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New 1,2,3-Triazole-genipin Analogues and Their Anti-Alzheimer's Activity

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Cite This: *ACS Omega* 2022, 7, 24302−24316

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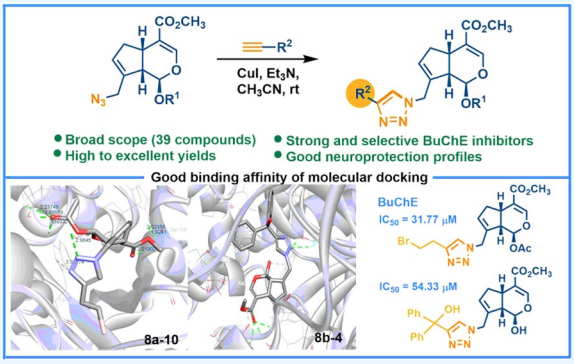
ABSTRACT: A novel series of 1,2,3-triazole-genipin analogues were designed, synthesized, and evaluated for neuroprotective activity, acetylcholinesterase (AChE), and butyrylcholinesterase (BuChE) inhibitory activity. The genipin analogues bearing bromoethyl- and diphenylhydroxy-triazole showed *in vitro* neuroprotective properties against H_2O_2 toxicity along with potent inhibitory activity on BuChE with IC_{50} values of 31.77 and 54.33 μM, respectively, compared with galantamine (IC_{50} = 34.05 μM). The molecular docking studies of these genipin analogues showed good binding energy and interact well with the key amino acids of BuChE *via* hydrogen-bonding and hydrophobic interactions. Triazole genipins might be promising lead compounds as anti-Alzheimer's agents.



1. INTRODUCTION

Alzheimer's disease (AD) is the most common form of neurodegenerative disorder and the most prevalent cause of dementia, making it one of the major public health problems.[1] A report by the World Health Organization (WHO) showed that about 50 million people are affected by dementia worldwide, and it is projected to affect around 115.4 million people worldwide by 2050.[2] Nowadays, four common drugs for the treatment of Alzheimer's disease have been approved by the European and United States regulatory authorities including tacrine,[3] memantine,[4] galantamine,[5] and donepezil[6] (Figure 1). The therapeutic drugs on the market are not widely available since their efficacy is limited by diverse unpleasant side effects. Thus, there is an urgent need for the development of effective anti-Alzheimer's agents with low side effects.

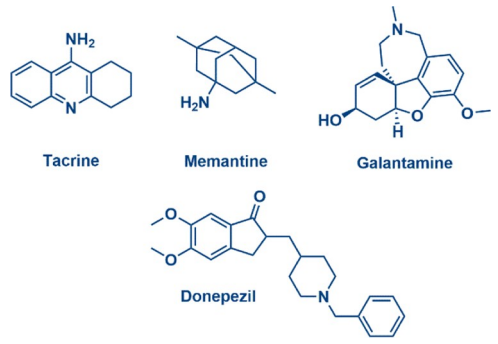


Figure 1. Examples of drugs used for Alzheimer's disease (AD) available on the market.

AD is a multifactorial disease commonly featuring neuronal cell death and loss of cholinergic neurons due to a decrease in acetylcholine availability at neuronal synapses.[7] From a physiological point of view, the activity of acetylcholine in the synapses can be diminished by the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE).[8] Therefore, one efficient approach to cure AD is to restore the level of acetylcholine using AChE and BuChE inhibitors.[9] In normal healthy brains, AChE plays an important role and BuChE is supportive in the hydrolysis of acetylcholine.[10] As AD progresses, the level of AChE in the brain declines by approximately 50% of normal values whereas BuChE progressively increases to 120% of normal levels. Thus, the BuChE activity progressively increases as the graveness of dementia increases but AChE activity diminishes. Therefore, BuChE was examined as a key target for the treatment of AD.[11,12] Hence, BuChE inhibitors with neuroprotection potential may have a special therapeutic effect on AD.[13,14]

Gardenia jasminoides Ellis is a flowering plant belonging to the gardenia genus in the Rubiaceae family. The fruits are used as a therapeutic herb that is rich in biological activity, such as

Received: March 16, 2022
Accepted: June 14, 2022
Published: July 6, 2022

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https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316

inflammation, jaundice, and hepatic disorders.[15] Generally, this herb is used in herbal medicines or functional food supplements displaying therapeutic effects on central nervous system (CNS) diseases, including dementia, cerebral stroke, and antioxidants with nonharmful and nontoxic side effects.[16] Geniposide, the main component in the fruit, belongs to the class of iridoid glycoside and can be hydrolyzed into genipin **1** by intestinal bacteria after ingestion (Figure 2).[17]

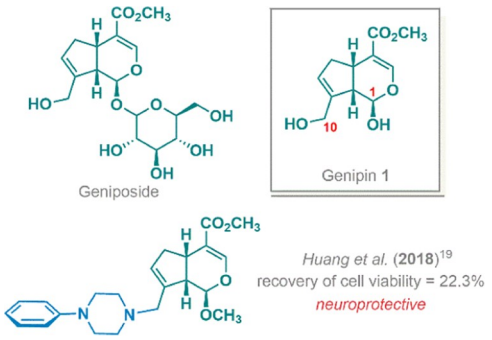

Figure 2. Chemical structures of geniposide, genipin **1**, and derivatives.

Pharmacokinetic studies have suggested that genipin is the main active compound and showed promising bioactivities as a strong neuroprotection agent by inhibiting high-level lactate dehydrogenase (LDH) in the blood, which causes amyloid-β (Aβ) peptide toxicity in cultured neuronal cells.[18] Recently, Huang et al.[19] reported that piperazine-genipin analogues are dual AChE/Aβ_{1-42} aggregation inhibitors, which repair the neuronal cell damage from amyloid-β (Aβ) peptide toxicity by 22.3% (Figure 2). These results led us to design and modify the structure of genipin to explore the potential of its derivatives as candidates for the treatment of AD.

1,2,3-Triazole is a five-membered heterocyclic compound containing two carbon and three nitrogen atoms. 1,2,3-Triazole is found in abundance in medicinal compounds.[20,21] The triazole ring displays bond acceptor properties capable of forming significant interactions with biomolecular targets through H-bonding, $\pi-\pi$ stacking, and dipole interactions. These scaffolds are commonly synthesized through Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition between alkynes and azides (CuAAC) by the concept of click.[22−26] Previously, some triazole derivatives were synthesized as potent and highly selective BuChE inhibitors and neuroprotective agents (Figure 3).[27−30]

Considering the work on genipin and 1,2,3-triazole mentioned above, the linking of these two units might lead to hybrids with higher neuroprotective activity than the parent genipin. Therefore, in this work, a new series of 1,2,3-triazole-genipin analogues were designed and synthesized and were focused on the biological evaluation as selective BuChE inhibitors with neuroprotective properties. The molecular docking studies were also explored for further understanding of enzyme inhibition (Figure 4).

2. RESULTS AND DISCUSSION

2.1. Chemistry. The synthetic route for modification of genipin to 1,2,3-triazole-genipin analogues **8a** and **8b** is depicted in Scheme 1. The target compounds were synthesized *via* six- or seven-step reactions. Initially, genipin **1** was silylated

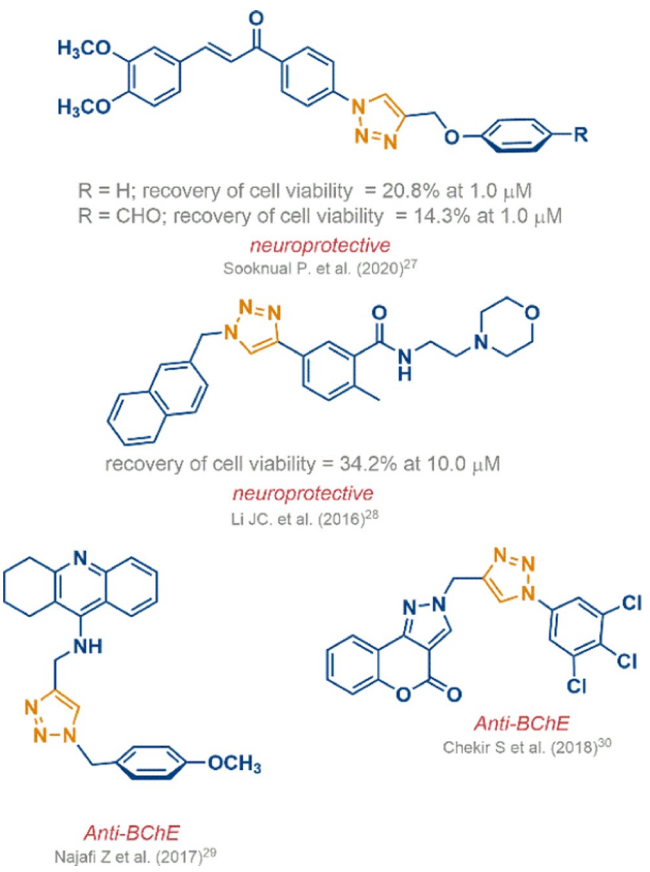

Figure 3. Some examples of 1,2,3-triazole used as inhibitors of butyrylcholinesterase (BuChE) and neuroprotective agents.

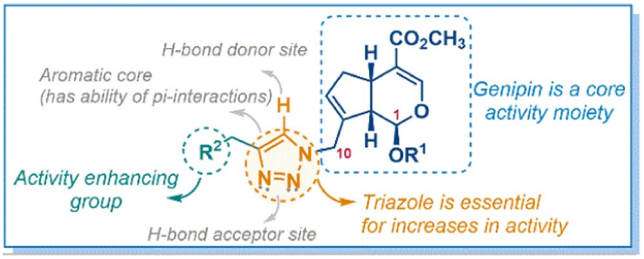

Figure 4. Design of novel 1,2,3-triazole-genipin analogues.

to protect the hydroxy at C-10 by stirring in *tert*-butyldimethylsilyl chloride (TBSCl) in pyridine for 10 min to obtain **2**. Compound **2** was further reacted with imidazole and acetic anhydride (Ac_2O) or *tert*-butyldiphenylsilyl chloride (TBDPSCl) for conversion of the hydroxy of the hemiacetal to acetyl or silyl ether giving compounds **3a** or **3b**, respectively. Subsequently, deprotection of *tert*-butyldimethylsilyl (TBS)-ether at the C-10 position of genipin was achieved by dropwise addition of HCOOH/H_2O (9:1) at 0 °C and stirring for 6 h to obtain a crude product **4a** or **4b**. Mesylation of the resulting hydroxy group afforded the corresponding mesyl derivatives. No further chromatography purification was necessary for the four steps. Azidation of mesylate group to desired azido precursor **6a** yielded 72% in five steps. Desilylation of the TBDPS group at C-1 of **6b** was carried out using tetra-*n*-butylammonium fluoride (TBAF) to obtain the hemiacetal analogue **7b** in 43% yield in six steps. The azide−alkyne Huisgen cycloaddition reaction was performed in the final step

https://doi.org/10.1021/acsomega.2c01593
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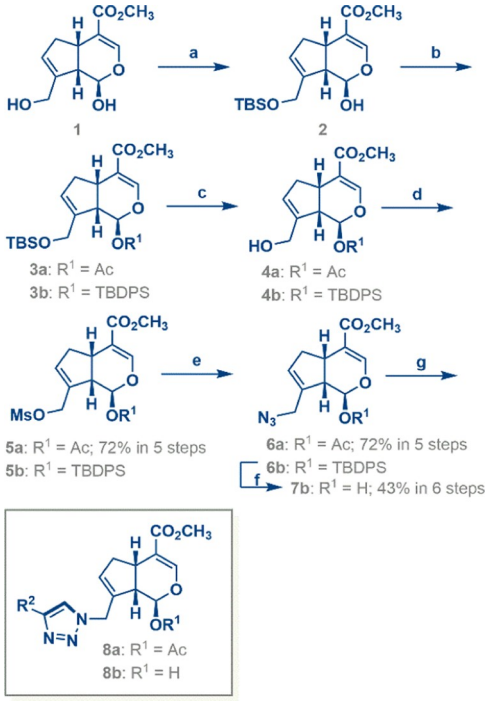
Scheme 1. Synthesis of the 10-Triazolylgenipin Analogues 8a and 8b[a]



[a]Reaction conditions: (a) TBSCl, pyridine, 10 min; (b) Ac_2O or TBDPSCl, imidazole, dichloromethane (DCM), 1 h; (c) HCOOH/H_2O (9:1), tetrahydrofuran (THF), 0 °C to room temperature (rt), 6 h; (d) MsCl, Et_3N, DCM, 0 °C to rt, 24 h; (e) NaN_3, dimethylformamide (DMF), 0.5 h; (f) TBAF, DCM, 0.5 h; (g) alkyne, CuI, Et_3N, CH_3CN, rt.

by mixing **6a** or **7b** with various alkynes using copper iodide to promote reaction to give a series of C-10 triazole analogues **8a** or **8b**.

As shown in Scheme 2, the reactions of different alkynes with azido genipin **6a** and **7b** were explored. Genipin analogues **8a** and **8b** bearing phenyl, benzyl ether, benzylamine, and aliphatic, phthalimide, and alicyclic substituted triazoles with different carbon chain lengths were successfully obtained in good to excellent yields. It was observed that phenyl-substituted, benzyl ether, and benzylamine afforded the corresponding products (**8a-1**−**8a-8**) in moderate to excellent yields (52−99%). Different substituents on the aromatic ring (−OCH_3, −F) in compounds **8a-2** and **8a-3** did not affect the yields in this transformation. A series of aliphatic chains bearing bromine **8a-9**, hydroxy group **8a-10** and **8a-11**, silyl group (**8a-12**−**8a-15**), trityl **8a-16**, and long-chain aliphatic chains (**8a-17**−**8a-19**) were reacted smoothly, affording the desired products in good to excellent yields (66−92%). Moreover, the reaction proceeded in good to excellent yields with alkynyl-phthalimides and hydroxy alicyclic alkyne (**8a-20**−**8a-26**).

