รายงานวิจัยฉบับสมบูรณ์

โครงการ
การปรับเปลี่ยน Geniposide จากสมุนไพร
เพื่อศึกษาฤทธิ์ต้านอัลไซเมอร์

Modification of Geniposide from natural product
for study bioactivity against Alzheimer's disease

รุ่งนภา แซ่เอ็งและคณะ

โครงการวิจัยประเภทงบประมาณเงินรายได้
จากเงินอุดหนุนรัฐบาล (งบประมาณแผ่นดิน)
ประจำปีงบประมาณ 2561
มหาวิทยาลัยบูรพา

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28 กุมภาพันธ์ 2562

กิตติกรรมประกาศ

งานวิจัยนี้ได้รับทุนสนับสนุนการวิจัยจากงบประมาณเงินรายได้จากเงินอุดหนุนรัฐบาล
(งบประมาณแผ่นดิน) ประจำปีงบประมาณพ.ศ. 2561 มหาวิทยาลัยบูรพา
ผ่านสำนักงานคณะกรรมการการวิจัยแห่งชาติเลขที่สัญญา142/2561

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คำนำ

โครงการวิจัย “การปรับเปลี่ยน Geniposide จากสมุนไพรเพื่อศึกษาฤทธิ์ต้านอัลไซเมอร์” ได้รับการสนับสนุนทุนการวิจัยงบประมาณแผ่นดินประจำปีงบประมาณ 2561 มหาวิทยาลัยบูรพา รายงานการวิจัยฉบับนี้เสนอรายละเอียดของการวิจัยซึ่งประกอบด้วยบทนำที่เสนอผลงานวิจัยที่เกี่ยวข้อง ผลการทดลองวิจัย การอภิปรายสรุปผล และฤทธิ์ทางชีวภาพของสาร

การวิจัย “การปรับเปลี่ยน Geniposide จากสมุนไพรเพื่อศึกษาฤทธิ์ต้านอัลไซเมอร์”สำเร็จลุล่วงไปด้วยดี โดยผู้วิจัยต้องขอขอบคุณทีมวิจัยซึ่งประกอบด้วยที่ปรึกษาโครงการ ศ.ดร. อภิชาต สุขสำราญ คณะวิทยาศาสตร์ มหาวิทยาลัยรามคำแหง ผศ.ดร. จิราภรณ์ โตจรัส คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ผู้ร่วมโครงการ ดร. อนันต์ อธิพรชัย รวมทั้งนิสิตปริญญาเอก สาขาวิชาเคมี นางสาวปฐมาวดี ศิลาลาย งานวิจัยนี้ได้รับการสนับสนุนจากภาควิชาเคมี คณะวิทยาศาสตร์และทุนเรียนดีวิทยาศาสตร์แห่งประเทศไทย

ผศ. ดร. รุ่งนภา แซ่เอ็ง
อาจารย์ประจำภาควิชาเคมี คณะวิทยาศาสตร์
หัวหน้าโครงการวิจัย

บทคัดย่อ

Genipin เป็นสาร aglycone ที่มาจากสารอิริดอยด์ไกลโคไซด์ที่มีชื่อว่า geniposide สารธรรมชาติที่พบในผลของ *Gardenia jasminoides* ทีมวิจัยได้เน้นการปรับเปลี่ยนโครงสร้างของสาร genipin และตรวจสอบฤทธิ์ต้านอัลไซเมอร์ สารอนุพันธ์ใหม่ของ triazolylgenipin ได้ถูกวางแผนและสังเคราะห์ผ่านปฏิกิริยาเคมีหกขั้นตอน คือปฏิกิริยา silylation, acetylation, desilylation, mesylation, azidation และ Huisgen 1,3-dipolar cycloaddition ตามลำดับ ได้สารอนุพันธ์ใหม่ genipin-triazole จำนวน 20 อนุพันธ์ ด้วยร้อยละการเกิดผลิตภัณฑ์ที่ดีถึงดีมาก สารอนุพันธ์จำนวน 9 อนุพันธ์ แสดงฤทธิ์ต้านอัลไซเมอร์ที่ดี

Abstract

Genipin is an aglycone derived from an iridoid glycoside namely geniposide present in fruit of *Gardenia jasminoides*. We focus on structure modification of genipin and screening for their bioactivity against Alzheimer's disease. The new triazolylgenipin analogues were designed and synthesized *via* six steps including silylation, acetylation, desilylation, mesylation, azidation and Huisgen 1,3-dipolar cycloaddition reaction, respectively. Twenty analogues of genipin-triazole were obtained in good to excellent yields. Nine compounds showed promising results of bioactivity against Alzheimer's disease.

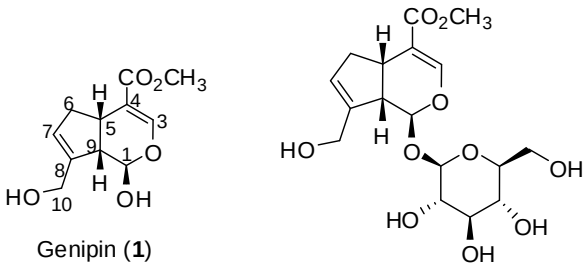
Chapter 1 Introduction and Literature reviews

Introduction

Alzheimer's disease (AD) is the part of most common form of dementia that causes problems with loss of cognitive function including memory, language, and motor skills. The accumulation of Aβ peptide aggregates[1, 2] in the brain is one of reason cause the Alzheimer's disease (AD), the memory loss and inefficient ability to do work and, eventually die due to the brain to have problems and cannot to cure which currently affects millions of people worldwide. The report from The world Alzheimer Report 2015 (Alzheimer's Disease International, 2015)[3], showed that the people in worldwide about 46.8 million with dementia in 2015 and have a tendency increase to 74.7 million in 2030 which suppose to increase rapidly to 131.5 million in 2050. Cause of Alzheimer's disease (AD) is complicated and still, etiology is not clear. Several factors have been related in Alzheimer's disease (AD) pathology, such as reduced acetylcholine (ACh) level, oxidative stress, aggregated amyloid-β-peptide (Aβ) and tau protein [4]. Aβ peptide aggregate in the brain is the one's factors causing to Alzheimer's disease (AD). The fibrils causing to Alzheimer's disease was formed by amyloid beta (Aβ) peptides as an abnormal structure called plaques and tangles which they have been killing nerve cells and build up in the spaces between nerve cells.[5-7]. Amyloid plaques are the small peptide fragment comprise with 40 or 42 of amino acid [8, 9], the fragment of the amino acid can be cleaved by β-secretase and γ-secretase *via* proteolysis of the amyloid precursor protein (APP) Moreover, Aβ peptide was was reported to reduce nerve efficiency because mitochondrial redox activity and induces oxidative stress by generation of reactive oxygen species (ROS) such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and reactive nitrogen species (RNS) such as nitric oxide (NO)[10-12]. The increment oxidative stress and activation of the apoptotic pathway play an important role about Aβ-induced neurotoxicity [13-15] and neural cell death *via* mitochondrial apoptotic pathway. Therefore, the inhibition of Aβ-induced neurotoxicity is a good choice to treat Alzheimer's patients. Currently, only five drugs against Alzheimer's disease (AD) have been approved by the U.S. Food and Drug Administration (FDA) and available in the market now such as donepezil (DNP)[16], rivastigmine[17], and galantamine[18] but these drugs can help only to mitigate the symptoms and cannot inhibited of Aβ-induced neurotoxicity.

Genipin (**1**) and geniposide (**2**) are the natural product found in gardenia fruit extract. Genipin is an aglycone derived from an iridoid glycoside geniposide (**2**) present in fruit of *Gardenia jasminoides*. Genipin can be prepared from geniposide (**2**) by hydrolysis at glycosidic

bond using β-glucosidase enzyme [19]. Genipin is a type of monoterpenoid with the skeleton of cyclopenta[c]pyran showed intriguing biological properties of a multiple disease such as anti-inflammatory[20, 21], antidiabetic[22], anticancer [23], and anti-Alzheimer's activities[24-26].



Genipin (**1**) Geniposide (**2**)

Figure 1 Structure of genipin (**1**) and geniposide (**2**)

1,2,3-Triazoles is a heterocyclic compound which gaining attention from chemist because of convenient synthesis by 1,3-dipolar cycloaddition [27] and can be found in many important drugs. Equipped with attractive features, they exhibit numerous biological activities including anti-Alzheimer's activities[28], [29]) and [30]. Due to the anti-Alzheimer's activities of genipin and triazoles, we designed to combine these two molecules and synthesize a new class of 10-triazolylgenipin analogues *via* Huisgen 1,3-dipolar cycloaddition reaction. All the synthetic analogues of the triazole linked with genpin will be evaluated for the anti-amyloid β aggregation against Alzheimer's disease

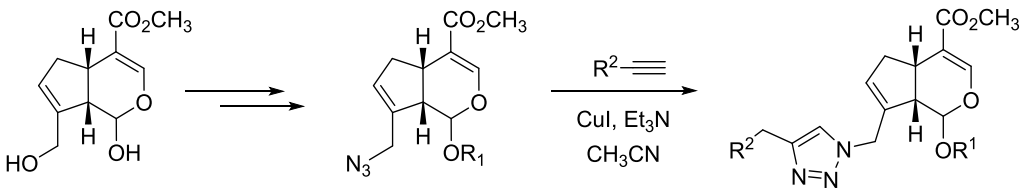


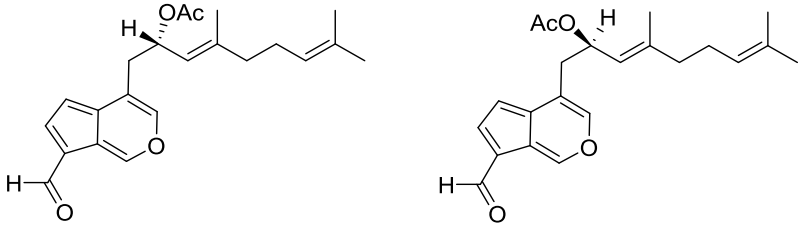
Figure 2 The synthetic plan for 10-triazolylgenipin analogues

Literature reviews

Genipin is an aglycone derived from an iridoid glycoside geniposide present in fruit of *Gardenia jasminoides*. In this work, we aimed to study the synthesis of 10-triazolylgenipin analogues by chemical modification of genipin. Genipin is an aglycone derived from an iridoid glycoside geniposide (**2**) present in fruit of *Gardenia jasminoides*. Substituted triazole ring- was introduced at C-10-position of genipin. All synthetic compounds will be investigated to reduce Aβ self-induced aggregation and inhibit Aβ1-42. Some recent reports and relate work on modifications of genipin skeleton and biological activity study of genipin and derivatives will be reviewed.

