5-Methyl-4-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl) benzene-1,2,3-triol (8c)

Alkylation of **14** (100.0 mg, 0.71 mmol) with geraniol (177 μL, 0.71 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography ($CHCl_3$/MeOH, 50:1) yielded **8c** as colorless oil (34.8 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, H-6), 5.06–5.17 (overlapped, H-2′, H-6′ and H-10′), 3.30 (brd, J = 6.8 Hz, H-1′), 2.18 (s, H-7), 2.01–2.07 (overlapped, H-4′ H-5′, H-8′ and H-9′), 1.79 (s, H-13′), 1.68 (s, H-12′), 1.59 (s, H-15′), 1.59 (s, H-14′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (C-7), 141.7 (C-5), 137.7 (C-3′), 135.6 (C-7′), 131.4 (C-11′), 129.9 (C-4), 127.7 (C-1), 124.3 (C-10′), 123.6 (C-6′), 122.1 (C-2′), 118.0 (C-2), 109.2 (C-6), 39.9 (C-8′), 39.7 (C-4′), 26.7 (C-9′), 26.3 (C-5′), 25.7 (C-12′), 25.7 (C-1′), 19.4 (C-7), 17.7 (C-15′), 16.3 (C-13′), 16.1 (C-14′); HREIMS m/z: 344.2353 $[M]^+$ (calcd. for $C_{22}H_{32}O_3$, 344.2351). The structure was confirmed by comparison of spectroscopic data with the published data.[3]

4.2.32. 2,3-Dihydroxy-5-methyl-6-(3-methylbut-2-en-1-yl)cyclohexa-2,5-diene-1,4-dione (16a)

Alkylation of **15** (100.0 mg, 0.64 mmol) with 3-methyl-2-buten-1-ol (64 μL, 0.64 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography ($CHCl_3$/MeOH, 50:1) and ODS silica gel column chromatography (MeOH/H_2O 8:2) yielded **16a** as red oil (38.1 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (overlapped, 4-OH and 5-OH), 4.92 (m, H-2′), 3.19 (brd, J = 7.2 Hz, H-1′), 2.06 (s, H-7), 1.73 (s, H-5′), 1.68 (s, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5 (C-6), 183.8 (C-3), 140.9, 138.0 (C-1 and C-2), 134.5, 133.9 (C-4 and C-5), 133.9 (C-3′), 118.5 (C-2′), 25.7 (C-4′), 18.0 (C-5′), 11.7 (C-7); HREIMS m/z: 222.0890 $[M]^+$ (calcd. for $C_{12}H_{14}O_4$, 222.0892).

4.2.33. (E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-5,6-Dihydroxy-3-methylcyclohexa-2,5-diene-1,4-dione (16b)

Alkylation of **15** (100.0 mg, 0.64 mmol) with geraniol (112 μL, 0.64 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography ($CHCl_3$/MeOH, 50:1) and ODS silica gel column chromatography (MeOH/H_2O 8:2) yielded **16b** as red oil (14.1 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (overlapped, 4-OH and 5-OH), 5.03 (m, H-2′), 4.92 (m, H-6′), 3.21 (brd, J = 7.0 Hz, H-1′), 2.06 (s, H-7), 1.96–2.05 (overlapped, H-4′ and H-5′), 1.73 (s, H-9′), 1.65 (s, H-8′), 1.57 (s, H-10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4 (C-6), 183.7 (C-3), 141.0, 138.0 (C-1 and C-2), 138.0, 133.9 (C-4 and C-5), 133.8, 131.6 (C-3′ and C-7′), 123.9 (C-6′), 118.5 (C-2′), 39.6 (C-4′), 26.4 (C-5′), 25.7 (C-8′), 25.1 (C-1′), 17.7 (C-10′), 16.3 (C-9′), 11.7 (C-7); HREIMS m/z: 290.1525 $[M]^+$ (calcd. for $C_{17}H_{22}O_4$, 290.1518).

4.2.34. 2,3-Dihydroxy-5-methyl-6-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)cyclohexa-2,5-diene-1,4-dione (16c)