For a series of hemiacetal triazole genipin analogues **8b**, phenyl-substituted with the electron-withdrawing group fluorine **8b-3** were more favorable for conversions than the electron-donating group methoxy **8b-2**. Triazoles bearing diphenyl or aliphatic chains provided the desired genipin analogues (**8b-4**−**8b-6**) in 46−78% yields. Additionally, the reaction of the long-chain aliphatic substituted triazole delivered the corresponding products (**8b-7**−**8b-9**) in moderate yields. The triazole substituted with phthalimide gave products **8b-10** and **8b-11** in 68 and 80% yields, respectively.

Finally, hydroxy alicyclic reacted smoothly to furnish corresponding triazole products **8b-12** and **8b-13** in excellent yields.

Based on the above experimental results, the hemiacetal products **8b** gave products with lower yields and stability than acetoxy-substituted analogues **8a**.

2.2. Biological Evaluations. *2.2.1. Neuroprotective Effects of 1,2,3-Triazole-genipin Analogues on the H_2O_2 Induced Decrease in Cell Viability.* The protective effect of 1,2,3-triazole-genipin analogues on the H_2O_2-induced cell viability was studied. As shown in Table 1, 250 μM H_2O_2 significantly reduced cell viability (43.0 ± 0.9%). During treatment with our synthetic compounds, 14 analogues exhibited significant neuroprotective activity with a level up to 70% of cell viability at 0.075 μM and some analogues showed better activity than the parent genipin **1** (78.0%). In the series of acetoxy analogues **8a**, compound **8a-2** with substituted *p*-methoxy and **8a-3** with *p*-fluoro substituent on aryltriazole exhibited neuroprotective activity with 72.5 and 70.9% cell viability at 0.075 μM, respectively. Both the electron-withdrawing and electron-donating groups on aryltriazole showed similar results. Triazole genipin analogue **8a-5** with benzyl ether (79.7% of cell viability) and 3,4-OCH_3 **8a-7** (78.1% of cell viability) showed better cell viabilities than the analogues 4-OCH_3 **8a-6** (62.7% of cell viability) and benzylamine **8a-8** (50.8% of cell viability). When the benzyl ether substituent (**8a-5**−**8a-8**) was replaced by an alkyl chain (**8a-9**−**8a-19**), the neuroprotective activity was significantly increased. Substituents such as Br and OH aryltriazoles on compounds **8a-10**, **8a-11**, and **8a-14** showed superior neuroprotective activity, while compounds **8a-20**−**8a-24** containing substituted phthalimide displayed moderate neuroprotective activity. The exception was **8a-20**, which showed remarkable cell viability of up to 78.5% at 0.075 μM. Furthermore, hydroxy-hexacyclic compound **8a-26** showed better activity than the pentacyclic compound **8a-25** at 0.075 μM, which indicated the effect of substituted groups on the neuroprotective activity.

For the series of hemiacetal triazole genipin analogues **8b**, compounds bearing electron-donating 4-OCH_3 aryl (compound **8b-2**, 78.6%) exhibited remarkably higher neuroprotective activity than the electron-withdrawing *p*-fluoroaryl (compound **8b-3**, 59.9%) at the same concentration of 0.6 μM. When the concentration was reduced to 0.075−0.3 μM, the cell viability decreased. The activity results of **8a-2** and **8b-2** demonstrated that a substituted group at the C-1 position showed a significant difference between the neuroprotective potencies. In addition, at a concentration of 0.15 μM, compound **8b-4** exhibited significant neuroprotective effects and the cell viability was up to 80.9%. When the concentration was reduced to 0.075 μM, the cell viability decreased to 73.0%. Therefore, a concentration of 0.15 μM was suitable for treatment by the synthetic compounds. For the replacement of long-chain aliphatic ether groups on triazole with different carbon chain lengths, both **8b-7** and **8b-8** decreased the cell viability compared with an aromatic substituted triazole (**8b-2** and **8b-4**). On replacing alkyl with phthalimide, compounds **8b-10** and **8b-11** exhibited strong neuroprotective activities of 77.2 and 75.5%, respectively. Moreover, compounds **8b-12** and **8b-13** bearing a hydroxyl cyclic group increased cell viability

https://doi.org/10.1021/acsomega.2c01593
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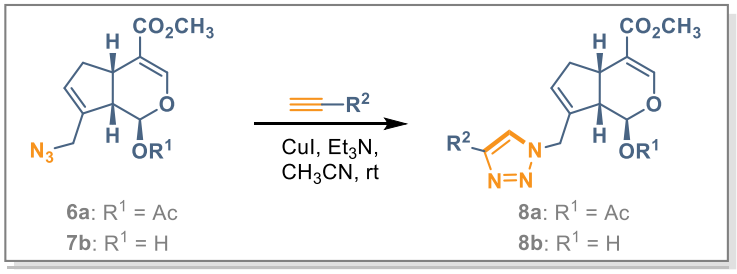
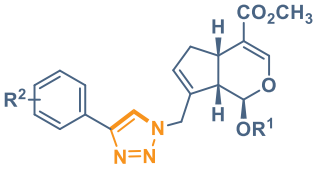
Scheme 2. Scope of Alkyne for Synthesis of the 1,2,3-Triazole-genipin Analogues 8a and 8b[a]

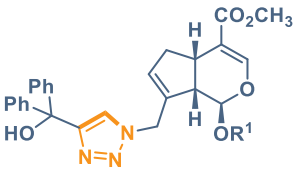


6a: R^1 = Ac
7b: R^1 = H

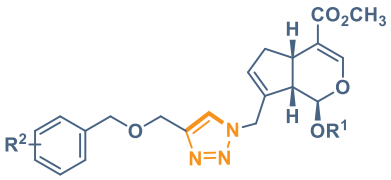
8a: R^1 = Ac
8b: R^1 = H



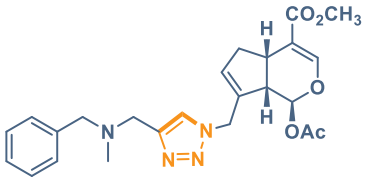
8a-1; R^1 = Ac, R^2 = H, 2 h, 52%
8a-2; R^1 = Ac, R^2 = 4-OCH_3, 24 h, 75%
8a-3; R^1 = Ac, R^2 = 4-F, 4 h, 78%
8b-1; R^1 = H, R^2 = H, 3 h, 67%
8b-2; R^1 = H, R^2 = 4-OCH_3, 23 h, 45%
8b-3; R^1 = H, R^2 = 4-F, 4 h, 78%



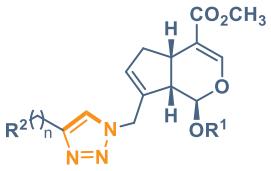
8a-4; R^1 = Ac, 4 h, >99%
8b-4; R^1 = H, 10 min, 64%



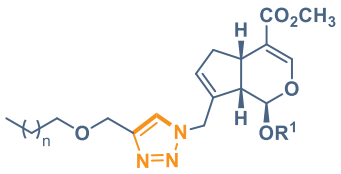
8a-5; R^1 = Ac, R^2 = H, 1 h, 86%
8a-6; R^1 = Ac, R^2 = 4-OCH_3, 1 h, 82%
8a-7; R^1 = Ac, R^2 = 3,4-OCH_3, 10 min, 86%



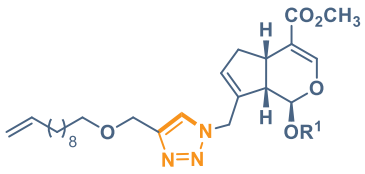
8a-8; 0.5 h, 99%



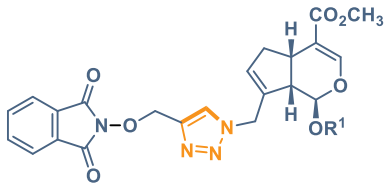
8a-9; n = 1, R^1 = Ac, 10 min, R^2 =OTr, 84%
8a-10; n = 2, R^1 = Ac, R^2 = Br, 0.5 h, 75%
8a-11; n = 2, R^1 = Ac, R^2 = OH, 0.5 h, 81%
8a-12; n = 2, R^1 = Ac, R^2 = OTBDPS, 10 min, 80%
8a-13; n = 2, R^1 = Ac, R^2 = OTBS, 45 min, 76%
8a-14; n = 3, R^1 = Ac, R^2 = OH, 0.5 h, 72%
8a-15; n = 3, R^1 = Ac, R^2 = OTBDPS, 1.5 h, 72%
8a-16; n = 3, R^1 = Ac, R^2 = OTIPS, 3 h, 92%
8b-5; n = 1, R^1 = H, R^2 = OTBDPS, 10 min, 78%
8b-6; n = 3, R^1 = H, R^2 = OTBDPS, 3 h, 46%



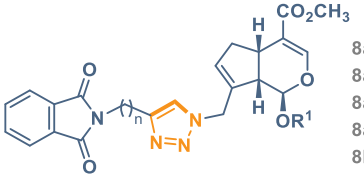
8a-17; n = 6, R^1 = Ac, 1 h, 90%
8a-18; n = 8, R^1 = Ac, 3 h, 89%
8b-7; n = 6, R^1 = H, 1 h, 55%
8b-8; n = 8, R^1 = H, 2 h, 53%



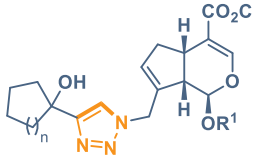
8a-19;R^1 = Ac, 10 min, 66%
8b-9;R^1 = H, 2 h, 69%



8a-20; R^1 = Ac, 6 h, 57%
8b-10; R^1 = H, 8 h, 68%



8a-21; n = 1, R^1 = Ac, 1 h, 99%
8a-22; n = 2, R^1 = Ac, 1 h, 99%
8a-23; n = 3, R^1 = Ac, 10 min, 77%
8a-24; n = 4, R^1 = Ac, 10 min, 60%
8b-11; n = 1, R^1 = H, 1 h, 80%



8a-25; n = 1, R^1 = Ac, 0.5 h, 99%
8a-26; n = 2, R^1 = Ac, 0.5 h, 99%
8b-12; n = 1,R^1 = H, 10 min, 97%
8b-13; n = 2,R^1 = H, 10 min, 92%

[a]Reaction conditions: **6a** (0.3413 mmol) or **7b** (0.3980 mmol), CuI (20 mol %), Et3N (0.5 equiv), and alkyne (1.5 equiv) in CH_3CN (1.0 mL) at rt (10 min to 24 h). % is yields of isolated products after purification by column chromatography.

with percentages of 79.9 and 77.3%, respectively, at 0.15 μM, which might be due to its favorable conformation that allows these scaffolds to fit within the active site of the enzyme.

The overall results indicated that some 1,2,3-triazole-genipin analogues (**8a-5**, **8a-7**, **8a-10**, **8a-11**, **8a-14**, **8a-20**, **8b-2**, **8b-4**, **8b-12**, and **8b-13**) at concentrations of 0.075−0.6 μM significantly improved the cell viability rate of H_2O_2-treated neuronal cells by up to 78% (Figure 5). Compound **8a-11** showed the highest protective capability (83.5% of cell viability) at 0.075 μM recovering the neuronal cell damage from H_2O_2 toxicity with 40.5%. Compounds **8a-10** and **8b-4** displayed similar protective ability (80.9% of cell viability) recovering the neuronal cell damage by H_2O_2 toxicity with 37.9%. These three analogues evidenced the most significant protection in reducing H_2O_2-induced neurotoxicity in neuroblastoma cells.