Selected examples of modification and biological evaluation of genipin and derivatives

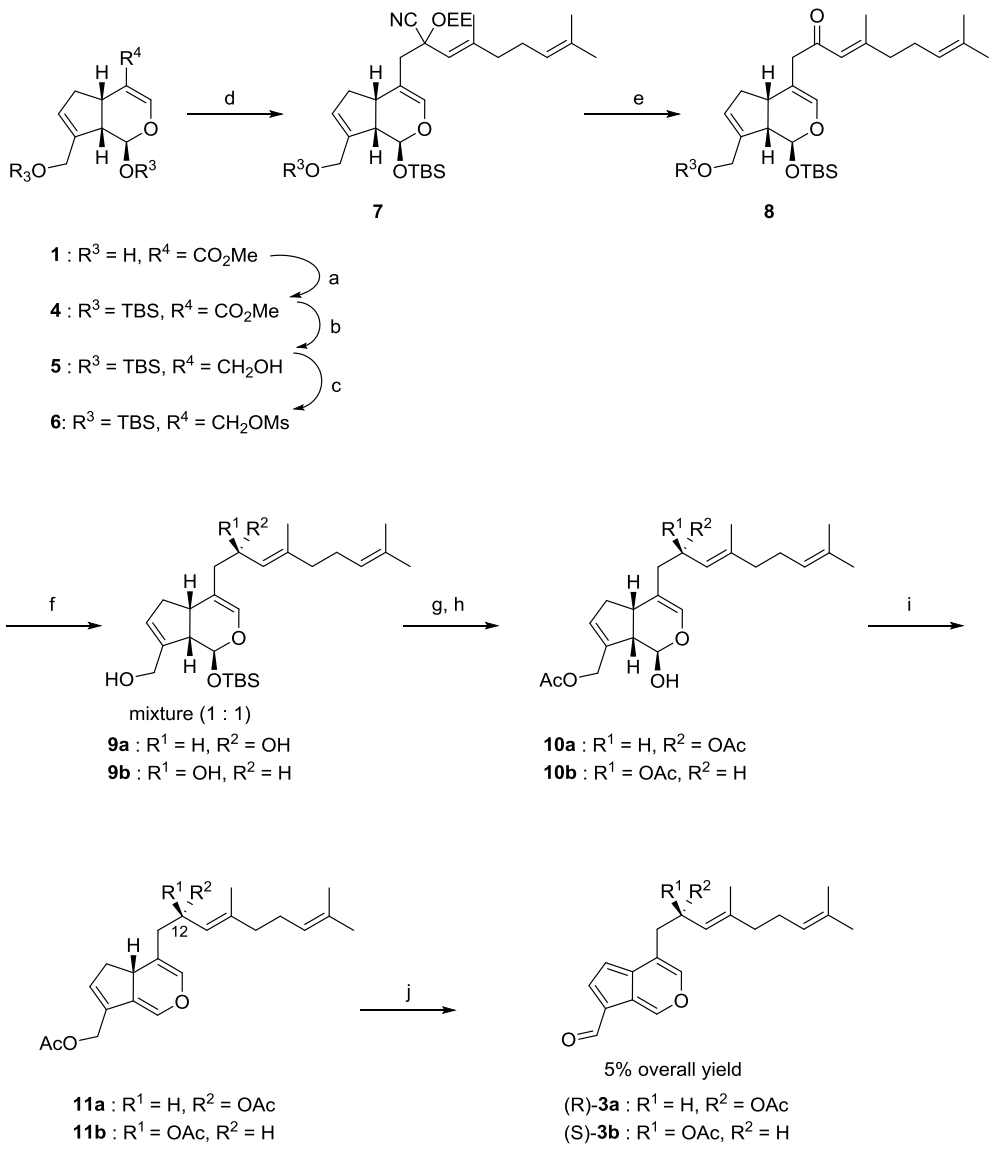
The R- and S- enantiomers of iridoid halitunal (**3**) were isolated from marine algae halimeda tuna. Halitunal (**3**) were synthesized from genipin (**1**) by (Shimano, Ge, Sakaguchi, & Isoe, 1996)[31] and evaluation for antivirus activity (coronavirus strain A59).



R-(3) **S-(3)**

Figure 3 The structure of halitunal (**3**)

Genipin was employed as starting material for the total synthesis of natural halitunal (**3**). Initially, silylation and reduction of genipin using DIBAL-H followed by the mesylation to provide compound (**6**) which was reacted with carbanion of cyano ether. Enone (**8**) was obtained after hydrolysis and decyanation under acidic conditions. Upon treatment with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$, compound (**8**) was regioselectivity reduced to the diastereomeric mixture of allylic alcohol (**9a**) and (**9b**). Then compound (**9**) was acetylated and desilylated to afford diacetate (**10**). Dehydration and oxidative dehydrogenation of coumpound (**10**) eventually gave the title product (**3a**) and (**3b**) over 10 steps (5% overall yield) as shown in Figure 4.



Reagents and conditions (a) TBSCl, $AgNO_3$, DMF (89%). (b) DIBAL-H, CH_2Cl_2, -78 °C (91%). (c) n-BuLi, MsCl, THF (d) cyanoethoxyethyl ether, LDA (e) PPTS, MeOH. (f) $NaBH_4$, $CeCl_3.7H_2O$, MeOH (26%, 4 steps), (g) Ac_2O, pyridine (95%). (h) TBAF, AcOH, (96%) (i) 1,1'-thiocarbonyldiimidazole, benzene, rt. (j) DDQ, benzene, rt (47%, 2 steps).

Figure 4 The synthesis of both enantiomers of halitunal (**3**)

Lactate dehydrogenase (LDH) is the enzyme that can be found all over the body, when cell body is damaged, the level of lactate dehydrogenase (LDH) in blood increases. The age is related with dehydrogenase (LDH), the lactate increases in brain with the growth of the age, which leads to Alzheimer's disease (Datta & Chakrabarti, 2018)[32].

Yamazaki reported the effect of genipin (**1**) to protect of the high-level lactate dehydrogenase (LDH) in blood cause to Alzheimer's amyloid β protein (Aβ) toxicity in cultured hippocampal neurons (Yamazaki et al., 2001)[24]. The toxic on cultured hippocampal neurons is

depend on lactate dehydrogenase (LDH) release. When added the β-amyloid 40 μM to the neuron cultures, the LDH release and the level concentration of LDH raised up but if the genipin 20 μM was added, the concentration of LDH decreased. So genipin shows strongly prevent of the neurotoxicity of the Amyloid β Protein.

Suzuki reported the *O*-alkylation of genipin at C-1 position for improved stability and screened the toxicity of neurotogenic activities in PC12h cells (Suzuki, Yamazaki, Chiba, Uemori, & Sawanishi, 2010)[25]. 1-Alkyloxy substituents (**12a-12f**) were screened for the neurotogenic activity, the result showed that (1R)-1-isopropylgenipin is the most active compound (**12d**).

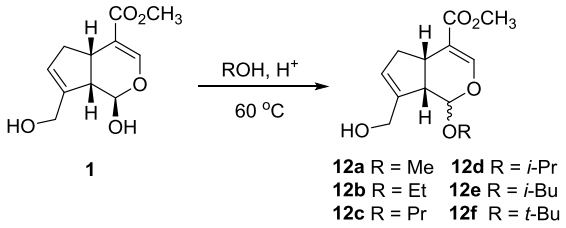


Figure 5 The synthesis of 1-alkyloxygenipins (**12a-12f**)

Tamura used genipin (**1**) as starting material for the total synthesis of 5,6-dihydrovaltrate (**14**) and derivatives (**14a**, **14b** and **14c**) (Tamura, Fujiwara, Shimizu, Todo, & Murakami, 2010)[33]. To study their anti-HIV activity, evaluation of inhibition to nuclear export of Rev was conducted. Compound (**14b**) showed higher anti-HIV activity than natural product valtrate (**13**).

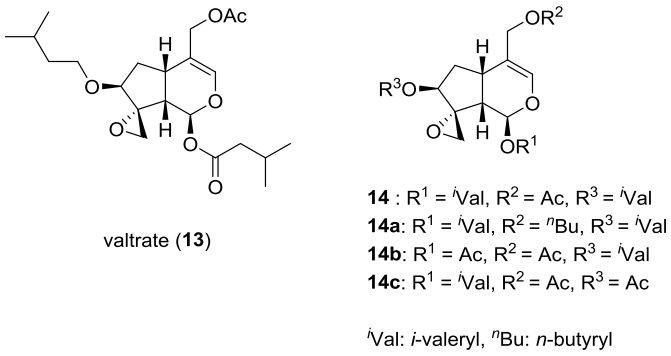
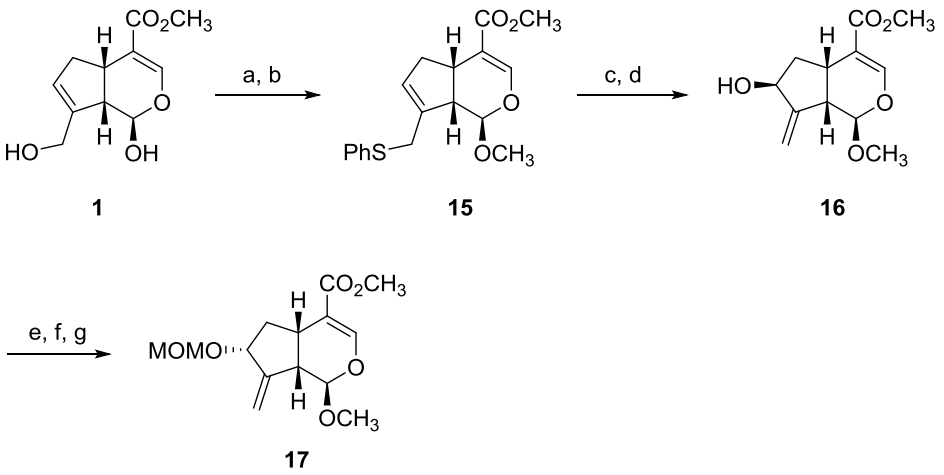