Alkylation of **15** (200.0 mg, 1.28 mmol) with farnesol (319 μL, 1.28 mmol) followed to general procedure A. Purification of the crude mixture by silica-gel column chromatography ($CHCl_3$/MeOH, 50:1) and ODS silica gel column chromatography (MeOH/H_2O 8:2) yielded **16c** as red oil (43.0 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (overlapped, 4-OH and 5-OH), 5.04 (overlapped, H-6′and H-10′), 4.93 (m, H-2′), 3.22 (brd, J = 6.9 Hz, H-1′), 2.05 (s, H-7), 1.84–2.07 (overlapped, H-4′ H-5′, H-8′ and H-9′), 1.72 (s, H-13′), 1.68 (s, H-12′), 1.58 (s H-14′), 1.57 (s, H-15′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4 (C-6), 183.7 (C-3), 140.9, 138.1 (C-1 and C-2), 138.0 (C-3′), 135.4 (C-7′), 135.3, 133.9 (C-4 and C-5), 131.6 (C-11′), 124.5 (C-10′), 124.2 (C-6′), 118.4 (C-2′), 39.7 (C-4′ and C-8′), 26.7, 26.6 (C-5′ and C-9′), 25.7 (C-12′), 25.1 (C-1′), 17.7 (C-15′), 16.3 (C-13′), 16.0 (C-14′), 11.7 (C-7); HREIMS m/z: 358.2142 $[M]^+$ (calcd. for $C_{22}H_{30}O_4$, 358.2144).

4.3. MAO-B inhibition assay

MAO-B inhibitory activity was assayed using the method of Novaroli *et al.* with slight modifications.[19] 0.1 M potassium phosphate buffer (pH 7.4), 8 µL of 0.75 mM kynuramine (Sigma-Aldrich, St. Louis, MO), and 2 µL of a dimethyl sulfoxide (DMSO) inhibitor solution (final DMSO concentration of 1% (v/v), were preincubated at 37 °C for 10 min. Diluted human recombinant MAO-B (M7441, Sigma-Aldrich) was then added to obtain a final protein concentration of 0.015 mg/mL in the assay mixture. The reaction mixture was further incubated at 37 °C and the reaction was stopped after 20 min by the addition of 75 µL of 2 M NaOH. The product generated by MAO-B, 4-quinolinol, is fluorescent and was measured at Ex 310 nm/Em 400 nm using a microplate reader (SPECTRA MAX M2, Molecular Devices, Tokyo, Japan). DMSO without test compound was used as the negative control and pargyline (Sigma-Aldrich) was used as a positive control (IC_{50} = 0.22 µM). The IC_{50} values were estimated using Prism software (version 5.02; GraphPad, San Diego, CA).

4.4. Cell culture

Human neuroblastoma SH-SY5Y cells were purchased from European Collection of Authenticated Cell Cultures and cultured at 37 °C, 5% CO_2 in Eagle's Minimal Essential Medium/Ham's F-12 medium (E-MEM/F12: FUJIFILM Wako Pure Chemical Corporation) supplemented with 0.3% fetal bovine serum (FBS: Funakoshi, Tokyo, Japan), 0.01% penicillin (MP Bio Japan, Tokyo, Japan) and 0.01% Minimal Essential Medium Non-Essential Amino Acids (MP Bio Japan).

4.5. Protective effect on SH-SY5Y against H_2O_2 toxicity assay

Each compound was dissolved in DMSO. The final DMSO concentration in the culture medium was less than 0.5% and this concentration had no effect on SH-SY5Y cells. Cells were seeded on the 96-well plate (5.0×10^4 cells/100 µL/well). After incubation for 24 h, the usual medium was removed, then each test sample and H_2O_2 (the final concentration was 500 µM) was added in the E-MEM/F12 medium without FBS. After incubation for 24 h at 37 °C in 5% CO_2, cell viability was determined using the MTT assay. The medium was removed and 100 µL of MTT reagent solved in E-MEM/F12 medium (5 mg/mL) was added to each well. The plate was incubated for 24 h at 37 °C in 5% CO_2, then the absorbance at 595 nm was measured. Results are shown as mean ± SD (n = 3). Data were analyzed using one-way ANOVA, followed by Dunnet's test using Prism software. The cytotoxic activity of **2c**, **3c**, **8c** and **16c** was tested with the same method without H_2O_2. **2c** showed cytotoxicity at 5 and 10 µM (63 and 60% of cell viability). **3c**, **8c** and **16c** didn't show cytotoxicity at most 10 µM.

4.6. Docking study

The MAO-B crystal structure was retrieved from the Protein Data Bank (PDB code: 4A79) and imported into the Auto-Dock program (Version 4.2). The structures of compounds were drawn using ChemBioDrawUltra 11.0 and subjected to energy minimization using molecular mechanics (MM2). AutoGrid was used to calculate the grid maps and the grid was centered on the ligand binding site of MAO-B such that it would totally cover the ligand molecule. The centroid of the grid map was set to X: 17, Y: 125, Z: 29, and the number of grid points was X: 54, Y: 60, Z: 54. The maximum number of energy evaluations was set to 250,000. Both ligand and receptor docking were performed using the Lamarckian Genetic Algorithm (Runs 20) after using the default parameter settings generated by AutoDockTools for docking. The binding mode was visualized by Discovery Studio Visualizer (version 19; Accelrys, Inc. San Diego, CA).

Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2019.115156.

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