2.2.2. Cholinesterase Inhibition Assay. The inhibitory activity of the newly synthesized 1,2,3-triazole-genipin

https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316

Table 1. Neuroprotective Effects of 1,2,3-Triazole-genipin Analogues

	cell viability (%)[a]/recovery of cell viability (%)[b]			
compounds	0.075 μM	0.15 μM	0.3 μM	0.6 μM
control	100			
H_2O_2 (250 μM)	43.0 ± 0.9			
genipin 1	78.0 ± 0.5 (35.0)	71.4 ± 0.5 (28.4)	57.8 ± 0.7 (14.8)	64.4 ± 0.5 (21.4)
8a-1	NA[c]	NA[c]	NA[c]	NA[c]
8a-2	72.5 ± 0.6 (29.5)	66.6 ± 0.7 (23.6)	60.1 ± 1.0 (17.1)	54.2 ± 0.8 (11.2)
8a-3	70.9 ± 1.5 (27.9)	64.9 ± 1.2 (21.9)	58.6 ± 0.9 (15.6)	52.3 ± 0.9 (9.3)
8a-4	NA[c]	NA[c]	NA[c]	NA[c]
8a-5	79.7 ± 0.4 (36.7)	73.0 ± 0.2 (30.0)	67.1 ± 0.2 (24.1)	60.6 ± 0.4 (17.6)
8a-6	62.7 ± 0.3 (19.7)	65.9 ± 0.7 (22.9)	67.6 ± 0.5 (24.6)	69.5 ± 0.2 (26.5)
8a-7	78.1 ± 0.4 (35.1)	71.7 ± 0.06 (28.7)	65.3 ± 0.21 (22.3)	59.0 ± 0.21 (16.0)
8a-8	50.8 ± 0.9 (7.8)	50.8 ± 0.6 (7.8)	52.9 ± 0.5 (9.9)	51.2 ± 0.8 (8.2)
8a-9	NA[c]	NA[c]	NA[c]	NA[c]
8a-10	**80.9 ± 0.4 (37.9)**[d]	74.8 ± 0.6 (31.8)	68.9 ± 0.5 (25.9)	61.9 ± 0.2 (18.9)
8a-11	**83.5 ± 2.5 (40.5)**[d]	77.1 ± 2.1 (34.1)	71.2 ± 2.8 (28.2)	65.3 ± 0.29 (22.3)
8a-12	49.6 ± 0.6 (6.6)	48.5 ± 0.8 (5.5)	47.8 ± 0.3 (4.8)	53.2 ± 0.5 (10.2)
8a-13	74.2 ± 0.4 (31.2)	68.6 ± 0.15 (25.6)	62.8 ± 0.2 (19.8)	56.6 ± 0.2 (13.6)
8a-14	78.8 ± 0.4 (35.8)	72.7 ± 0.4 (29.7)	66.6 ± 0.1 (23.6)	60.8 ± 0.8 (17.8)
8a-15	NA[c]	NA[c]	NA[c]	NA[c]
8a-16	NA[c]	NA[c]	NA[c]	NA[c]
8a-17	56.1 ± 0.5 (13.1)	62.5 ± 0.4 (19.5)	68.1 ± 0.1 (25.1)	74.4 ± 0.6 (31.4)
8a-18	52.1 ± 0.5 (9.1)	58.2 ± 0.3 (15.2)	60.8 ± 0.6 (17.8)	61.2 ± 0.8 (18.2)
8a-19	57.1 ± 0.3 (14.1)	63.2 ± 0.3 (20.2)	69.2 ± 0.4 (26.2)	75.3 ± 0.5 (32.3)
8a-20	78.5 ± 0.4 (35.5)	71.6 ± 0.1 (28.6)	66.4 ± 0.1 (23.4)	60.1 ± 0.1 (17.1)
8a-21	53.5 ± 0.6 (10.5)	54.2 ± 1.1 (11.2)	56.8 ± 1.3 (13.8)	58.2 ± 1.7 (15.2)
8a-22	53.2 ± 2.5 (10.2)	54.9 ± 2.7 (11.9)	60.8 ± 1.6 (17.8)	65.5 ± 2.7 (22.5)
8a-23	50.9 ± 0.4 (7.9)	52.9 ± 0.7 (9.9)	61.6 ± 0.5 (18.6)	66.1 ± 0.8 (23.1)
8a-24	50.7 ± 0.5 (7.7)	51.7 ± 0.7 (8.7)	60.5 ± 0.7 (17.5)	65.9 ± 1.1 (22.9)
8a-25	52.3 ± 0.8 (9.3)	58.1 ± 1.1 (15.1)	60.2 ± 1.2 (17.2)	63.4 ± 0.2 (20.4)
8a-26	75.1 ± 0.9 (32.1)	69.2 ± 1.1 (26.2)	63.3 ± 1.0 (20.3)	57.1 ± 1.2 (14.1)
8b-1	NA[c]	NA[c]	NA[c]	NA[c]
8b-2	54.9 ± 2.5 (11.9)	63.0 ± 2.6 (20.0)	75.2 ± 2.3 (32.2)	78.6 ± 1.9 (35.6)
8b-3	50.9 ± 1.2 (7.9)	52.6 ± 1.6 (9.6)	55.9 ± 1.1 (12.9)	59.9 ± 0.7 (16.9)
8b-4	73.0 ± 3.1 (30.0)	**80.9 ± 3.0 (37.9)**[d]	72.7 ± 2.6 (29.7)	69.2 ± 1.7 (26.2)
8b-5	NA[c]	NA[c]	NA[c]	NA[c]
8b-6	NA[c]	NA[c]	NA[c]	NA[c]
8b-7	51.6 ± 1.4 (8.6)	53.2 ± 1.7 (10.2)	53.7 ± 2.5 (10.7)	65.9 ± 1.1 (22.9)
8b-8	52.1 ± 0.5 (9.1)	58.2 ± 0.3 (15.2)	60.8 ± 0.6 (17.8)	61.2 ± 0.8 (18.2)
8b-9	NA[c]	NA[c]	NA[c]	NA[c]
8b-10	52.0 ± 1.8 (9.0)	70.9 ± 1.3 (27.9)	73.6 ± 1.6 (30.6)	77.2 ± 1.8 (34.2)
8b-11	70.1 ± 1.5 (27.1)	72.7 ± 1.5 (29.7)	75.5 ± 0.1 (32.5)	72.2 ± 0.9 (29.2)
8b-12	75.0 ± 2.5 (32.0)	78.3 ± 1.8 (35.3)	78.2 ± 0.9 (35.2)	77.2 ± 0.9 (34.2)
8b-13	72.5 ± 2.5 (29.5)	79.9 ± 0.5 (36.9)	79.2 ± 1.0 (36.2)	74.1 ± 1.7 (31.1)

[a]Cell viability (%): the cell viability in control was taken as 100%; all data were expressed as mean ± standard deviation (SD) (n = 3). [b]Recovery of cell viability (%): the difference value between the cell viability of compound-treated cells and that of H_2O_2-treated cells. [c]NA: not active. [d]Bold values highlight the most potent activity.

analogues (**8a** and **8b**) was evaluated against electric eel-derived AChE (eeAChE) and equine serum-derived BuChE (eqBuChE)[31] and compared with galantamine, a reference drug with IC_{50} values 12.7 and 34 μM, respectively. As shown in Table 2, the results of inhibitory activity for butyrylcholinesterase (BuChE) were superior to acetylcholinesterase (AChE). All synthetic analogues demonstrated inhibition of AChE less than 50%, and hence further IC_{50} measurement was not carried out. Almost all synthesized compounds gave higher inhibitory activities against BuChE than the natural product geniposide and genipin **1** indicating that the introduction of the triazole ring greatly influenced the inhibitory behavior of genipin.

The series of acetoxy analogues **8a** with a diverse range of substituents on the triazole ring resulting in different activities were indicated by both the % inhibition of BuChE and IC_{50} values. Genipin analogue **8a-1** bearing phenyl triazole exhibited moderate inhibitory activity against BuChE, and replacement with 4-OMe and 4-F aryltriazole (**8a-2** and **8a-3**) resulted in the loss of activity.

Di- and triphenyl, benzyl ether, and benzylamine triazole genipin **8a-4**−**8a-9** showed no improved activity compared to phenyl triazole genipin **8a-1**−**8a-3**. When triazoles were substituted with an alkyl chain (**8a-10**−**8a-19**), they exhibited low to high inhibitory activity. Surprisingly, genipin analogue **8a-10** with a bromoethyltriazole scaffold exhibited the most

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ACS Omega 2022, 7, 24302−24316

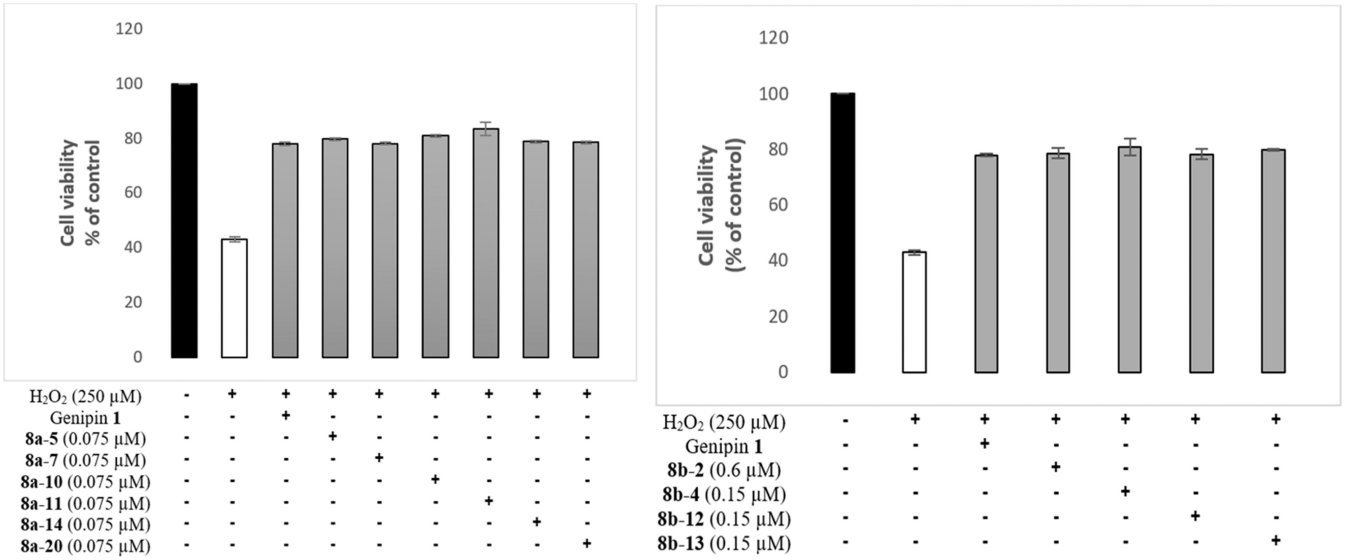

Figure 5. Neuroprotective effect of 1,2,3-triazole-genipin analogues on survival of H_2O_2-treated neurons, Compounds **1**, **8a-5**, **8a-7**, **8a-10**, **8a-11**, **8a-14**, **8a-20**, **8b-2**, **8b-4**, **8b-12**, and **8b-13** significantly exhibited the neuroprotective effect with >78% cell viability.

potent inhibitory activity with an IC_{50} value of 31.8 μM better than galantamine (IC_{50} value: 34.1 μM). In contrast, triazolgenipin containing long-chain aliphatic groups showed lower activity than the compound comprising a bromoethyl group (**8a-10**). Furthermore, the replacement of the long-chain alkyl group with phthalimide scaffolds (**8a-21**−**8a-23**) leads to significant improvement in BuChE inhibitory potencies and exhibited IC_{50} values of 273.9, 203.4, and 418.5 μM, respectively. Hydroxy-cyclic compounds such as **8a-25** and **8a-26** showed no significant change in inhibitory activity.

The series of hemiacetal triazole genipin analogues **8b** exhibited promising inhibitory potential against BuChE. The behavior of phenyl substitution in the triazole ring (**8b-1**−**8b-4**) showed relatively more than 50% inhibitory potential against BuChE. Among all investigated compounds, the diphenylhydroxy analogue **8b-4** displayed the most potent inhibitory potential against BuChE with an IC_{50} of 54.3 μM. While alkyl-chain-substituted compounds **8b-5**−**8b-9** and the hydroxy-cyclic analogues **8b-12** and **8b-13** showed less inhibitory activities. Changing to phthalimide groups at triazoles (**8b-10** and **8b-11**) increased the inhibitory activity but less than compound **8b-4**. Triazole genipin **8a-10** with a bromoethyl group showed the best BuChE inhibitory activity (IC_{50} = 31.8 μM) and selectivity toward BuChE, surpassing that of the control galantamine (IC_{50} = 34.1 μM), while **8b-4** with a diphenylhydroxy group showed comparable activity to galantamine.

Compared with the report of neuroprotective activity of piperazine-genipin analogues (Figure 2) by Huang et al.,[19] triazole genipin analogues **8a-11** in this work showed neuroprotective capability (83.5% of cell viability at 0.075 μM) higher than piperazine analogues in the previous report (22.29% at 32 μM). Moreover, triazole genipin analogues showed selective BuChE activity better than galantamine while piperazine analogues exhibited inhibitory potential against anti-AChE.

2.2.3. Kinetic Study for the Inhibition of BuChE. To gain further insights into the inhibitory mechanism of 1,2,3-triazole-genipin analogues, the kinetic behavior of the most active compounds **8a-10** and **8b-4** was investigated using Ellman's method reference. The inhibition model and inhibition constant K_i were obtained from plots between 1/velocity *versus* 1/substrate produced with five different concentrations of the substrate butylthiocholine iodide (0.3125, 0.625, 1.25, 2.5, and 5.0 mM). The results showed that the plots of $1/v$ *versus* $1/[S]$ gave straight lines with different slopes but the same x-intercept points. This graphical presentation of Lineweaver−Burk plots indicated that the selected compounds were a noncompetitive enzyme inhibitor and the inhibition constants (KI, KIS) are nearly identical. The inhibition constants (KI, KIS) for compounds **8a-10** and **8b-4** were estimated to be 0.03 and 0.1 mM, respectively (Figure 6).

2.2.4. Docking Study of BuChE. The molecular docking simulation study of the most potent compounds **8a-10** and **8b-4** was performed to understand the inhibition mechanism within the active site of the target enzymes BuChE (PDB code: 4BDS) using AutoDock 4.2 software.

Analog **8a-10** showed a good fit in the pocket site of the enzyme by interaction with important amino acid residues and exhibited a binding free energy of −9.77 kcal/mol with BuChE (Table 3). Molecular docking of **8a-10** showed three hydrogen bonds of the ester unit at the C4-position of the iridoid moiety with the residues His438 (catalytic subsite) and Ser198 of the CAS along with the interaction of the acetoxy group at the C1-position. The carbonyl group of acetoxy formed three hydrogen bonds with the Trp82 (a key residue in the CAS of BuChE), Trp430, and Tyr440 moieties. Furthermore, the triazole group also formed a hydrogen-bond interaction with the Tyr332 and showed remarkable ionic interaction with Asp70 residue in the PAS region (Figure 7). These interaction behaviors indicated the potential of **8a-10** to inhibit BuChE. The molecular docking studies of **8b-4** also showed preferential interaction with the active site of BuChE with a binding energy of −9.74 kcal/mol (Table 3). The iridoid core of **8b-4** is mostly surrounded by residues of the CAS pocket while diphenyl moiety is oriented toward the PAS pocket. The carbonyl group of the iridoid formed a hydrogen-bond interaction with the Trp82, a key residue in the CAS of BuChE. Meanwhile, the diphenylhydroxy group of **8b-4** showed the same binding orientation within the active site of

https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316

Table 2. ChE Inhibitory Activity of 1,2,3-Triazole-genipin Analogues[a]