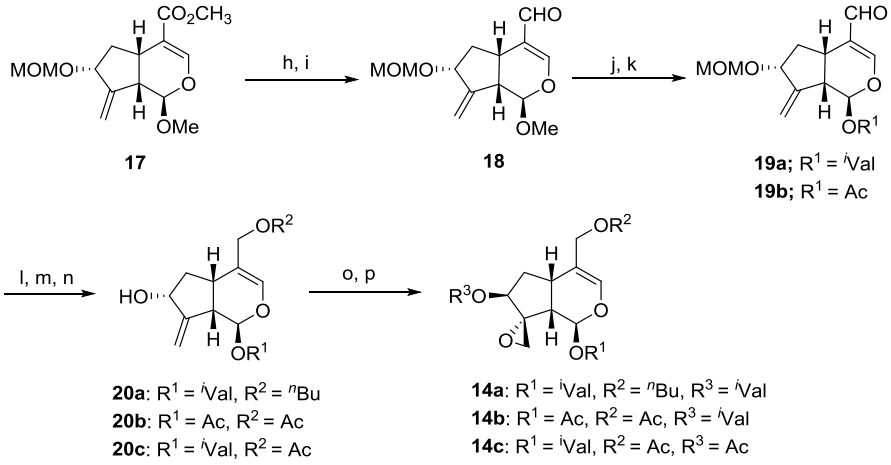
Figure 6 The structure of valtrate (**13**) and 5,6-dihydrovaltrate (**14**) and derivatives

As depicted in Figure 7 and 8, compound (**17**) was prepared through 7-steps transformation. Reduction of ester of (**17**), modification of oxygen-containing groups at C-1, C-4 and C-7 and epoxidation of double bond led to compound (**14**) which was examined on the Rev-export inhibitory potency.



Reagents and conditions (a) Amberlyst-15, MeOH, rt, 95%; (b) PhSSPh, *n*-Bu_3P, toluene, rt, 82%; (c) Oxone, acetone-H_2O, rt; (d) $(MeO)_3P$, MeOH, reflux, 97%, two steps; (e) DMP, CH_2Cl_2, rt; (f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -78 ^oC; (g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 63%, three steps.

Figure 7 The synthesis of methyl ester (17)



Reagents and conditions h) DIBAL, CH_2Cl_2, -78 ^oC; (i) TPAP, NMO, CH_2Cl_2, rt, 90%, two steps; (j) 10% HCl-THF, rt, 50%, recovery of (**18**) 31%; (k) isovaleric acid or AcOH, Im_2CO, DBU, CH_2Cl_2, 0 ^oC, 85% for (**19a**), quant for (**19b**); (l) BCl_3, CH_2Cl_2, 0 ^oC; (m) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 78 ^oC; (n) *n*-butyryl chloride or AcCl, *i*-Pr_2NEt, CH_2Cl_2, 0 ^oC, 48% for (**20a**), 50% for (**20b**), three steps; (o) TBHP, $VO(acac)_2$, C_6H_6, rt; (p) isovaleric acid or AcOH, DEAD, PPh_3, C_6H_6, rt, 70% for (**14a**), 71% for (**14b**), 65% for (**14c**), two steps.

Figure 8 The synthesis of 5,6-dihydrovaltrate analogs (**14a**), (**14b**) and (**14c**)

Oh reported the total synthesis of 7, 8-epi-valtrate (**21**) possessing stereogenic center opposite to natural valtrate (**13**) at C-7. 7, 8-epi-valtrate and its derivatives were evaluated for proliferation inhibition on various cancer cell lines and HUVEC which exhibiting strong inhibitory activity (Oh, Kwon, Shin, Ham, & Lee, 2012)[34].

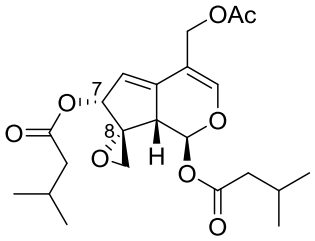
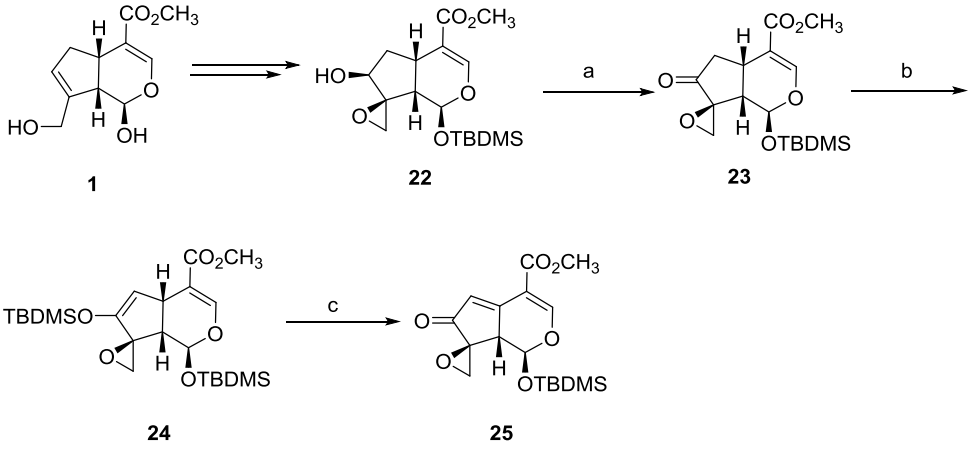


Figure 9 The structure of 7,8-epi-valtrate (**21**)

The total synthesis of 7,8-epi-valtrate (**21**) used genipin (**1**) as a starting material to provide the epoxy alcohol (**22**). Swern oxidation and silyl-protection of compound (**22**) afforded TBDMS-protected enol (**24**). Subsequent oxidation with DDQ in pyridine gave 5,6-unsaturated ketone (**25**) in 56% yield (Figure 10).

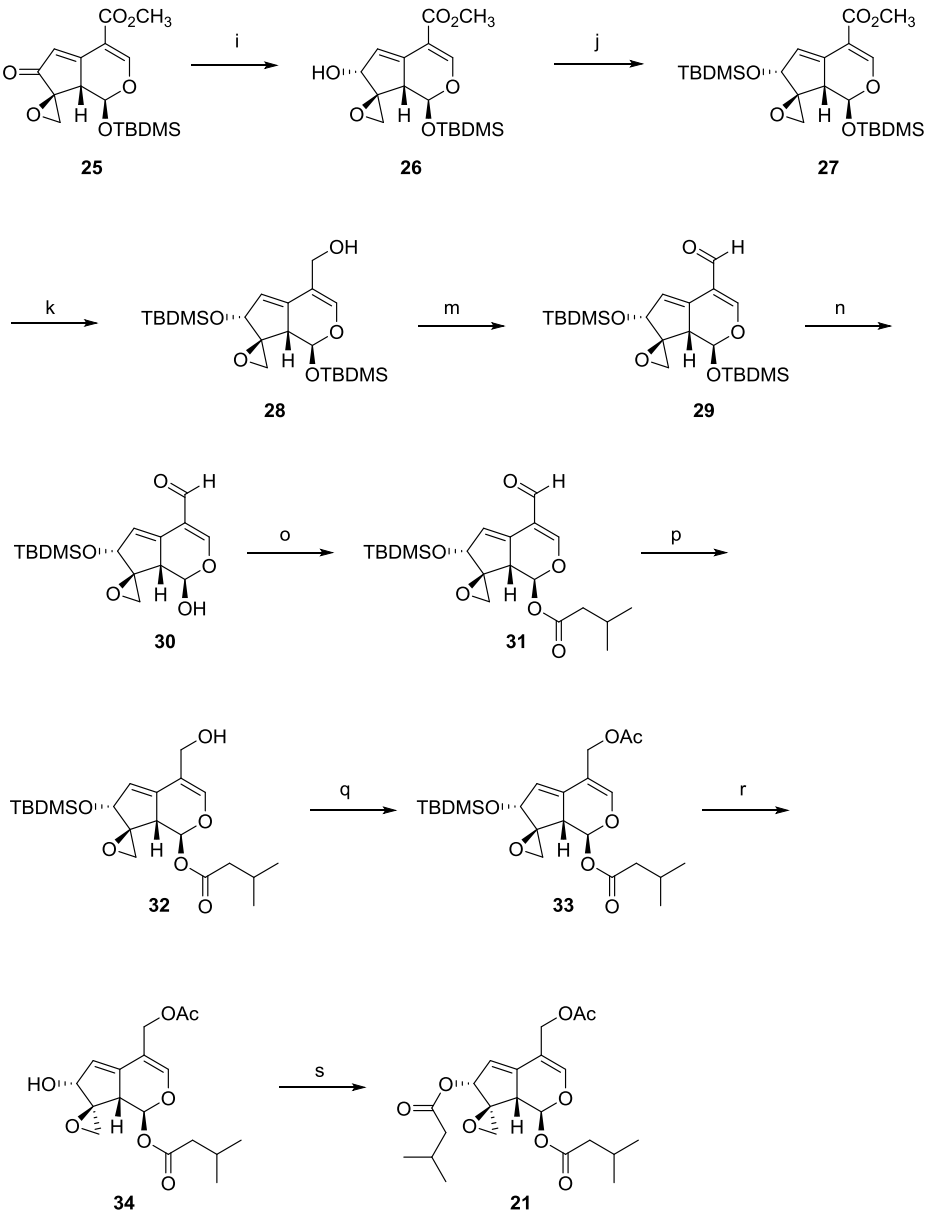


Reagents and conditions: (a) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 97%; (b) LDA, TBDMSOTf, THF, -78 °C, 75%; (c) DDQ, pyridine, C_6H_6, 50 °C, 56%.

Figure 10 Synthesis of 5,6-unsaturated ketone (**25**)

5,6-Unsaturated ketone (**25**) was treated with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ producing 7α-alcohol (**26**) in 94% yield. Subsequently, the silylation of 7α-alcohol (**26**) with TBDMSCl furnished the corresponding silyl ester (**27**) in 92% yield. The ester at C-4 position was reduced by DIBAL-H to provide primary alcohol which was oxidized with TPAP and NMO giving the aldehyde (**29**). Desilylation of compound **(29)** followed by acylation of the hydroxyl group

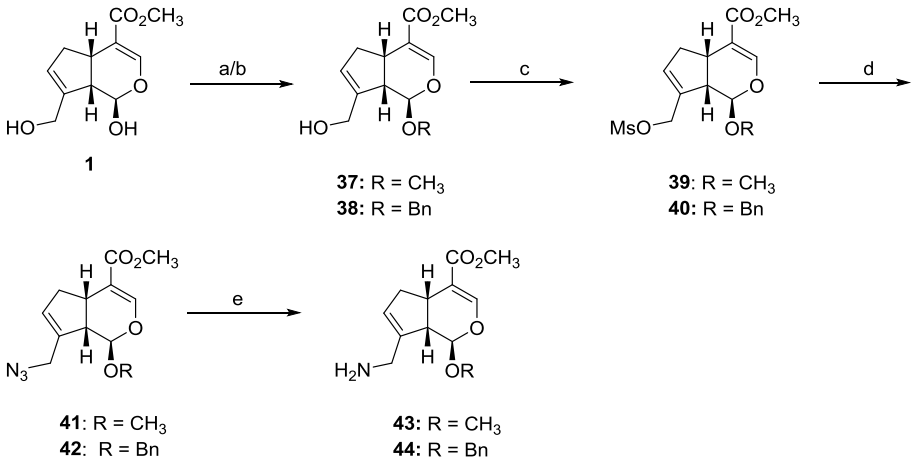
afforded isovaleryl ester (**31**) in 46% yield. The reduction of aldehyde and reacted with AcCl followed by desilylation at C-7 position to obtained 7,8-epi-valtrate in 60% yield which was possessing stereogenic center opposite to natural valtrate (**13**) at C-7.



Reagents and conditions: (i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 ^oC, 94%; (j) TBDMSCl, imidazole, CH_2Cl_2, rt, 92%; (k) DIBAL-H, CH_2Cl_2, -78 ^oC, 78%; (m) TPAP, NMO, CH_2Cl_2, rt, 62%; (n) TBAF, THF, 0 ^oC, 83%; (o) isovaleryl chloride, pyridine, CH_2Cl_2, -78 ^oC, 46%; (p) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 ^oC, 67%; (q) acetyl chloride, pyridine, CH_2Cl_2, -78 ^oC, 78%; (r) TBAF, THF, rt, 70%; (s) isovaleryl chloride, pyridine, CH_2Cl_2, rt, 60%.

Figure 11 Synthesis of target 7, 8-epi-valtrate (**21**)

Genipin skeleton has been reported for potent anti-diabetic activity (Zhang et al., 2006) Thereafter, (Wei et al., 2013) reported the synthesis of new genipin analogues (**35**) and (**36**) for evaluated anti-diabetic activity (Figure 13). They focused on designing and synthesizing the target compound containing the amine group in genipin core. The synthesis was commenced with methylation or benzylation of genipin followed by mesylation, azidation to give azido compound (**41**) and (**42**). Then reduction of azido group was proceeded smoothly to provided amine (**43**) and (**44**) in high yield. (Figure 12)



1

37: R = CH_3
38: R = Bn

39: R = CH_3
40: R = Bn

41: R = CH_3
42: R = Bn

43: R = CH_3
44: R = Bn

Reagents and conditions: (a) CH_3OH, BF_3OEt_2, rt, 24 h, for (**37**), 100%; (b) $C_6H_5CH_2OH$, $BF_3{\cdot}OEt_2$, THF, reflux, 24 h, for (**38**), 70%; (c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 ^oC, 0.5 h, for (**39**), 98%, for (**40**), 97%; (d) NaN_3, DMF, 50 ^oC, 24 h, for (**41**), 80%, for (**42**), 82%; (e) $SnCl_2$, MeOH, rt, 3 h for (**43**), 80%, for (**44**), 78%.

Figure 12 Synthesis of (**43**) and (**44**)

In the final step, genipin-amide analogues (**35**, **36**) were obtained in 90-98% yield by utilizing variety of acyl chlorides to react with amino group at C-10 position under basic conditions.

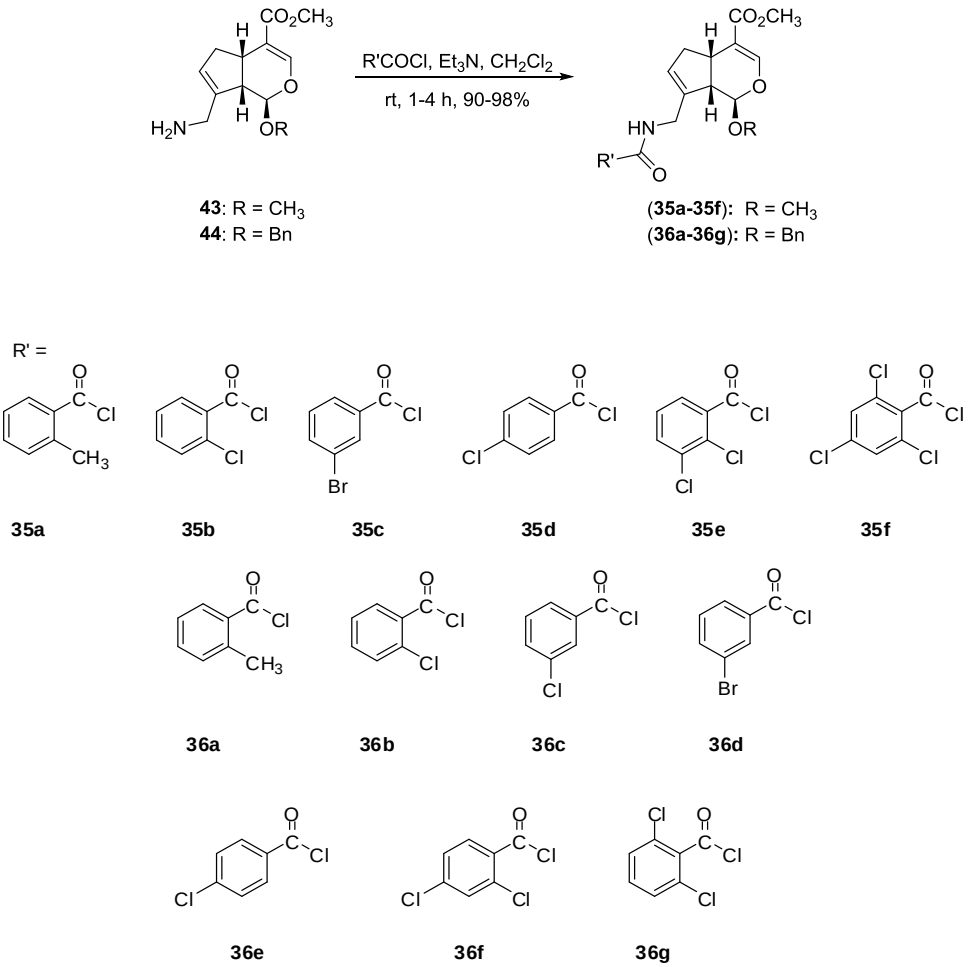


Figure 13 Synthesis of target compounds (**35a-35f**) and (**36a-36g**)

All of synthetic compounds were screened for anti-diabetic activities using DPP IV assay. Compound (**36f**) was found to exhibit highest activity for inhibited rate up to 31.2%. Jian reported the synthesis of gardenamide A derivatives for evaluation of neurodegenerative diseases in PC12-cell as shown in Figure 14, 15 and 16 (Jian, Jun, Zhao, & He-ru, 2013)[35].

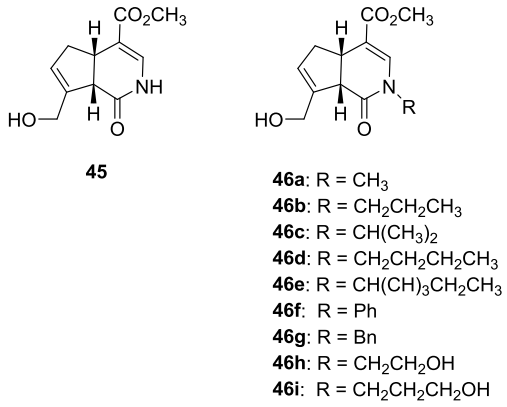
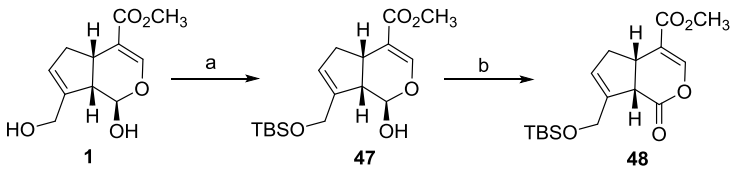
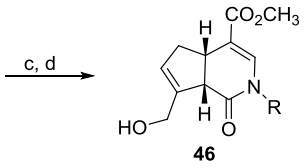


Figure 14 Structure of gardenamide A (**45**) and derivatives (**46**)





46a; R=CH_3
46b; R=$CH_2CH_2CH_3$
46c; R=$CH(CH_3)_2$
46d; R=$CH_2CH_2CH_2CH_3$
46e; R=$CH(CH)_3CH_2CH_3$
46f; R=Ph
46g; R=Bn
46h; R=CH_2CH_2OH
46i; R=$CH_2CH_2CH_2OH$

Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 1.5 h, 80-95%; (b) DMP, CH_2Cl_2, rt, 75-85%; (c) pyridine, RNH_2, 60-130 ^oC; 2 h; (d) TFA, THF, 60-80 ^oC, 2 h, 50-70%.