	AChE inhibitory activity		BuChE inhibitory activity	
compounds	inhibition (%)[b]	IC_{50} (μM ± SD)[b]	inhibition (%)[b]	IC_{50} (μM ± SD)[b]
geniposide	0.73 ± 0.11	NA[c]	2.09 ± 0.18	NA[c]
genipin **1**	4.94 ± 0.05	NA[c]	2.42 ± 0.18	NA[c]
8a-1	1.31 ± 0.08	NA[c]	47.75 ± 0.29	NA[c]
8a-2	9.28 ± 0.14	NA[c]	34.97 ± 0.26	NA[c]
8a-3	7.89 ± 0.05	NA[c]	33.37 ± 0.18	NA[c]
8a-4	20.89 ± 0.22	NA[c]	27.14 ± 0.09	NA[c]
8a-5	0.30 ± 0.31	NA[c]	39.26 ± 0.18	NA[c]
8a-6	6.03 ± 0.15	NA[c]	42.91 ± 0.20	NA[c]
8a-7	20.35 ± 0.06	NA[c]	35.99 ± 0.29	NA[c]
8a-8	36.60 ± 0.42	NA[c]	41.96 ± 0.12	NA[c]
8a-9	9.39 ± 0.11	NA[c]	1.21 ± 0.18	NA[c]
8a-10	9.27 ± 0.19	NA[c]	97.34 ± 0.18	**31.77 ± 0.17**
8a-11	0.26 ± 0.15	NA[c]	35.48 ± 0.59	NA[c]
8a-12	1.16 ± 0.14	NA[c]	1.79 ± 0.17	NA[c]
8a-13	0.43 ± 0.19	NA[c]	9.03 ± 0.30	NA[c]
8a-14	1.33 ± 0.08	NA[c]	27.54 ± 0.20	NA[c]
8a-15	0.28 ± 0.21	NA[c]	22.32 ± 0.52	NA[c]
8a-16	8.00 ± 0.79	NA[c]	10.70 ± 0.15	NA[c]
8a-17	8.12 ± 0.22	NA[c]	37.35 ± 0.61	NA[c]
8a-18	12.11 ± 0.30	NA[c]	23.68 ± 0.17	NA[c]
8a-19	44.70 ± 0.19	NA[c]	25.56 ± 0.05	NA[c]
8a-20	5.52 ± 0.32	NA[c]	27.29 ± 0.17	NA[c]
8a-21	6.62 ± 0.36	NA[c]	78.64 ± 0.10	274 ± 3.9
8a-22	19.46 ± 0.20	NA[c]	99.85 ± 0.13	203 ± 1.7
8a-23	0.13 ± 0.29	NA[c]	71.55 ± 0.22	419 ± 4.4
8a-24	0.88 ± 0.30	NA[c]	47.55 ± 0.13	NA[c]
8a-25	0.62 ± 0.24	NA[c]	40.70 ± 0.23	NA[c]
8a-26	0.48 ± 0.17	NA[c]	42.73 ± 0.18	NA[c]
8b-1	8.19 ± 0.11	NA[c]	67.51 ± 0.16	537 ± 2.0
8b-2	4.41 ± 0.03	NA[c]	98.69 ± 0.24	109.1 ± 0.61
8b-3	7.53 ± 0.18	NA[c]	84.64 ± 0.12	281 ± 2.7
8b-4	11.11 ± 0.88	NA[c]	99.72 ± 0.18	**54.3 ± 0.34**
8b-5	2.30 ± 0.14	NA[c]	24.94 ± 0.23	NA[c]
8b-6	16.44 ± 0.25	NA[c]	35.42 ± 0.20	NA[c]
8b-7	1.70 ± 0.09	NA[c]	42.57 ± 0.16	NA[c]
8b-8	0.49 ± 0.22	NA[c]	25.04 ± 0.23	NA[c]
8b-9	2.73 ± 0.43	NA[c]	31.51 ± 0.14	NA[c]
8b-10	1.06 ± 0.18	NA[c]	42.30 ± 0.64	NA[c]
8b-11	0.51 ± 0.09	NA[c]	81.22 ± 0.38	289. ± 1.0
8b-12	0.97 ± 0.13	NA[c]	27.26 ± 0.27	NA[c]
8b-13	6.14 ± 0.12	NA[c]	32.03 ± 0.74	NA[c]
galantamine	98.52 ± 0.12	12.67 ± 0.07	96.21 ± 0.18	34.05 ± 0.32

[a]The most potent compound is given in bold. [b]Inhibition % and IC_{50} values represent the concentration of inhibitor required to decrease enzyme activity by 50% and are the mean of three independent experiments, each performed in triplicate (SD = standard deviation). [c]NA = no activity. Compounds defined as "no activity" means that the percent inhibition is less than 50% at a concentration of 10.0 mM in the assay conditions. AChE from electric eel., BuChE from horse serum.

the target enzyme *via* two $\pi-\pi$ interactions with Tyr332 (a key residue in the PAS of BuChE) (Figure 8). Furthermore, hydrogen bonds and a $\pi-\pi$ interaction between the triazole moiety and His438, Ser198, and Phe329 of the CAS were also observed (Figure 8). The modification of introducing a substituted triazole to genipin led to analogues **8a-10** and **8b-4**, which increased the potential interaction of the molecule with Trp82 and Tyr332, the important active site of BuChE.

3. CONCLUSIONS

In summary, a novel series of 1,2,3-triazole-genipin analogues **8** were successfully designed and synthesized as efficient multitarget agents for the treatment of AD. Among the synthesized compounds, analogues **8a-10** and **8b-4** were found as the most active inhibitors with IC_{50} values of 31.8 and 54.3 μM, respectively. These two analogues also showed inhibitory activity of BuChE selectively over AChE and showed better activity than the standard drug galantamine. Moreover, compounds **8a-10** and **8b-4** were able to rescue the cells from the toxicity induced by H_2O_2. Molecular docking studies of these two compounds confirmed their preferable binding with BuChE and showed interactions with key amino acid residues. Therefore, 1,2,3-triazole-genipin analogues **8a-10** and

https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316

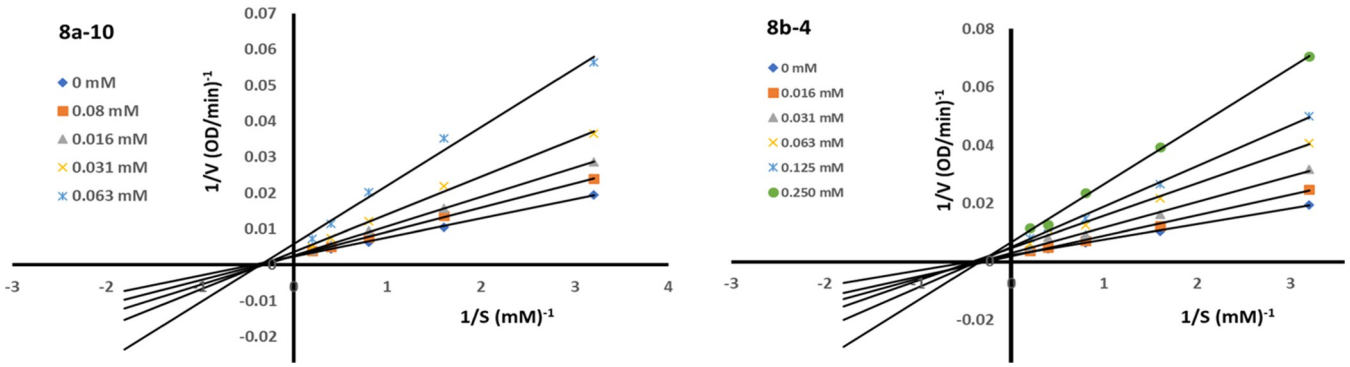

Figure 6. Lineweaver–Burk plot for the inhibition of BuChE by compounds **8a-10** and **8b-4** at different concentrations of substrate.

Table 3. Molecular Docking Analysis of BuChE with 1,2,3-Triazole-genipin Analogues 8a-10 and 8b-4[a]

compounds	binding energy (kcal/mol)	intermolecular hydrogen bonding		intermolecular $\pi-\pi$ interaction
		amino acid interaction	distance (Å)	
8a-10	−9.77	Trp82	2.10	Asp70
		Ser198	1.92	
		Ser198	2.01	
		Tyr332	2.98	
		Trp430	2.22	
		His438	2.03	
		Tyr440	1.84	
8b-4	−9.74	Trp82	2.34	Tyr332, Trp231, Phe329
		Tyr440	2.11	
		Trp430	2.25	
		Ser198	2.06	
		Ser198	2.66	

[a]The binding energies were evaluated using AutoDock 4.2 software.

8b-4 have the potential for the treatment of neurodegenerative diseases.

4. EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and used without further purification. Proton NMR spectra were recorded using a BRUKER AVANC (400 MHz) spectrometer. All spectra were recorded in $CDCl_3$ solvent, and chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ 0.00), $CDCl_3$ (δ 7.26) as internal standard. Carbon NMR spectra were recorded on a BRUKER AVANC (100 MHz) spectrometer. All spectra were recorded in $CDCl_3$ solvent, and chemical shifts are reported as δ values in parts per million (ppm) relative to $CDCl_3$ (δ 77.0) as the internal standard. High-resolution mass spectra (HRMS) were recorded at Naresuan University. Analytical thin-layer chromatography (TLC) was conducted on pre-coated TLC plates; silica gel 60F-254 [E. Merck, Darmstadt, Germany]. Silica gel columns for open-column chromatography utilized silica gel 60 PF254 [E. Merck, Darmstadt, Germany]. Melting points were measured using a melting point apparatus (Griffin) and are uncorrected. Genipin as a starting material (CAS No. 6902-77-8) was purchased from commercial sources and used without further purification.

4.1. Synthesis of Compound 2. To a rapidly stirring solution of genipin **1** (2.00 g, 8.850 mmol) in pyridine (10.0 mL) was added *tert*-butyldimethylsilyl chloride (2.00 g, 13.275 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 min. After TLC showed that the reaction was complete, the mixture was diluted with EtOAc (30 mL), quenched with saturated NH_4Cl solution, and then extracted with EtOAc. The mixture was quenched with $CuSO_4 \cdot 5H_2O$ to remove the pyridine and extracted with

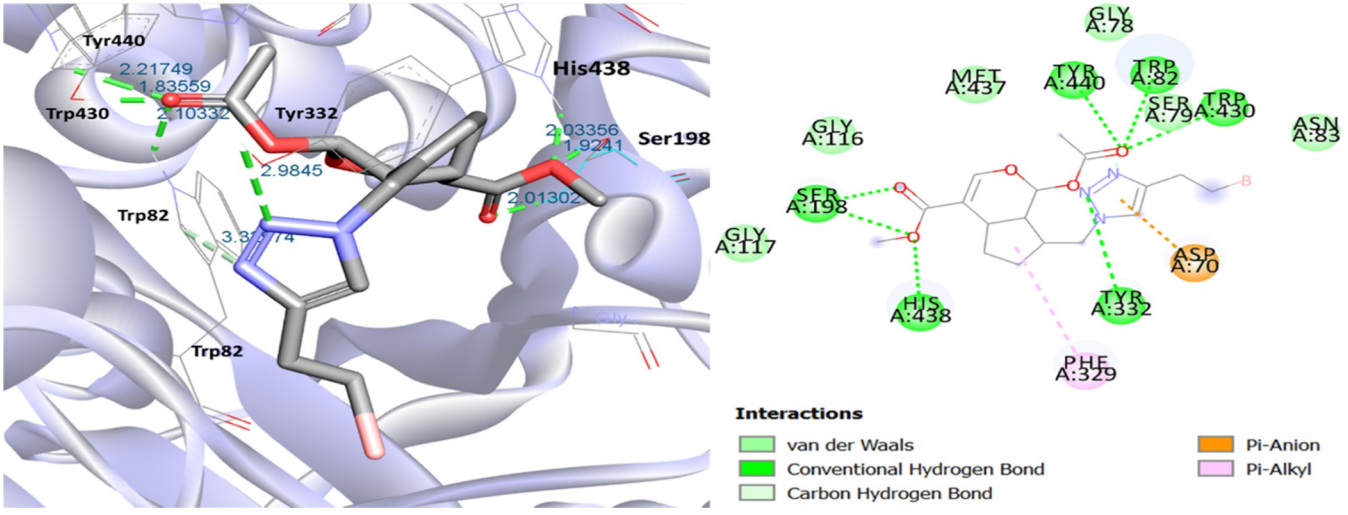

Figure 7. Proposed binding mode of compound **8a-10** in the active site of BuChE (PDB code: 4BDS).

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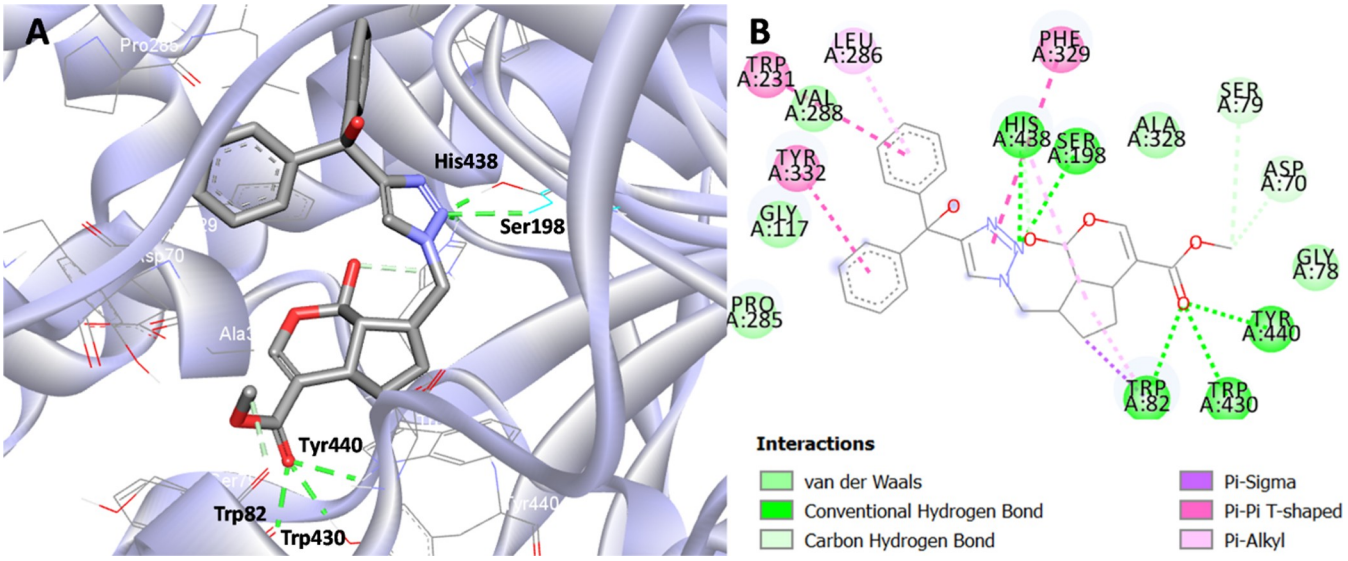

Figure 8. Proposed binding mode of compound **8b-4** in the active site of BuChE (PDB code: 4BDS). (A) The protein structure is shown as a ribbon, and 1,2,3-triazole-genipin **8b-4** is shown as a stick model. (B) Two-dimensional (2D) interaction molecular docking diagrams. Hydrogen bonds and $\pi-\pi$ interactions are shown as green and pink dotted lines, respectively.