Figure 15 Synthesis of gardenamide A derivatives (**46**)

Initially, they investigated the selectively silylation at primary alcohol using TBS-Cl and oxidation of the hydroxyl group at C-1 to afford the lactone compound (48). At the end, formal substitution of various amines to oxygen atom of lactone under acidic conditions afforded the gardenamide A derivative (**46**) containing lactam moiety in 50-70% yield (Figure 15). The target compounds were evaluated for the neurodegenerative activity on PC12-cell, suggesting compound (**46c**) and (**46h**) were the most active compound in the series. (Figure 16)

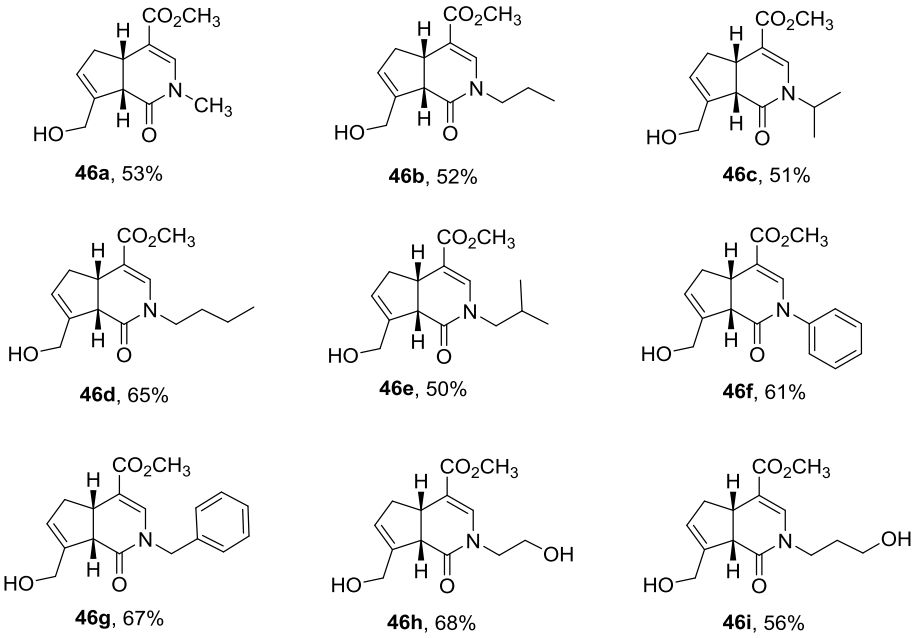


Figure 16 Structure of gardenamide A derivatives (**46a-46i**).

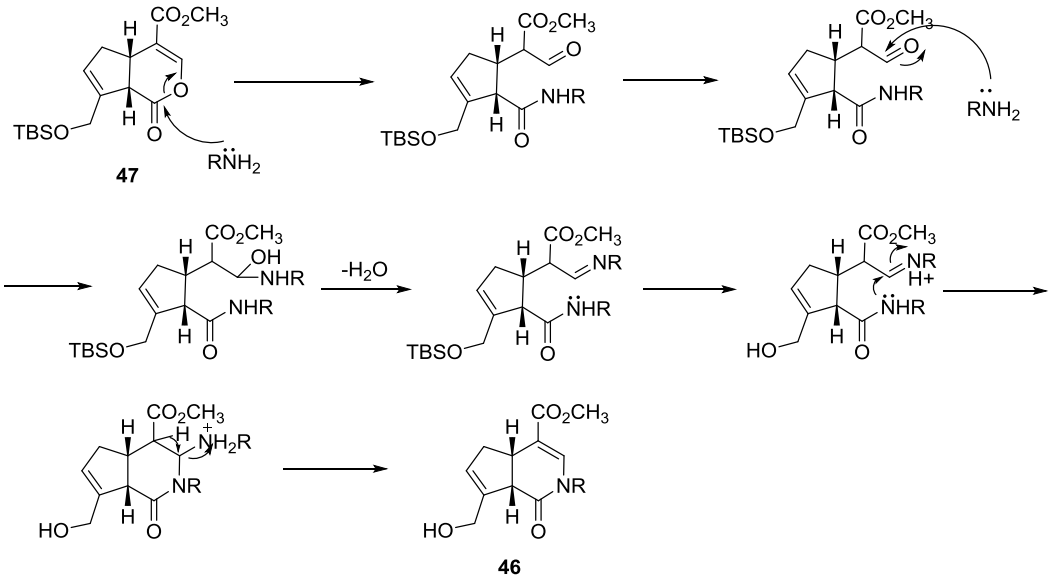


Figure 17 The mechanism of gardenamide A derivatives (**46**)

The mechanism of lactamization after treatment of lactone compound (**48**) with amine in the presence of trifluoroacetic acid was proposed in Figure 17. Addition of amine to the lactone leads to ring opening, generating an aldehyde group activated by another amine. Then, ring closure happened through intramolecular addition of amide to imine, followed by elimination of amino group affording the lactam (**46**).

Wang reported the stereoselective reduction of 1-*O*-isopropyloxygenipin for increasing the flexibility and enhancing the neuroprotective effect. The (1R)-1-isopropylgenipin is the most active compound (**50**) for neuroprotective effect and more stable than genipin (Wang et al., 2014)[36].

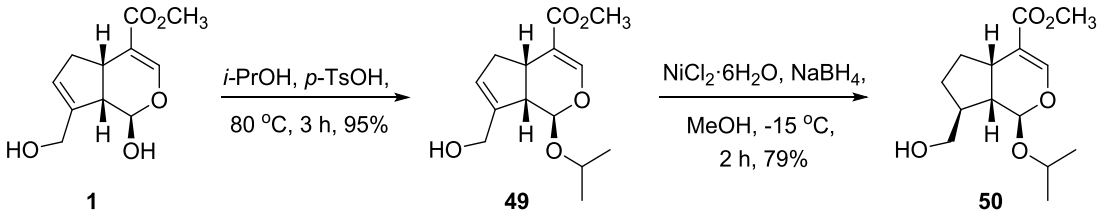


Figure 18 The stereoselective reduction of 1-*O*-isopropyloxygenipin.

Huang and co-worker (2018)[37] reported the synthesis of twenty-two novel genipin derivatives (**51**). They designed the structure incorporating the substituted arylmethyl piperazine moiety and alkylation of C-1 position of genipin (**1**) to stability that for inhibitory activity against acetylcholinesterase (AChE) comparing with donepezil as a drug candidate.

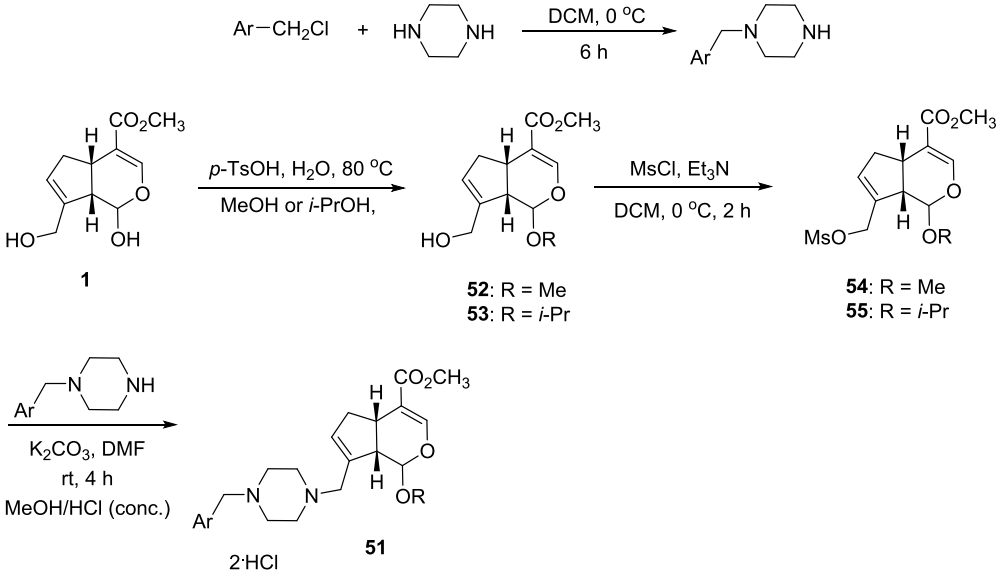


Figure 19 Synthetic route of the target compounds (**51**)

Piperazine derivatives were prepared by substituted benzyl chlorides reacted with anhydrous piperazine and futher employed as nucleophile to react with mesylate genipin (**55**) and (56). The series of novel genipin derivatives (**51**) was started from genipin (**1**) reacted with p-TsOH·H_2O in methanol or isopropanol to obtain the *O*-alkylated product (**52**, **53**) followed by methylsulfonylation to afford the key intermediates (**54**, **55**). Finally, the target compound can be generated from mesylate compound (**54**, **55**) reacted with K_2CO_3 and piperazine derivatives then

treatment with hydrochloride in methanol. All the target compounds (**51**) were evaluated for the neuroprotective activity. Compound (**51a**) containing of the ligustrazine substituted on aryl group showed the most potent AChE inhibitory.

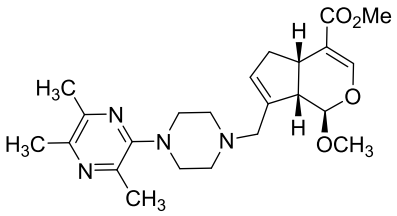
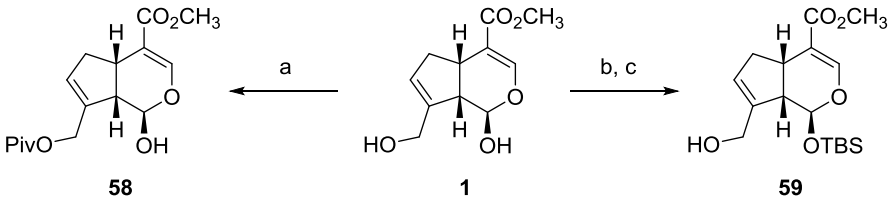


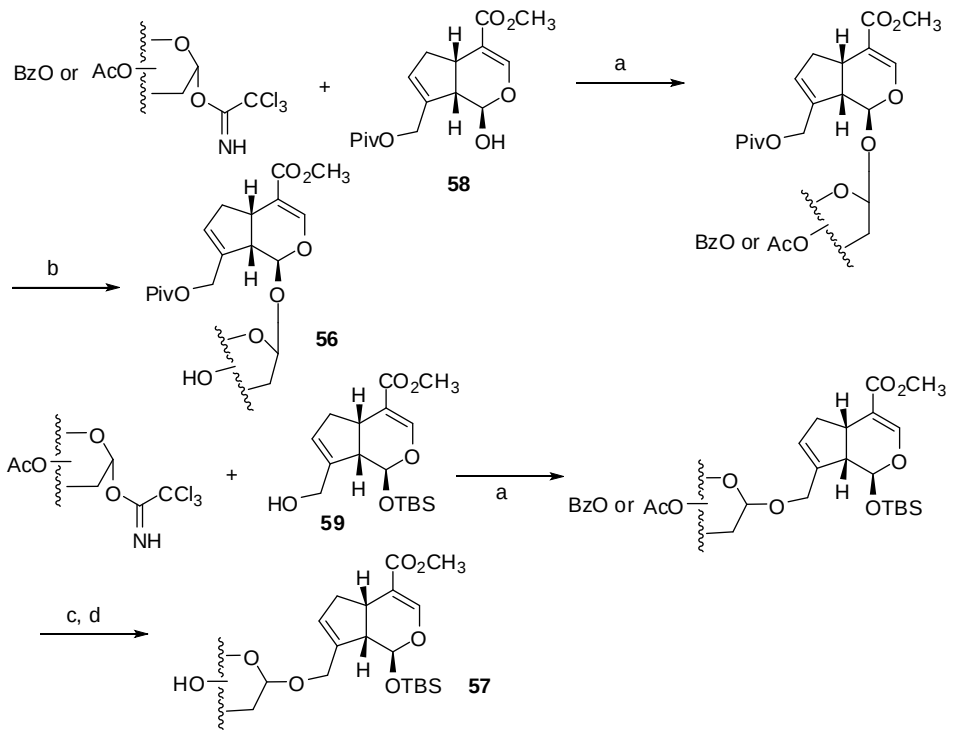
Figure 20 The structures of genipin derivative (**51a**).

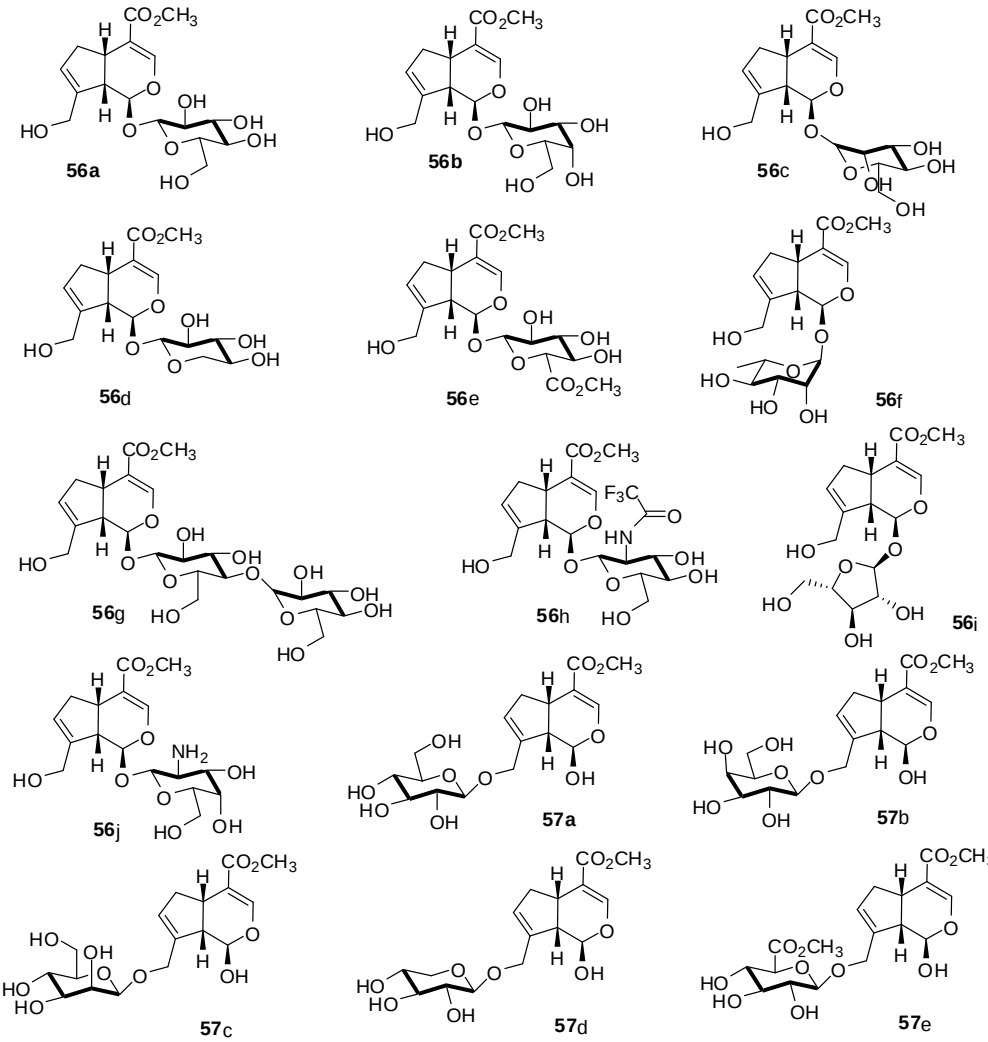
Xia reported the synthesis of a series of geniposide and genipin glycoside derivatives which were designed for evaluated anti-TMV activities as a novel antiviral, insecticidal, and fungicidal agents (Xia et al., 2018)[38]. A series of novel genipin glycoside derivatives (**56**) were designed to prepare by the reaction of glycosides with genipin at C-1 and C-10 positions. All compounds were evaluated for inhibitory activities against tobacco mosaic virus and comparing with ribavirin as an antiviral drug. The results showed that C-10 mannosyl genipin (**56c**) is the best to inhibit tobacco mosaic virus. Moreover, compound (**56h**) showed good insecticidal activity against diamondback moth and compounds (**57b**), (**57c**), and (**57g**) showed moderate insecticidal activity against three kinds of Lepidoptera pests (oriental armyworm, cotton bollworm, and corn borer). Compound (**57e**) showed excellent larvacidal activities against mosquito.



Reagents and conditions: (a) PivCl, pyridine, CH_2Cl_2, from 0 °C to rt, overnight; (b) TBSCl, $AgNO_3$, DMF, from 0 °C rt, overnight; and (c) catalyst PPTS, EtOH, 48 h

Figure 21 Synthetic route of protect genipin (**58**) and (**59**)

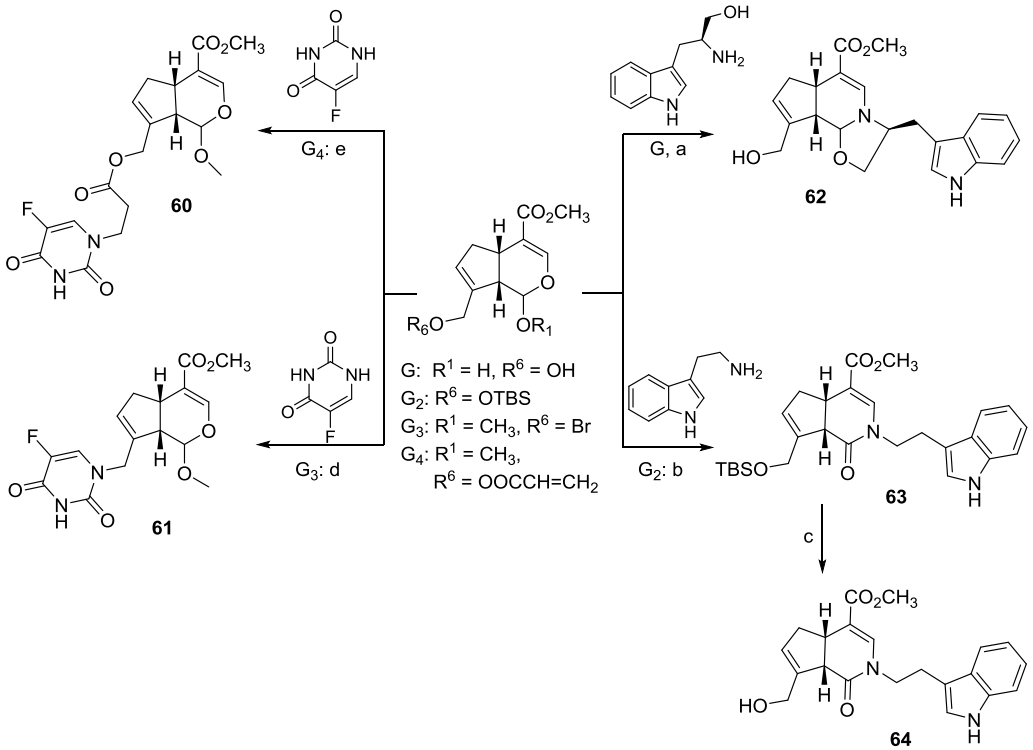

BzO or AcO
CCl3
NH
PivO
CO2CH3
OH
58
a
BzO or AcO
b
56
HO
AcO
59
OTBS
c, d
57


56a
56b
56c
56d
56e
56f
56g
56h
56i
56j
57a
57b
57c
57d
57e

Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 4 Å molecular sieves, Ar, -30 °C for 3 h and then rt for 0.5 h; (b) 0.5 M NaOMe/MeOH, 50 °C, 3 h; (c) 0.05 M NaOMe/MeOH, 1 h; and (d) 1 M TBAF/THF, 0.5 h.

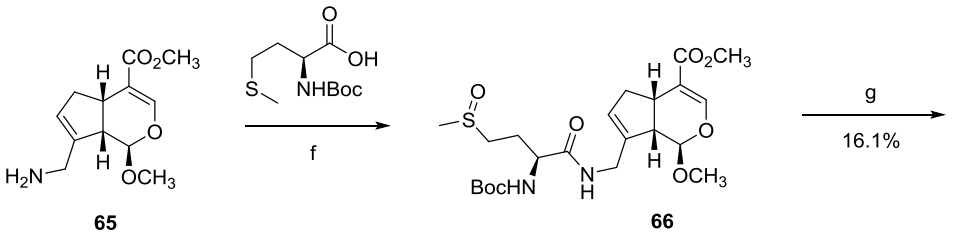
Figure 22 Synthesis of glycosylated genipin derivatives (**56**) and (**57**)

Fang reported the synthesis of 34 novel monoterpenoid indole alkaloid (MIA) analogues and evaluated cytotoxic activities against five cancer cell lines (SW-480, A-549, HL-60, SMMC-7721, and MCF-7) (Fang et al., 2018)[39]. The synthesis was carried out *via* Pictet-Spengler condensation, reductive amination, nucleophilic substitution, alkene addition, coupling to amide, and the conjugate addition reactions. All the 34 novel compounds were screened for cytotoxicity and the result revealed that fourteen genipin derivatives (**76**, **78d**, **80a**, **80b** and **84a-84i**) showed higher anti-proliferation than cisplatin, anticancer drug. Interestingly the compound (**80a**) and (**80b**) displayed maximum cytotoxic activity against the HL-60 cell line with the IC_{50} value 0.90 μM and 0.43 μM, respectively. The relationship between the structure and the activity was analyzed, which suggested the substituent indole at the C-10 position of genipin is important for the antitumor activity.