EtOAc and washed with brine, the combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed by rotary evaporation to obtain the crude product of compound **2**.

4.2. Synthesis of Compound 3. To a solution of crude product compound **2** (8.85 mmol) in DCM (20 mL), imidazole (1.8 g, 26.55 mmol) was added and stirred for 10 min, then acetic anhydride (2.5 mL, 26.55 mmol) or *tert*-butyldiphenylsilyl chloride (6.9 mL, 26.55 mmol) was added to the mixture, and stirred at room temperature for further 1 h. After TLC indicated that the reaction was complete, the reaction mixture was diluted with DCM (10 mL) and quenched with cold-saturated $NaHCO_3$, extracted with DCM and washed with brine, then dried over with Na_2SO_4 anhydrous, and concentrated in *vacuo* to obtain crude product **3a** and **3b**.

4.3. Synthesis of Compound 4. To a stirred solution of compound **3a** or **3b** (8.85 mmol) in THF (20 mL) was added $HCOOH/H_2O$ (9:1) (40 mL) dropwise at 0 °C and stirred for 6 h. After TLC showed that the reaction was complete, the reaction mixture was diluted with EtOAc (30 mL) and quenched with cold-saturated $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine solution, dried (Na_2SO_4), filtered, and concentrated to obtain a crude product of compound **4a** or **4b**.

4.4. Synthesis of Compounds 5 and 6. To a solution of crude products **4a** and **4b** (8.85 mmol) in DCM (50 mL), Et_3N (1.8 mL, 13.28 mmol) was added and stirred for 30 min. Then, methanesulfonyl chloride (1.0 mL, 13.28 mmol) was added to the reaction mixture at 0°C and stirred at room temperature for 24 h. After TLC showed that the reaction was complete, the reaction mixture was diluted with DCM (30 mL) and cold-saturated $NaHCO_3$. The reaction mixture was extracted with DCM, washed with water, then dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo* to obtain the mesylate crude product (**5a**, **5b**). The mesylate of crude product (**5a**, **5b**) was dissolved in DMF (30 mL), and NaN_3 (0.863 g, 13.28 mmol) was added at 0 °C. The reaction was stirred at room temperature, and stirring was continued for 30 min. After TLC showed that the reaction was complete, the reaction mixture was diluted with EtOAc (30 mL) and quenched with cooled water. The reaction mixture was extracted with EtOAc, washed with brine, then dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo* to obtain the crude product of **6a** and **6b**. The crude product **6a** was purified by column chromatography (10% EtOAc/*n*-hexane) to afford **6a** in 72% in five steps.

4.5. Synthesis of Compound 7b. To a stirred solution of compound **6b** (8.85 mmol) in DCM (30 mL), TBAF (2.5 g, 9.735 mmol) was added at 0 °C and stirred for 30 min. After TLC showed that the reaction was complete, the reaction mixture was diluted with DCM (30 mL) and quenched with cold-saturated NH_4Cl. The reaction mixture was extracted with DCM, washed with H_2O and brine, followed by drying over with Na_2SO_4 anhydrous, and concentrated *in vacuo* to obtain crude product and purified by column chromatography (10% EtOAc/*n*-hexane) to afford compound **7b** in 43% in six steps.

4.6. General Procedure for the Preparation of 1,2,3-Triazole-genipin Analogues (8a), (8b). To the solution of compound **6a** (100 mg, 0.3413 mmol) or compound **7b** (100 mg, 0.3980 mmol) in CH_3CN (1.0 mL) were added CuI (20 mol %), Et_3N (0.5 equiv), and alkyne (1.5 equiv). After TLC indicated that the reaction was complete, the reaction mixture was diluted with EtOAc (2 mL), quenched with cooled water, and extracted with EtOAc (3 × 30 mL). The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine solution, dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography to obtain 1,2,3-triazole-genipin analogues **8a** and **8b**.

4.6.1. 10-[4′-Phenyl-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-1***. 52% yield as a yellow oil; IR (film) 2950, 1760, 1705, 1634, 1436, 1179, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (2H, d, J = 7.2 Hz, H-Ar), 7.76 (1H, s, H-5′), 7.50−7.29 (4H, m, H-3, H-Ar), 5.92 (1H, brs, H-7), 5.88 (1H, d, J = 7.6 Hz, H-1), 5.09 (2H, brs, H-10), 3.72 (3H, s, OCH_3), 3.27 (1H, q, J = 7.6 Hz, H-5), 2.94 (1H, dd, J = 16.4, 8.4 Hz, H-6a), 2.72 (1H, t, J = 7.2 Hz, H-9), 2.29−2.14 (4H, m, H-6b,

https://doi.org/10.1021/acsomega.2c01593
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CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.10, 166.91, 151.54, 148.06, 135.86, 134.55, 130.29, 128.75 (2C), 128.16, 125.61 (2C), 119.21, 110.97, 91.59, 51.29, 49.59, 44.90, 38.55, 35.05, 20.90; HRMS (m/z): calcd for $C_{21}H_{21}N_3O_5$ $[M + Na]^+$ 418.1379, found 418.1373.

4.6.2. 10-[4′-(4-Methoxypheny)l-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-2***. 75% yield as a yellow solid, mp: 110−112 °C; IR (film) 2970, 1739, 1712, 1626, 1499, 1216, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, d, J = 8.8 Hz, H-Ar), 7.66 (1H, s, H-5′), 7.45 (1H, brs, H-3), 6.95 (2H, d, J = 8.8 Hz, H-Ar), 5.93 (1H, brs, H-7), 5.89 (1H, d, J = 7.6, Hz, H-1), 5.08 (2H, brs, H-10), 3.84 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.28 (1H, q, J = 8.0 Hz, H-5), 2.95 (1H, dd, J = 16.4, 7.6 Hz, H-6a), 2.73 (1H, t, J = 7.6 Hz, H-9), 2.29−2.17 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.95, 166.77, 159.42, 151.37, 147.68, 135.80, 134.25, 126.75(2C), 122.90, 118.44, 114.01(2C), 110.86, 91.43, 55.04, 51.13, 49.36, 44.77, 38.39, 34.85, 20.74; HRMS (m/z): calcd for $C_{22}H_{23}N_3O_6$ $[M + Na]^+$ 448.1485, found 448.1486.

4.6.3. 10-[4′-(4-Fluorophenyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-3***. 78% yield as a yellow solid, mp: 110−113 °C; IR (film) 2970, 1738, 1700, 1633, 1499, 1229, 1155, 1047, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83−7.76 (2H, m, H-Ar), 7.71 (1H, s, H-5′), 7.44 (1H, s, H-3), 7.11 (2H, t, J = 8.8 Hz, H-Ar), 5.94 (1H, brs, H-7), 5.89 (1H, d, J = 7.6, H-1), 5.09 (2H, brs, H-10), 3.73 (3H, s, OCH_3), 3.28 (1H, q, J = 8.0 Hz, H-5), 2.95 (1H, dd, J = 17.2, 8.8 Hz, H-6a), 2.72 (1H, t, J = 7.6 Hz, H-9), 2.29−2.17 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.01, 166.81, 162.68 (d, J_{C-F} = 246 Hz, C−F), 151.42, 147.04, 135.72, 134.53, 127.30 (d, J_{C-F} = 8.0 Hz, C−F), 127.22 (d, J_{C-F} = 3.0 Hz, C−F), 126.50, 119.06, 115.73, 115.52, 110.91, 91.45, 51.21, 49.50 44.85, 38.45, 34.90, 20.80; HRMS (m/z): calcd for $C_{21}H_{20}FN_3O_5$ $[M + Na]^+$ 436.1285, found 436.1284.

4.6.4. 10-[4′-(6′,6′-Diphenyl-6′-hydroxymethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-4***. 99% yield as a yellow oil; IR (film) 3300, 2949, 1759, 1704, 1634, 1447, 1180, 1083, 759, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, brs, H-3), 7.38−7.27 (10H, m, H-Ar), 7.12 (1H, s, H-5′), 5.85 (1H, d, J = 7.2 Hz, H-1), 5.82 (1H, s, H-7), 5.01 (2H, brs, H-10), 3.73 (3H, s, OCH_3), 3.71 (1H, s, OH), 3.25 (1H, q, J = 8.0 Hz, H-5), 2.92 (1H, dd, J = 18.2, 8.0 Hz, H-6a), 2.71 (1H, t, J = 7.6 Hz, H-9), 2.27−2.12 (4H, m, H-6b, CH_3−OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.95, 166.84, 154.23, 151.40, 145.58, 145.53, 135.53, 134.15, 127.82 (4C), 127.28 (2C), 127.02 (3C), 126.99, 122.39, 110.94, 91.35, 76.49, 51.21, 49.35, 45.06, 38.38, 34.65, 20.76; HRMS (m/z): calcd for $C_{28}H_{27}N_3O_6$ $[M + H]^+$ 474.2030, found 474.2036. $[M + Na]^+$ 496.2788, found 496.2786.

4.6.5. 10-[4′-(Benzyloxymethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-5***. 86% yield as a yellow oil; IR (film) 2927, 1754, 1705, 1634, 1436, 1179, 1080, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (1H, s, H-5′), 7.43 (1H, brs, H-3), 7.35−7.27 (5H, m, H-Ar) 5.88−5.83 (2H, s, H-7, H-1), 5.02 (2H, brs, H-10), 4.67 (2H, s, CH_2), 4.59 (2H, s, CH_2), 3.71 (3H, s, OCH_3), 3.24 (1H, q, J = 8.0 Hz, H-5), 2.91 (1H, dd, J = 16.0, 8.0 Hz, H-6a), 2.67 (1H, t, J = 7.6 Hz, H-9), 2.26−2.14 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.02, 166.89, 151.50, 145.55, 137.63, 135.71, 134.51, 128.30 (2C), 127.77 (2C), 127.67, 122.17, 110.95, 91.57, 72.49, 63.58, 51.27, 49.45, 44.82, 38.49, 34.98, 20.88; HRMS (m/z): calcd for $C_{23}H_{25}N_3O_6$ $[M + Na]^+$ 462.1641, found 462.1640.

4.6.6. 10-[4′-(4-Methoxybenzyloxymethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-6***. 82% yield as a colorless oil; IR (film) 2970, 1755, 1706, 1612, 1513, 1179, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, brs, H-5′), 7.44 (1H, s, H-3), 7.27 (2H, d, J = 8.4 Hz, H-Ar), 6.87 (2H, d, J = 8.4 Hz, H-Ar), 5.87 (1H, brs, H-7), 5.84 (1H, d, J = 8.0 Hz, H-1), 5.03 (2H, brs, H-10), 4.64 (2H, s, OCH_2), 4.53 (2H, s, OCH_2), 3.79 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.25 (1H, q, J = 8.0 Hz, H-5), 2.92 (1H, dd, J = 17.2, 8.0 Hz, H-6a), 2.68 (1H, t, J = 7.6 Hz, H-9), 2.28−2.13 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.01, 166.87, 159.19, 151.48, 145.61, 135.72, 134.46, 129.69, 129.43 (2C), 122.15, 113.69 (2C), 110.95, 91.55, 72.12, 63.23, 55.12, 51.25, 49.41, 44.81, 38.48, 34.95, 20.86; HRMS (m/z): calcd for $C_{24}H_{27}N_3O_7$ $[M + Na]^+$ 492.1747, found 492.1745.

4.6.7. 10-[4′-(3,4-Dimethoxybenzyloxymethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-7***. 72% yield as a colorless oil; IR (film) 2948, 1758, 1705, 1634, 1515, 1179, 1080, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (1H, brs, H-5′), 7.43 (1H, s, H-3), 6.93−6.79 (3H, m, H-Ar), 5.90−5.80 (2H, m, H-7, H-1), 5.03 (2H, brs, H-10), 4.64 (2H, brs, CH_2), 4.53 (2H, brs, CH_2), 3.87 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.25 (1H, q, J = 7.6 Hz, H-5), 2.91 (1H, dd, J = 17.2, 8.0 Hz, H-6a), 2.68 (1H, t, J = 8.0 Hz, H-9), 2.27−2.14 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.03, 166.89, 151.50, 148.92, 148.64, 145.54, 135.72, 134.56, 130.15, 122.20, 120.51, 111.25, 110.96, 110.84, 91.57, 72.45, 63.25, 55.81, 55.76, 51.30, 49.47, 44.85, 38.51, 35.00, 20.90; HRMS (m/z): calcd for $C_{25}H_{29}N_3O_8$ $[M + Na]^+$ 522.1852, found 522.1851.

4.6.8. 10-[4′-(N-Methyl-N-benzylamine)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-8***. 99% yield as a yellow oil; IR (film) 2970, 1753, 1708, 1634, 1436, 1282, 1179, 1081, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, brs, H-5′), 7.44 (1H, s, H-3), 7.40−7.33 (4H, m, H-Ar), 7.32−7.20 (1H, m, H-Ar), 5.88−5.83 (2H, m, H-7, H-1), 5.04 (2H, brs, H-10), 3.76−3.68 (5H, m, OCH_3, CH_2), 3.56 (2H, brs, CH_2), 3.26 (1H, q, J = 8.0 Hz, H-5), 2.93 (1H, dd, J = 16.0, 7.2 Hz, H-6a), 2.68 (1H, t, J = 8.0 Hz, H-9), 2.30−2.21 (4H, m, H-6b, CH_3−Ac), 2.19 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.09, 166.96, 151.56, 145.40, 138.01, 135.87, 134.36, 129.07 (2C), 128.25 (2C), 127.17, 122.50, 111.02, 91.60, 61.23, 51.88, 51.34, 49.54, 44.95, 41.95, 38.55, 35.00, 20.96; HRMS (m/z): calcd for $C_{24}H_{28}N_4O_5$ $[M + H]^+$ 453.2138, found 453.2144.