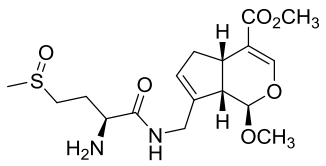


Reagents and conditions: (a) THF, r.t., 48 h. (b) DCM, r.t., 5 h. (c) THF, TFA, r.t., 20 min. (d) Dry DMF, Et_3N, 60 °C. (e) Dry DMF, NaH, 40 °C, 8 h.

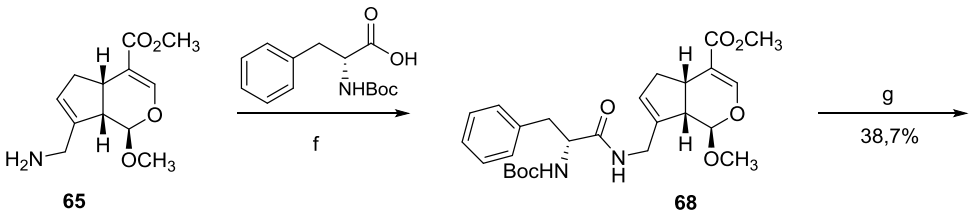
Figure 2 Synthesis of compounds (**62-64**)



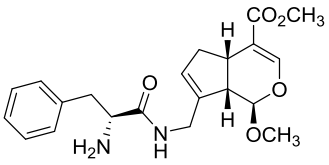
65 **66**



67



65 **68**



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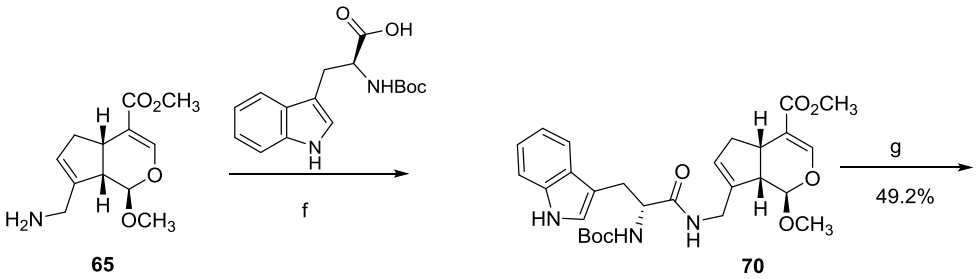
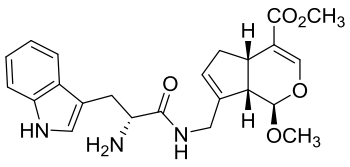
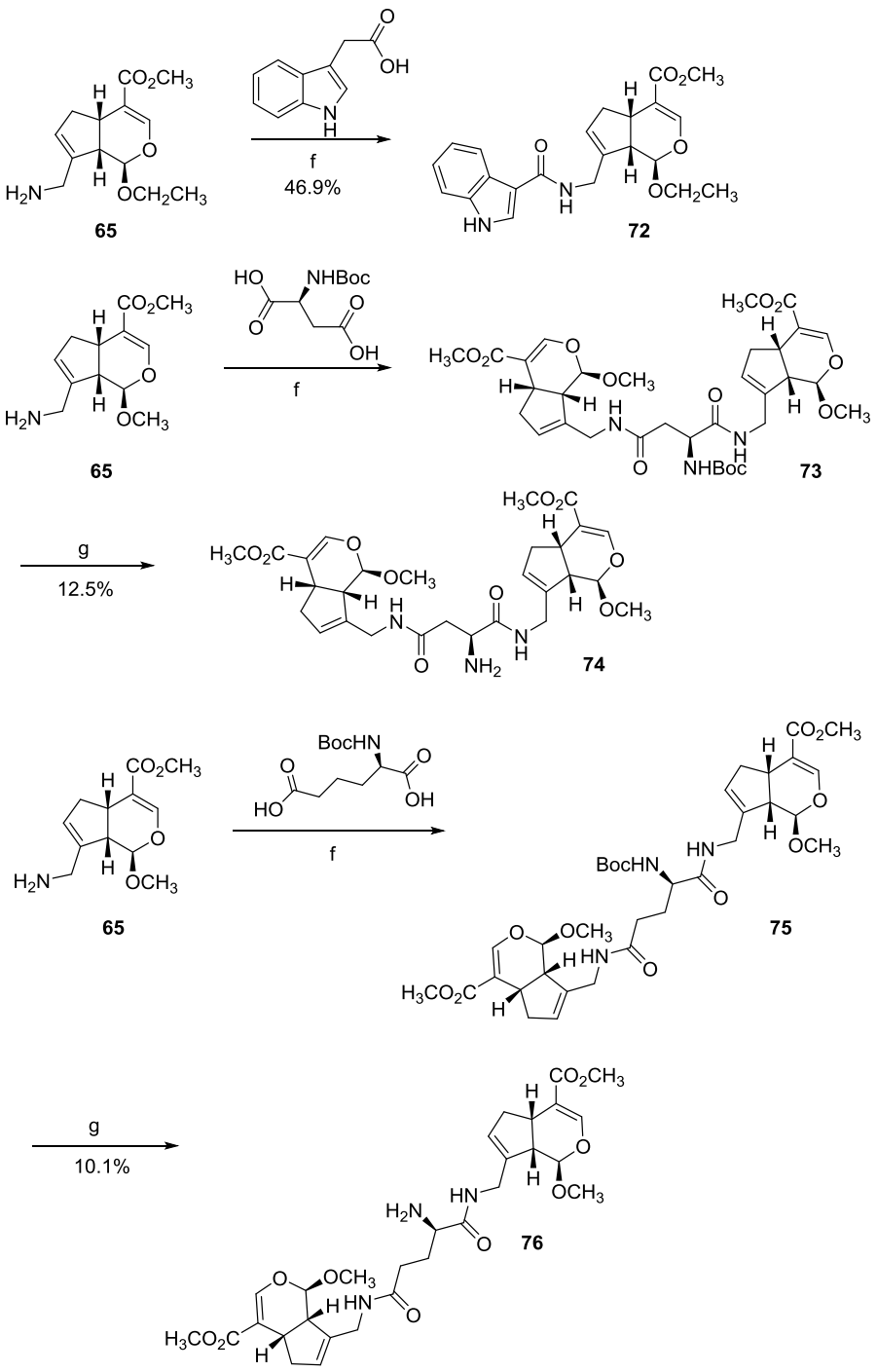