4.6.9. 10-[4′-(7′-Bromoethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-9***. 75% yield as a yellow oil; IR (film) 2951, 1755, 1705, 1634, 1436, 1180, 1082, 731, 557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (1H, brs, H-5′), 7.45 (1H, brs, H-3), 5.87 (1H, brs, H-7), 5.85 (1H, d, J = 7.6 Hz, H-1), 5.04 (2H, brs, H-10), 3.73 (3H, s, OCH_3), 3.66 (2H, t, J = 6.8 Hz, CH_2−Br), 3.33−3.22 (3H, m, CH_2, H-5), 2.94 (1H, dd, J = 16.4, 8.0 Hz, H-6a), 2.68 (1H, t, J = 8.0 Hz, H-9), 2.28−2.16 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.89, 166.76, 151.35, 144.91, 135.75, 134.10, 121.46, 110.86, 91.41, 51.16, 49.33, 44.78, 38.37, 34.80, 31.37, 29.13, 20.78; HRMS (m/z): calcd for $C_{17}H_{20}BrN_3O_5$ $[M + H]^+$ 448.0484, found 448.0490.

4.6.10. 10-[4′-(7′-Hydroxyethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-10***. 81% yield as a yellow oil; IR (film) 3383, 2970, 1753, 1705, 1634, 1436, 1365, 1282, 1179, 1081, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, brs, H-5′), 7.39 (1H, s, H-3), 5.92 (1H, brs, H-7), 5.83 (1H, d, J = 7.6

https://doi.org/10.1021/acsomega.2c01593
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Hz, H-1), 5.03 (2H, brs, H-10), 3.95 (2H, t, J = 5.6 Hz, CH_2), 3.73 (3H, s, OCH_3), 3.27 (1H, q, J = 8.0 Hz, H-5), 2.99−2.87 (3H, m, H-6a, CH_2), 2.72 (1H, t, J = 8.0 Hz, H-9), 2.30−2.14 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.05, 166.81, 151.34, 146.05, 135.54, 134.40, 121.94, 110.86, 91.33, 61.17, 51.16, 49.36, 44.89, 38.33, 34.66, 28.63, 20.74; HRMS (m/z): calcd for $C_{17}H_{21}N_3O_6$ $[M + H]^+$ 386.1328, found 386.1314.

4.6.11. 10-[4′-(7′-Hydroxypropyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-11***. 72% yield as a yellow oil; IR (film) 3383, 2948, 1755, 1705, 1634, 1436, 1365, 1217, 1179, 1081, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, brs, H-5′), 7.30 (1H, s, H-3), 5.86 (1H, brs, H-7), 5.84 (1H, d, J = 7.6 Hz, H-1), 5.01 (2H, brs, H-10), 3.74−3.69 (5H, m, OCH_3, CH_2), 3.26 (1H, q, J = 8.0 Hz, H-5), 2.92 (1H, dd, J = 17.2, 8.4 Hz, H-6a), 2.83 (2H, t, J = 7.2 Hz, CH_2), 2.68 (1H, t, J = 7.6 Hz, H-9), 2.27−2.16 (4H, m, H-6b, CH_3−Ac), 1.98−1.89 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.02, 166.86, 151.40, 147.74, 135.78, 134.13, 120.74, 110.89, 91.40, 61.21, 51.19, 49.25, 44.86, 38.36, 34.77, 31.78, 21.77, 20.77; HRMS (m/z): calcd for $C_{18}H_{23}N_3O_6$ $[M + Na]^+$ 400.1485, found 400.1498.

4.6.12. 10-[4′-(tert-Butyldiphenylsilyoxylpropyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-12***. 76% yield as a yellow oil; IR (film) 2932, 1759, 1709, 1634, 1428, 1282, 1180, 1085, 1052, 701, 504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.60 (4H, m, H-Ar), 7.45 (1H, s, H-5′), 7.43−7.33 (6H, m, H-3, H-Ar), 7.16 (1H, s, H-Ar), 5.84 (1H, d, J = 7.6 Hz, H-1), 5.81 (1H, s, H-7), 4.97 (2H, brs, H-10), 3.78−3.68 (5H, m, OCH_3, CH_2), 3.24 (1H, q, J = 7.6 Hz, H-5), 2.91 (1H, dd, J = 17.2, 8.0 Hz, H-6a), 2.84 (2H, t, J = 8.0 Hz, CH_2), 2.67 (1H, t, J = 8.0 Hz, H-9), 2.25−2.14 (4H, m, H-6b, CH_3−Ac), 2.00−1.89 (2H, m, CH_2), 1.02 (9H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.10, 166.99, 151.58, 148.18, 136.11, 135.49 (4C), 134.11 (2C), 133.83, 129.52 (2C), 127.57 (4C), 120.46, 111.04, 91.66, 62.93, 51.33, 49.38, 44.95, 38.56, 35.08, 31.95, 26.81 (3C), 22.04, 20.94, 19.17; HRMS (m/z): calcd for $C_{34}H_{41}N_3O_6Si$ $[M + H]^+$ 616.2843, found 616.2853.

4.6.13. 10-[4′-(Triisopropysilyoxylpropyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-13***. 92% yield as a yellow oil; IR (film) 2943, 2865, 1763, 1709, 1634, 1436, 1282, 1180, 1084, 1052, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, s, H-5′), 7.28 (1H, s, H-3), 5.88−5.82 (2H, m, H-7, H-1), 5.00 (2H, brs, H-10), 3.77−3.70 (5H, m, OCH_3, CH_2), 3.26 (1H, q, J = 8.0 Hz, H-5), 2.92 (1H, dd, J = 16.4, 7.2 Hz, H-6a), 2.82 (2H, t, J = 7.2 Hz, CH_2), 2.67 (1H, t, J = 7.6 Hz, H-9), 2.25−2.16 (4H, m, H-6b, CH_3−Ac), 1.98−1.87 (2H, m, CH_2), 1.08−1.01 (21H, m, CH_3, Si-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.92, 166.82, 151.43, 148.14, 136.07, 133.97, 120.38, 110.90, 91.55, 62.21, 51.16, 49.24, 44.80, 38.43, 34.97, 32.20, 21.85, 20.78, 17.81 (6C), 11.77 (3C); HRMS (m/z): calcd for $C_{27}H_{43}N_3O_6Si$ $[M + H]^+$ 534.2999, found 534.3010.

4.6.14. 10-[4′-(tert-Butyldiphenylsilyoxylethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-14***. 80% yield as a yellow oil; IR (film) 2931, 1760, 1709, 1634, 1428, 1180, 1082, 701, 502 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63−7.55 (4H, m, H-Ar), 7.46−7.32 (8H, m, H-5′, H-3, H-Ar), 5.85−5.81 (2H, m, H-1, H-7), 4.99 (2H, brs, H-10), 3.93 (2H, t, J = 6.0 Hz, CH_2), 3.72 (3H, s, OCH_3), 3.19 (1H, q, J =7.6 Hz, H-5), 2.99 (2H, t, J = 6.0 Hz, CH_2), 2.87 (1H, dd, J = 16.8, 8.0 Hz, H-6a), 2.65 (1H, t, J = 7.6 Hz, H-9), 2.23−2.11 (4H, m, H-6b, CH_3−Ac), 1.02 (9H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.93, 166.79, 151.43, 145.53, 135.96 (4C), 135.25, 134.15, 133.32, 129.51, 127.51 (4C), 121.51, 110.88, 91.58, 62.79, 60.15, 51.16, 49.24, 44.66, 38.40, 34.96, 29.10, 26.62 (3C), 20.79, 18.99, 13.99; HRMS (m/z): calcd for $C_{33}H_{39}N_3O_6Si$ $[M + H]^+$ 602.2686, found 602.2690.

4.6.15. 10-[4′-(tert-Butylsilyoxylethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-15***. 80% yield as a yellow oil; IR (film) 2952, 1737, 1709, 1634, 1436, 1180, 1083, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, s, H-5′), 7.36 (1H, s, H-3), 5.87−5.80 (2H, m, H-7, H-1), 4.99 (2H, brs, H-10), 3.85 (2H, t, J = 6.4 Hz, CH_2), 3.71 (3H, s, OCH_3), 3.24 (1H, q, J = 8.4 Hz, H-5), 2.97−2.85 (3H, m, H-6a, CH_2), 2.66 (1H, t, J = 7.6 Hz, H-9), 2.25−2.12 (4H, m, H-6b, CH_3−Ac), 0.84 (9H, s, 3× CH_3) 0.01 (6H, s, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.90, 166.80, 151.42, 145.57, 135.98, 134.06, 122.47, 110.86, 91.53, 61.96, 51.16, 49.21, 44.70, 38.39, 34.93, 29.25 (2C), 25.63 (3C), 20.77, −5.61 (2C); HRMS (m/z): calcd for $C_{23}H_{35}N_3O_6Si$ $[M + H]^+$ 478.2373, found 478.2380.

4.6.16. 10-[4′-(Triphenyloxylmethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-16***. 84% yield as a colorless oil; IR (film) 2950, 1763, 1706, 1634, 1448, 1436, 1284, 1220, 1182, 1087, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.34 (8H, m, H-5′, H-3, H-Ar), 7.30−7.13 (9H, m, H-Ar), 5.85−5.74 (2H, m, H-7, H-1), 4.97 (2H, brs, H-10), 4.26 (2H, brs, CH_2), 3.66 (3H, s, OCH_3), 3.20 (1H, q, J = 8.0 Hz, H-5), 2.87 (1H, dd, J = 16.8 Hz, 7.6 Hz, H-6a), 2.63 (1H, t, J = 7.2 Hz, H-9), 2.25−2.08 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.13, 167.03, 151.64, 146.49, 143.70 (2C), 135.94, 134.43, 128.64 (6C), 127.91 (6C), 127.14 (4C), 121.65, 111.10, 91.71, 87.37, 58.74, 51.38, 49.56, 45.01, 38.63, 35.11, 20.99; HRMS (m/z): calcd for $C_{35}H_{33}N_3O_6$ $[M + Na]^+$ 614.2267, found 614.2276.

4.6.17. 10-[4′-(Octyloxymethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-17***. 90% yield as a yellow oil; IR (film) 2927, 2856, 1738, 1711, 1634, 1436, 1282, 1217, 1180, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, s, H-5′), 7.45 (1H, s, H-3), 5.88 (1H, brs, H-7), 5.85 (1H, d, J = 7.6 Hz, H-1), 5.04 (2H, brs, H-10), 4.62 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 3.52 (2H, t, J = 6.4 Hz, CH_2), 3.26 (1H, q, J = 8.0 Hz, H-5), 2.93 (1H, dd, J = 16.8, 8.0 Hz, H-6a), 2.69 (1H, t, J = 7.6 Hz, H-9), 2.28−2.10 (4H, m, H-6b, CH_3−Ac), 1.57−1.54 (2H, m, CH_2), 1.36−1.20 (10H, m, 5× CH_2), 0.87 (3H, t, J = 8.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.02, 166.89, 151.51, 145.88, 135.76, 134.49, 122.03, 110.95, 91.60, 70.89, 64.24, 51.28, 49.54, 44.84, 38.51, 35.01, 31.66, 29.49, 29.27, 29.08, 25.97, 22.49, 20.91, 13.94; HRMS (m/z): $C_{24}H_{35}N_3O_6$ $[M + H]^+$ 434.2666, found 434.2660.

4.6.18. 10-[4′-(Dodecyloxymethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-18***. 89% yield as a yellow oil; IR (film) 2914, 2850, 1742, 1698, 1647, 1446, 1380, 1235, 1081 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, s, H-5′), 7.44 (1H, s, H-3), 5.87 (1H, brs, H-7), 5.85 (1H, d, J = 7.6 Hz, H-1), 5.03 (2H, brs, H-10), 4.62 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 3.51 (2H, t, J = 6.4 Hz, CH_2), 3.26 (1H, q, J = 8.0 Hz, H-5), 2.93 (1H, dd, J = 16.8, 8.0 Hz, H-6a), 2.69 (1H, t, J = 7.6 Hz, H-9), 2.27−2.15 (4H, m, H-6b, CH_3−Ac), 1.62−1.54 (2H, m, CH_2), 1.36−1.20 (18H, s, 9× CH_2), 0.87 (3H, t, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.97, 166.85, 151.47, 145.87, 135.77, 134.40, 121.99, 110.93, 91.57, 76.98, 70.85, 64.18, 51.23, 49.44, 44.81, 38.48, 34.98, 31.74, 29.48, 29.45 (2C), 29.42, 29.31, 29.17, 25.95, 22.51, 20.85, 13.94 HRMS (m/z): $C_{28}H_{43}N_3O_6$ $[M + H]^+$ 518.3230, found 518.3238.

https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316

4.6.19. 10-[4′-((Undec-10-enyloxy)methy)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-19***. 66% yield as a white solid, mp: 52−56 °C; IR (film) 2923, 2849, 1779, 1698, 1633, 1436, 1180, 1086, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, s, H-5′), 7.45 (1H, brs, H-3), 5.88 (1H, s, H-7), 5.85 (1H, d, J = 7.6 Hz, H-1) 5.83−5.74 (1H, m, CH-alkene), 5.04 (2H, brs, H-10), 5.02−4.89 (2H, m, CH-alkene), 4.62 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 3.51 (2H, t, J = 6.8 Hz, CH_2), 3.26 (1H, q, J = 7.6 Hz, H-5), 2.93 (1H, dd, J = 16.8, 8.4 Hz, H-6a), 2.69 (1H, t, J = 7.2 Hz, H-9), 2.27−2.17 (4H, m, H-6b, CH_3−Ac), 2.08−1.99 (2H, m, CH_2), 1.66−1.54 (2H, m, CH_2), 1.41−1.23 (12H, m, 6× CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.88, 166.77, 151.40, 145.80, 138.92, 135.75, 134.30, 121.96, 113.90, 110.89, 91.51, 70.75, 64.13, 51.16, 49.36, 44.78, 38.43, 34.91, 33.55, 29.41, 29.27, 29.19 (2C), 28.87, 28.68, 25.88, 20.78; HRMS (m/z): calcd for $C_{27}H_{39}N_3O_6$ $[M + Na]^+$ 524.2737, found 524.2740.

4.6.20. 10-[4′-(((Dioxoisoindolin-2-yl)oxy)methyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-20***. 66% yield as a white solid, mp: 76.6−78.6 °C; IR (film) 2970, 1728, 1633, 1436, 1365, 1217, 1083, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, s, H-5′), 7.80−7.68 (4H, m, H-Ar), 7.46 (1H, brs, H-3), 5.92 (1H, s, H-7), 5.84 (1H, J = 7.6 Hz, H-1), 5.40−5.32 (2H, m, CH_2), 5.04 (2H, brs, H-10), 3.74 (3H, s, OCH_3), 3.30 (1H, q, J = 8.0 Hz, H-5), 2.96 (1H, dd, J = 16.4, 8.4 Hz, H-6a), 2.68 (1H, t, J = 7.6 Hz, H-9), 2.30−2.14 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.09, 166.95, 163.31 (2C), 151.53, 141.86, 135.61, 134.58 (2C), 134.40 (2C), 128.63, 124.48, 123.42 (2C), 111.04, 91.65, 70.09, 51.31, 49.70, 44.60, 38.57, 35.00, 20.91; HRMS (m/z): calcd for $C_{24}H_{22}N_4O_8$ $[M + Na]^+$ 517.1335, found 517.1331.

4.6.21. 10-[4′-((1,3-Dioxoisoindolin-2-yl)methyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-21***. 99% yield as a white solid, mp: 68.0−72.0 °C; IR (film) 2927, 1738, 1709, 1634, 1428, 1366, 1179, 1082, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87−7.81 (2H, m, H-Ar), 7.74−7.69 (2H, m, H-Ar), 7.59 (1H, s, H-5′), 7.41 (1H, brs, H-3), 5.86 (1H, brs, H-7), 5.80 (1H, d, J = 7.6 Hz, H-1), 5.03−4.95 (4H, m, H-10, CH_2), 3.71 (3H, s, OCH_3), 3.24 (1H, q, J = 8.0 Hz, H-5), 2.91 (1H, dd, J = 16.8, 8.4 Hz, H-6a), 2.66 (1H, t, J = 7.6 Hz, H-9), 2.25−2.11 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.99, 167.50 (2C), 166.86, 151.45, 142.91, 135.55, 134.61 (2C), 133.97 (2C), 131.86, 123.28 (2C), 122.60, 110.90, 91.52, 51.24, 49.46, 44.83, 38.47, 34.89, 32.88, 20.81; HRMS (m/z): calcd for $C_{24}H_{22}N_4O_7$ $[M + Na]^+$ 501.1386, found 501.1385.

4.6.22. 10-[4′-((1,3-Dioxoisoindolin-2-yl)ethyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-22***. 99% yield as a yellow solid, mp: 61.6−64.6 °C; IR (film) 2970, 1738, 1634, 1366, 1217, 1084, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83−7.77 (2H, m, H-Ar), 7.74−7.66 (2H, m, H-Ar), 7.45 (1H, s, H-5′), 7.40 (1H, brs, H-3), 5.84 (1H, brs, H-7), 5.80 (1H, d, J = 8.0 Hz, H-1), 4.99 (2H, brs, H-10), 4.01 (2H, t, J = 7.2 Hz, CH_2), 3.74 (3H, s, OCH_3), 3.24 (1H, q, J = 8.4 Hz, H-5), 3.16 (2H, t, J = 6.8 Hz, CH_2), 2.91 (1H, dd, J = 16.8, 8.4 Hz, H-6a), 2.60 (1H, t, J = 8.0 Hz, H-9), 2.26−2.14 (4H, m, H-6b, CH_3−Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.08, 168.01 (2C), 166.95, 151.52, 144.56, 135.90, 134.22 (2C), 133.86 (2C), 131.83, 123.12 (2C), 121.15, 110.97, 91.66, 51.29, 49.46, 44.59, 38.52, 37.30, 35.01, 24.73, 20.89; HRMS (m/z): calcd for $C_{25}H_{24}N_4O_7$ $[M + Na]^+$ 515.1543, found 515.1541.

4.6.23. 10-[4′-((1,3-Dioxoisoindolin-2-yl)propyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-23***. 77% yield as a brown solid, mp: 130−135 °C; IR (film) 2925, 1738, 1707, 1628, 1432, 1364, 1176, 1079, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85−7.79 (2H, m, H-Ar), 7.74−7.67 (2H, m, H-Ar), 7.43 (2H, s, H-5′, H-3), 5.86 (1H, brs, H-7), 5.82 (1H, d, J = 7.6 Hz, H-1), 5.00 (2H, brs, H-10), 3.75−3.68 (5H, m, OCH_3, CH_2), 3.26 (1H, q, J = 7.6 Hz, H-5), 2.92 (1H, dd, J = 16.8, 8.4 Hz, H-6a), 2.76 (2H, t, J = 7.6 Hz, CH_2), 2.67 (1H, t, J = 7.6 Hz, H-9), 2.26−2.14 (4H, m, H-6b, CH_3−Ac), 2.11−2.028 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.02, 168.22 (2C), 166.89, 151.46, 146.98, 135.92, 134.22 (2C), 133.82 (2C), 131.88, 123.02 (2C), 120.87, 110.93, 91.61, 51.21, 49.34, 44.78, 38.47, 36.97, 34.97, 27.89, 22.76, 20.85; HRMS (m/z): calcd for $C_{26}H_{26}N_4O_7$ $[M + Na]^+$ 529.1699, found 529.1699.

4.6.24. 10-[4′-((1,3-Dioxoisoindolin-2-yl)butyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-24***. 60% yield as a brown oil; IR (film) 2943, 1761, 1703, 1634, 1365, 1179, 1081, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85−7.79 (2H, m, H-Ar), 7.74−7.67 (2H, m, H-Ar), 7.44 (1H, s, H-5′), 7.30 (1H, s, H-3), 5.85 (1H, brs, H-7), 5.83 (1H, d, J = 7.6 Hz, H-1), 5.00 (2H, brs, H-10), 3.75−3.68 (5H, m, OCH_3, CH_2), 3.27 (1H, q, J = 7.6 Hz, H-5), 2.92 (1H, dd, J = 17.2, 8.8 Hz, H-6a), 2.76 (2H, t, J = 6.4 Hz, CH_2), 2.67 (1H, t, J = 7.6 Hz, H-9), 2.26−2.14 (4H, m, H-6b, CH_3−Ac), 1.60−1.80 (4H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.12, 168.32 (2C), 166.99, 151.56, 147.82, 136.00, 134.30 (2C), 133.84 (2C), 132.07, 123.09 (2C), 120.56, 111.01, 91.69, 51.32, 49.40, 44.88, 38.54, 37.47, 35.06, 27.88, 26.46, 24.97, 20.94; HRMS (m/z): calcd for $C_{27}H_{28}N_4O_7$ $[M + Na]^+$ 521.2036, found 521.2034.

4.6.25. 10-[4′-(1-Hydroxycyclohexyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-25***. 99% yield; IR (film) 2937, 1759, 1706, 1635, 1265, 1181, 1086, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, s, H-5′), 7.43 (1H, s, H-3), 5.89 (1H, brs, H-7), 5.84 (1H, d, J = 7.6 Hz, H-1), 5.03 (2H, brs, H-10), 3.73 (3H, s, OCH_3), 3.27 (1H, q, J = 8.0 Hz, H-5), 2.94 (1H, dd, J = 16.8, 8.4 Hz, H-6a), 2.70 (1H, t, J = 7.6 Hz, H-9), 2.27−2.16 (4H, m, H-6b), 2.03−1.50 (10H, m, 5× CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.10, 166.93, 155.93, 151.51, 135.78, 134.67, 119.27, 110.96, 91.56, 69.44, 51.29, 49.44, 45.03, 38.53, 37.94 (2C), 34.96, 25.22, 21.84 (2C), 20.89; HRMS (m/z): calcd for $C_{21}H_{27}N_3O_6$ $[M + H]^+$ 418.1978, found 418.1970.

4.6.26. 10-[4′-(1-Hydroxycyclopentyl)-1H-1,2,3-triazole-1-yl]-1-acetoxygenipin ***8a-26***. 99% yield as a white oil; IR (film) 3418, 2951, 1737, 1706, 1634, 1436, 1217, 1179, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.45 (1H, s, H-5′), 7.42 (1H, s, H-3), 5.89 (1H, brs, H-7), 5.82 (1H, d, J = 7.6 Hz, H-1), 5.01 (2H, brs, H-10), 3.71 (3H, s, OCH_3), 3.25 (1H, q, J = 7.6 Hz, H-5), 2.91 (1H, dd, J = 16.4, 8.0 Hz, H-6a), 2.69 (1H, t, J = 6.8 Hz, H-9), 2.26−2.13 (4H, m, H-6b, CH_3−Ac), 2.11−1.88 (8H, m, 4× CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.15, 166.95, 151.51, 134.78, 134.33, 127.74, 119.19, 110.94, 91.57, 78.94, 51.31, 49.43, 44.82, 41.10, 38.51, 34.96, 33.02, 23.47, 22.96, 20.89; HRMS (m/z): calcd for $C_{20}H_{25}N_3O_6$ $[M + Na]^+$ 426.1641, found 426.1644.

4.6.27. 10-[4′-Phenyl-1H-1,2,3-triazole-1-yl]genipin ***8b-1***. 67% yield as a yellow oil; IR (film) 2921, 1697, 1637, 1437, 1179, 1079, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (1H, s, H-Ar), 7.80 (2H, d, J = 7.2 Hz, H-Ar), 7.50 (1H, s, H-3), 7.46−7.31 (3H, m, H-Ar, H-5′), 5.86 (1H, brs, H-7), 5.32 (1H, d, J = 15.2 Hz H-10a), 5.24 (1H, d, J = 15.6 Hz H-10b), 5.15 (1H, d, J = 8.0 Hz, H-1), 4.88 (1H, t, J = 8.0 Hz, OH),

https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316

3.71 (3H, s, OCH_3), 3.15 (1H, q, J = 8.4 Hz, H-5), 2.92 (1H, dd, J = 16.8, 7.6 Hz, H-6a), 2.43 (1H, t, J = 8.0 Hz, H-9), 2.15−2.05 (1H, m, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.75, 152.74, 147.76, 137.82, 132.35, 130.07, 128.84 (2C), 128.33, 125.71 (2C), 120.41, 110.31, 96.37, 51.24, 50.51, 47.22, 39.07, 36.11; HRMS (m/z): calcd for $C_{19}H_{19}N_3O_4$ [M + Na]$^+$ 376.1273, found 376.1276.

4.6.28. 10-[4′-(4-Methoxypheny)l-1H-1,2,3-triazole-1-yl]-genipin ***8b-2***. 45% yield as a yellow solid, mp: 148.6−150.6 °C; IR (film) 2923, 1699, 1629, 1499, 1106, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77−7.70 (3H, m, H-Ar, H- H-5′), 7.51 (1H, brs, H-3), 6.95 (2H, d, J = 8.8 Hz, H-Ar), 5.87 (1H, brs, H-7), 5.32 (1H, d, J = 15.6, Hz, H-10a), 5.21 (1H, d, J = 15.6 Hz, H-10b), 4.98 (1H, d, J = 6.8 Hz, H-1), 4.87 (1H, t, J = 8.0 Hz, OH), 3.84 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.15 (1H, q, J = 8.8 Hz, H-5), 2.92 (1H, dd, J = 16.8, 8.8 Hz, H-6a), 2.42 (1H, t, J = 8.0 Hz, H-9), 2.15−2.06 (1H, m, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.78, 159.69, 152.79, 147.59, 137.93, 132.23, 127.04 (2C), 122.74, 119.66, 114.24 (2C), 110.26, 96.39, 55.27, 51.23, 50.47, 47.21, 39.06, 36.12; HRMS (m/z): calcd for $C_{20}H_{21}N_3O_5$ [M + H]$^+$ 384.1559, found 384.1568.

4.6.29. 10-[4′-(4-Fluorophenyl)-1H-1,2,3-triazole-1-yl]-genipin ***8b-3***. 78% yield as a yellow solid, mp: 156.6−159.6 °C; IR (film) 2923, 1705, 1628, 1497, 1226, 1105, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.74 (3H, s, H-Ar), 7.50 (1H, s, H-3), 7.11 (2H, t, J = 8.8 Hz, H-Ar, H-5′), 5.88 (1H, brs, H-7), 5.33 (1H, d, J = 15.6 Hz, H-10a), 5.23 (1H, d, J = 16.0 Hz, H-10b), 4.88 (1H, d, J = 6.4 Hz, H-1), 4.80 (1H, brs, OH), 3.71 (3H, s, OCH_3), 3.16 (1H, q, J = 8.4 Hz, H-5), 2.94 (1H, dd, J = 16.8, 8.0 Hz, H-6a), 2.42 (1H, t, J = 8.4 Hz, H-9), 2.16−2.05 (1H, m, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.69, 162.72 (d, J_{C-F} = 247 Hz, C−F), 152.64, 146.97, 137.71, 132.59, 127.47 (d, J_{C-F} = 8.0 Hz, 2C−F), 126.32 120.09, 115.96, 115.74, 110.38, 96.35, 51.28, 50.52, 47.17, 39.08, 36.12; HRMS (m/z): calcd for $C_{19}H_{18}FN_3O_4$; [M + Na]$^+$ 394.1179, found 394.1184.

4.6.30. 10-[4′-(6′,6′-Diphenyl-6′-hydroxymethyl)-1H-1,2,3-triazole-1-yl]genipin ***8b-4***. 64% yield as a white solid, mp: 76.6−80.6 °C; IR (film) 3384, 2924, 1700, 1626, 1446, 1103, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, s, H-3), 7.35−7.22 (10H, m, H-Ar), 7.15 (1H, s, H-5′), 5.77 (1H, s, H-7), 5.23 (1H, d, J = 16.0 Hz, H-10a), 5.09 (1H, d, J = 15.6 Hz, H-10b), 4.99 (1H, t, J = 6.4 Hz, OH), 4.81−4.73 (1H, m, H-1), 3.92−3.85 (1H, m, OH), 3.72 (3H, s, OCH_3), 3.10 (1H, q, J = 8.4 Hz, H-5), 2.89 (1H, dd, J = 16.4, 8.0 Hz, H-6a), 2.34 (1H, t, J = 8.4 Hz, H-9), 2.11−1.98 (1H, m, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.71, 153.85, 152.59, 145.47, 145.41, 137.72, 132.05, 127.96 (4C), 127.48, 127.45 (2C), 127.08 (3C) 123.50, 110.14, 96.17, 76.53, 51.19, 50.34, 47.09, 38.84, 35.98; HRMS (m/z): calcd for $C_{26}H_{25}N_3O_5$ [M + H]$^+$ 460.1872, found 460.1871.

4.6.31. 10-[4′-(tert-Butyldiphenylsilyoxylpropyl)-1H-1,2,3-triazole-1-yl]genipin ***8b-5***. 76% yield as a yellow oil; IR (film) 2928, 2854, 1702, 1632, 1440, 1107, 703, 504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.65 (4H, m, H-Ar), 7.55 (1H, s, H-3), 7.50- 7.35 (6H, m, H-Ar), 7.31 (1H, s, H-5′), 5.79 (1H, brs, H-7), 5.52 (1H, brs, OH), 5.25 (1H, d, J = 15.6 Hz, H-10a), 5.16 (1H, d, J = 15.6 Hz, H-10b), 4.88 (1H, d, J = 8.8 Hz, H-1), 3.80−3.70 (5H, m, OCH_3, CH_2), 3.17 (1H, q, J = 8.4 Hz, H-5), 2.95 (1H, dd, J = 16.8, 8.8 Hz, H-6a), 2.88 (2H, t, J = 7.6 Hz, CH_2), 2.40 (1H, t, J = 7.2 Hz, H-9), 2.17−2.05 (1H, m, H-6b), 2.05−1.93 (2H, m, CH_2), 1.20−1.00 (9H, m, CH_3 × 3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.73, 152.78, 147.85, 138.15, 135.50 (4C), 133.80, 131.69, 129.42 (3C), 127.60 (4C), 121.55, 110.27, 96.31, 62.88, 51.18, 50.21, 47.23, 39.03, 36.10, 31.90, 26.83 (3C), 21.91, 19.18; HRMS (m/z): calcd for $C_{32}H_{39}N_3O_5Si$ [M + Na]$^+$ 596.2557, found 596.2554.

4.6.32. 10-[4′-(tert-Butyldiphenylsilyoxylpropyl)-1H-1,2,3-triazole-1-yl]genipin ***8b-6***. 78% yield as a colorless oil; IR (film) 2931, 1698, 1628, 1428, 1103, 701, 503 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (4H, d, J = 6.8 Hz, H-Ar), 7.49 (1H, s, H-5′), 7.45−7.31 (7H, m, H-Ar, H-3), 5.74 (1H, brs, H-7), 5.32−5.08 (3H, m, H-10, OH), 4.88 (2H, s, CH_2), 4.85−4.78 (1H, m, H-1), 3.72 (3H, s, OCH_3), 3.11 (1H, q, J = 8.4 Hz, H-5), 2.91 (1H, dd, J = 16.0, 8.0 Hz, H-6a), 2.31 (1H, t, J = 7.6 Hz, H-9), 2.12−2.00 (1H, m, H-6b), 1.20−1.00 (9H, m, CH_3 × 3), ^{13}C NMR (100 MHz, $CDCl_3$): ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.74, 152.76, 148.07, 137.99, 135.48 (4C), 133.05, 131.83, 129.81 (3C), 127.73 (4C), 122.40, 110.24, 96.29, 58.40, 51.19, 50.34, 47.16, 39.03, 36.08, 26.74 (3C), 19.14. HRMS (m/z): calcd for $C_{30}H_{35}N_3O_5Si$ [M + Na]$^+$ 568.2244, found 568.2245.

4.6.33. 10-[4′-(Octyloxymethyl)-1H-1,2,3-triazole-1-yl]-genipin ***8b-7***. 55% yield as a yellow oil; IR (film) 2926, 1708, 1628, 1436, 1083, 793 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, s, H-5′), 7.50 (1H, brs, H-3), 5.80 (1H, brs, H-7), 5.27−5.18 (3H, m, H-10, OH), 4.88−4.80 (1H, m, H-1), 4.62 (2H, s, CH_2), 3.71 (3H, s, OCH_3), 3.51 (2H, t, J = 6.8 Hz, CH_2), 3.14 (1H, q, J = 8.8 Hz, H-5), 2.91 (1H, dd, J = 16.8, 8.0 Hz, H-6a), 2.38 (1H, t, J = 7.6 Hz, H-9), 2.13−2.05 (1H, m, H-6b), 1.63−1.54 (2H, m, CH_2), 1.35−1.20 (10H, m, 5× CH_2), 0.87 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.85, 152.84, 145.26, 138.08, 132.05, 123.43, 110.24, 96.35, 71.08, 64.02, 51.17, 50.29, 47.13, 39.13, 36.10, 31.76, 29.54, 29.37, 29.18, 26.04, 22.59, 14.04; HRMS (m/z): $C_{22}H_{33}N_3O_5$ [M + H]$^+$ 420.2498, found 420.2502.

4.6.34. 10-[4′-(Dodecyloxymethyl)-1H-1,2,3-triazole-1-yl]-genipin ***8b-8***. 53% yield as a brown oil; IR (film) 2922, 2853, 1738, 1712, 1629, 1436, 1102 cm^{-1}; NMR (400 MHz, $CDCl_3$): δ 7.61 (1H, s, H-5′), 7.49 (1H, s, H-3), 5.79 (1H, brs, H-7), 5.27 (1H, brs, OH), 5.25 (1H, d, J = 15.6 Hz, H-10a), 5.18 (1H, d, J = 15.6 Hz, H-10b), 4.83 (1H, d, J = 8.4 Hz, H-1), 4.60 (2H, s, CH_2), 3.70 (3H, s, OCH_3), 3.50 (2H, t, J = 6.4 Hz, CH_2), 3.13 (1H, q, J = 8.8 Hz, H-5), 2.90 (1H, dd, J = 16.4, 8.8 Hz, H-6a), 2.39 (1H, t, J = 7.2 Hz, H-9), 2.11−2.04 (1H, m, H-6b), 1.62−1.53 (2H, m, CH_2), 1.37−1.19 (18H, s, 9× CH_2), 0.86 (3H, t, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.72, 152.71, 145.30, 137.90, 132.12, 123.23, 110.21, 96.26, 70.99, 64.00, 51.18, 47.07, 38.94, 36.03, 31.80, 29.55, 29.52 (4C), 29.49, 29.38, 29.24, 25.98, 22.57, 14.00; HRMS (m/z): $C_{26}H_{41}N_3O_5$ [M + H]$^+$ 476.3124, found 476.3120.

4.6.35. 10-[4′-((Undec-10-enyloxy)methy)-1H-1,2,3-triazole-1-yl]genipin ***8b-9***. 69% yield as a brown oil; IR (film) 2925, 2854, 1706, 1629, 1437, 1083, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, s, H-5′), 7.48 (1H, brs, H-3), 5.85−5.75 (1H, m, CH-alkene), 5.73 (1H, s, H-7), 5.22−5.14 (2H, m, H-10), 5.01−4.81 (3H, m, H-1, CH × 2), 4.60 (2H, s, CH_2), 3.70 (3H, s, OCH_3), 3.50 (1H, t, J = 8.0 Hz, CH_2), 3.14 (1H, q, J = 8.8 Hz, H-5), 2.88 (1H, dd, J = 16.4 Hz, 8.0 Hz, H-6a), 2.41 (1H, t, J = 8.0 Hz, H-9), 2.10−1.97 (3H, m, CH_2, H-6b), 1.62−1.50 (2H, m, CH_2), 1.40−1.19 (14H, m, 7× CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.69, 152.68, 145.17, 139.02, 137.91, 131.92, 123.20, 113.97, 110.13, 96.21, 70.89, 63.92, 51.13, 50.31, 46.98, 38.94, 35.96, 33.63, 29.52, 29.42,

https://doi.org/10.1021/acsomega.2c01593
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29.35, 29.27, 28.94, 28.74, 25.91; HRMS (m/z): calcd for $C_{25}H_{37}N_3O_5$ $[M + H]^+$ 482.2631, found 482.2630.

4.6.36. 10-[4′-(((Dioxoisoindolin-2-yl)oxy)methyl)-1H-1,2,3-triazole-1-yl] ***8b-10***. 68% yield as a white solid, mp: 57.6−61.6 °C; IR (film) 2923, 2853, 1729, 1627, 1437, 1081, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (1H, s, H-5′), 7.76−7.68 (4H, m, H-Ar), 7.53 (1H, brs, H-3), 5.98 (1H, s, H-7), 5.37 (2H, s, CH_2), 5.30−5.14 (2H, m, H-10), 4.82−4.68 (2H, m, H-1, OH), 3.73 (3H, s, OCH_3), 3.18 (1H, q, J = 8.8 Hz, H-5), 2.96 (1H, dd, J = 15.6, 8.4 Hz, H-6a), 2.28 (1H, t, J = 8.0 Hz, H-9), 2.16−2.06 (1H, m, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.69, 163.47 (2C), 152.59, 141.23, 137.45, 134.47 (2C), 132.82, 128.46, 125.65, 123.44 (2C), 110.18, 96.24, 69.90, 51.16, 50.40, 47.08, 39.01, 35.93, 29.52; HRMS (m/z): calcd for $C_{22}H_{20}N_4O_7$ $[M + H]^+$ 453.1410, found 453.141

4.6.37. 10-[4′-((1,3-Dioxoisoindolin-2-yl)methyl)-1H-1,2,3-triazole-1-yl] ***8b-11***. 80% yield as a white oil; IR (film) 2949, 1711, 1626, 1394, 1084, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83−7.75 (2H, m, H-Ar), 7.74 (1H, s, H-5′), 7.71−7.64 (2H, m, H-Ar), 7.41 (1H, brs, H-3), 6.26 (1H, brs, OH), 5.69 (1H, brs, H-7), 5.18 (2H, s, CH_2), 5.10−4.94 (2H, m, H-10), 4.84 (1H, d, J = 8.4 Hz, H-1), 3.66 (3H, s, OCH_3), 3.08 (1H, q, J = 8.4 Hz, H-5), 2.83 (1H, dd, J = 16.8, 8.4 Hz, H-6a), 2.38 (1H, t, J = 7.6 Hz, H-9), 2.08−2.01 (1H, m, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.80, 167.73 (2C), 152.74, 142.65, 137.70, 134.17, 132.46 (2C), 131.97, 123.56, 123.51 (2C), 110.31, 96.34, 51.28, 50.45, 47.21, 39.09, 36.07, 32.95, 29.69; HRMS (m/z): calcd for $C_{22}H_{20}N_4O_6$ $[M + H]^+$ 437.1456, found 437.1468.

4.6.38. 10-[4′-(1-Hydroxycyclohexyl)-1H-1,2,3-triazole-1-yl]genipin ***8b-12***. 97% yield as a white solid, mp: 128.6−132.6 °C; IR (film) 3511, 2929, 2855, 1738, 1697, 1444, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, s, H-5′), 7.46 (1H, brs, H-3), 6.59 (1H, brs, OH), 5.75 (1H, brs, H-7), 5.40−5.10 (2H, m, H-10), 4.82 (1H, d, J = 8.8 Hz, H-1), 3.69 (3H, s, OCH_3), 3.13 (1H, q, J = 8.0 Hz, H-5), 2.87 (1H, dd, J = 15.6, 8.8 Hz, H-6a), 2.41 (1H, t, J = 8.0 Hz, H-9), 2.09−2.04 (1H, m, H-6b), 2.00−1.30 (10H, m, 5×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.80, 155.23, 152.72, 138.03, 132.11, 120.80, 110.11, 96.26, 69.42, 51.18, 50.24, 47.13, 38.94, 37.72, 37.68, 36.02, 29.54, 25.20, 21.82. HRMS (m/z): calcd for $C_{19}H_{25}N_3O_5$ $[M + H]^+$ 376.1872, found 376.1877.

4.6.39. 10-[4′-(1-Hydroxycyclopentyl)-1H-1,2,3-triazole-1-yl]genipin ***8b-13***. 92% yield as a white solid, mp: 128.6−132.6 °C; IR (film) 3310, 2924, 2854, 1737, 1708, 1628, 1438, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, s, H-5′), 7.50 (1H, brs, H-3), 5.84 (1H, brs, H-7), 5.70 (1H, brs, OH), 5.24 (1H, d, J = 15.6 Hz, H-10a), 5.14 (1H, d, J = 16.0 Hz, H-10b), 4.88−4.79 (1H, m, H-1), 3.71 (3H, s, OCH_3), 3.16 (1H, q, J = 8.4 Hz, H-5), 2.91 (1H, dd, J = 16.8, 8.4 Hz, H-6a), 2.85−2.69 (1H, m, OH), 2.40 (1H, t, J = 8.0 Hz, H-9), 2.14−1.78 (9H, m, H-6b, 4× CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.79, 154.20, 152.72, 137.87, 132.72, 120.67, 110.38, 96.41, 78.91, 51.20, 50.26, 47.27, 41.12(2C), 39.07, 36.17, 23.49(2C); HRMS (m/z): calcd for $C_{18}H_{23}N_3O_5$ $[M + Na]^+$ 384.1535, found 384.1543.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01593.

Experimental details and protocols on protein expression and purification, inhibition and binding studies, and X-ray crystallography (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Research Unit in Synthetic Compounds and Synthetic Analogues from Natural Product for Drug Discovery (RSND). R.S. and P.S. are grateful for support through the Postdoctoral Fellowship Award from Burapha University. The authors thank Assistant Prof. Suchaya Pongsai, Faculty of Science, Burapha University, for helpful discussions on docking simulation techniques. Special thanks go to Dr Ron Beckett, Faculty of Science, Burapha University, for his comments and English correction.

■ ABBREVIATIONS

AD, Alzheimer's disease; AChE, acetylcholinesterase; BuChE, butyrylcholinesterase; TBSCl, *tert*-butyldimethylsilyl chloride; Ac_2O, acetic anhydride; TBDPSCl, *tert*-butyldiphenylsilyl chloride; DCM, dichloromethane; THF, tetrahydrofuran; MsCl, methanesulfonyl chloride; Et_3N, triethylamine; NaN_3, sodium azide; DMF, dimethylformamide; TBAF, tetra-*n*-butylammonium fluoride; CuI, copper(I)iodide; CH_3CN, acetonitrile; rt, room temperature; H_2O_2, hydrogen peroxide; NA, not active

https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316

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https://doi.org/10.1021/acsomega.2c01593
ACS Omega 2022, 7, 24302−24316