65 **70**

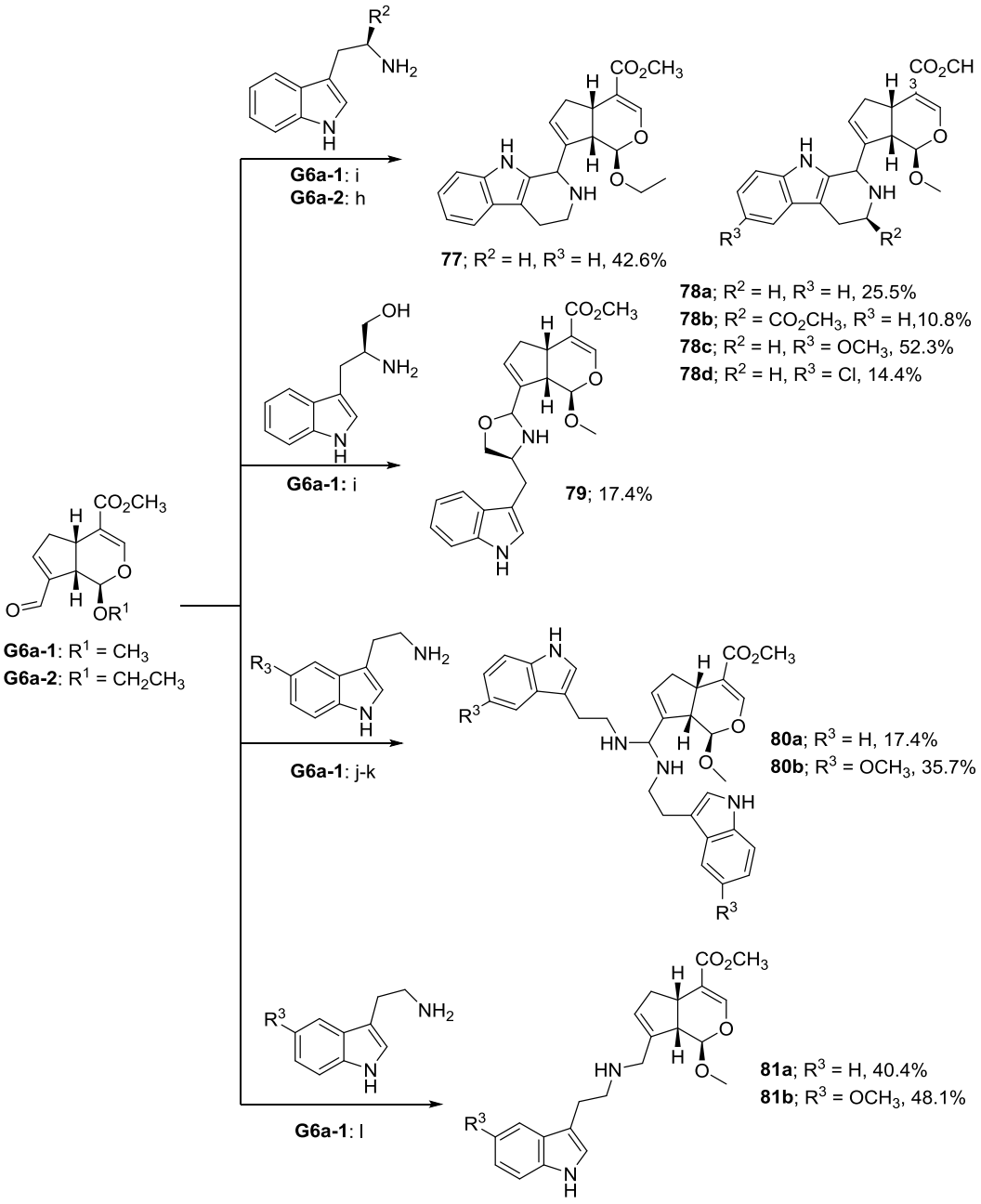


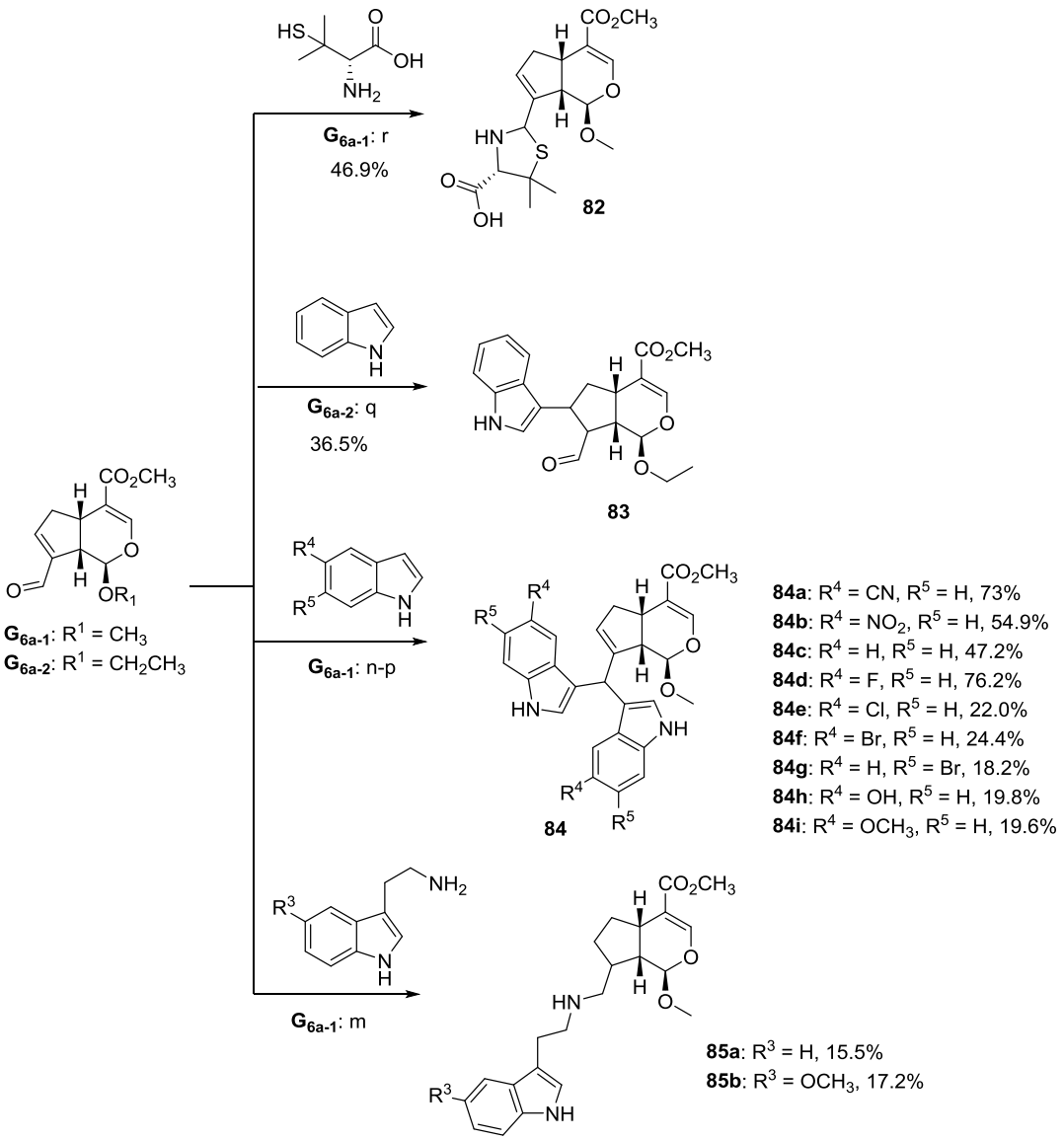
71



Reagents and conditions: (f) EDCI, HOBt, DMF, overnight, r.t. (g) HCl, dioxane, r.t.

Figure 24 Synthesis of compounds (**66-76**)


G6a-1: R1 = CH3
G6a-2: R1 = CH2CH3
G6a-1: i
G6a-2: h
77; R2 = H, R3 = H, 42.6%
78a; R2 = H, R3 = H, 25.5%
78b; R2 = CO2CH3, R3 = H,10.8%
78c; R2 = H, R3 = OCH3, 52.3%
78d; R2 = H, R3 = Cl, 14.4%
G6a-1: i
79; 17.4%
G6a-1: j-k
80a; R3 = H, 17.4%
80b; R3 = OCH3, 35.7%
G6a-1: l
81a; R3 = H, 40.4%
81b; R3 = OCH3, 48.1%



Reagents and conditions: (h) DCM, TFA, 35 °C, 40 h. (i) DCM, TFA, r.t./50 °C, overnight. (j) DCM, TFA, r.t., 48 h. (k) DCM, TFA, $MgSO_4$, 25 °C, 24 h. (l) DCM, TFA, STAB, r.t., overnight. (m) THF, TFA, $NaBH_3CN$, r.t., overnight. (n) DCM, TFA, $MgSO_4$, 50 °C, overnight. (o) DCM, TFA, $MgSO_4$, r.t., overnight. (p) DCM, TFA, $MgSO_4$, r.t., 10 min. (q) Et_2NH, $ZnCl_2$, EtOH, r.t., 24 h. (r) MeOH, r.t., 4 h.

Figure 25 Synthesis of compounds (**77**-**85**)

Selected examples of the synthesis of 1,2,3-triazole derivatives and biological evaluation

Alzheimer's disease (AD) relates to age, leading to loss of the memory accompanied by dementia until death. As a challenging work, the development of new drugs for the treatment of Alzheimer's disease has gained wide attention among many groups.

Saeedi reported the synthesis of novel chromenones linked to 1,2,3-triazole ring and evaluation for their anti-acetylcholinesterase activity (Saeedi et al., 2017)[40]. Chromenones and 1,2,3-triazole are heterocyclic compounds showing many biological activities including anti-acetylcholinesterase activity. The preparation of chromenones linked to 1,2,3-triazole ring (**86**) can be generated from 2-oxo-2H-chromene-3-carboxylic acid (**87**) with propargyl amine and EDCI followed by huisgen 1,3-dipolar cycloaddition with benzyl azide.

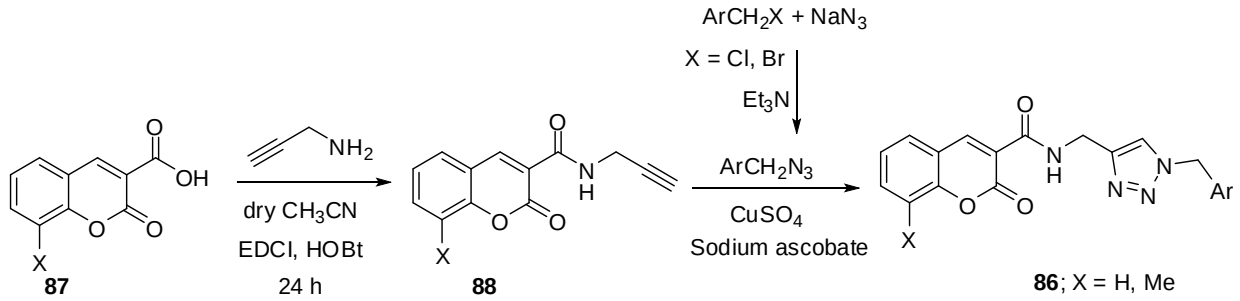


Figure 26 Synthesis of chromenones linked to 1,2,3-triazole ring (**86**)

All the chromenones linked to 1,2,3-triazole ring derivatives were screened to evaluate anti-acetylcholinesterase activity. Compound (**86g**) exhibited potent anti-acetylcholinesterase activity than rivastigmine the drug against H_2O_2-induced cell death in PC12 neurons. It is probably due to the structure can be binding with both the catalytic active site (CAS) and the peripheral anionic site (PAS) of acetylcholinesterase (Figure 27).

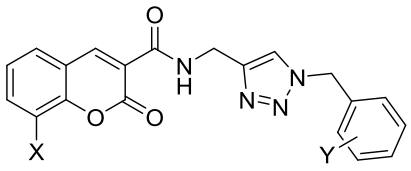


Figure 27 The structure of N-((1-(2-chlorobenzyl)-1H-1,2,3-triazol-5-yl)methyl)-8-methoxy-2-oxo-2H-chromene-3-carboxamide (**86g**)

Table 1 The IC_{50} values of chromenones-1,2,3-triazoles (**86**) against AChE and BChE.

Entry	X	Y	AChE inhibition [IC_{50} (μM)]	BChE inhibition [IC_{50} (μM)]
86a	H	C_6H_5	>100	>100
86b	H	2-Me-C_6H_4	78.92 ± 0.39	>100
86c	H	4-Me-C_6H_4	>100	>100
86d	H	3-F-C_6H_4	48.08 ± 0.310	>100
86e	H	4-F-C_6H_4	>100	>100
86f	H	2-Cl-C_6H_4	33.99 ± 0.24	>100
86g	H	3-Cl-C_6H_4	92.77 ± 0.03	>100
86h	H	2,3-diCl-C_6H_3	20.23 ± 0.17	67.01 ± 0.54
86i	H	3,4-diCl-C_6H_3	16.73 ± 0.36	>100
86j	H	2-Br-C_6H_4	31.04 ± 0.27	>100
86k	H	4-Br-C_6H_4	>100	75.27 ± 0.51
86l	OMe	2-Me-C_6H_4	24.09 ± 0.40	>100
86m	OMe	2-Cl-C_6H_4	15.42 ± 0.53	96.13 ± 0.37
86n	OMe	2,3-diCl-C_6H_3	33.76 ± 0.45	>100
86o	OMe	,4-diCl-C_6H_3	25.54 ± 0.46	>100
Rivastigmaine			11.07 ± 0.01	7.72 ± 0.02

[a] Data are expressed as Mean ± SE (three independent experiments).

As depicted in Figure 28, the molecular modeling of the 2-chlorophenyl connected to 1,2,3-triazole moiety could bind to peripheral anionic site (PAS) and catalytic anionic site (CAS) in the same way as active site of AChE binding to donepezil. Importantly 1,2,3-triazole moiety and chromenone bind by π-π interaction with Phe330 and Trp279. Besides, carbonyl of amide group interacts with Tyr121 of the PAS through hydrogen bonding. The chloride on phenyl ring display hydrophobic interaction with amino acids Trp84 of the CAS in AChE enzyme.

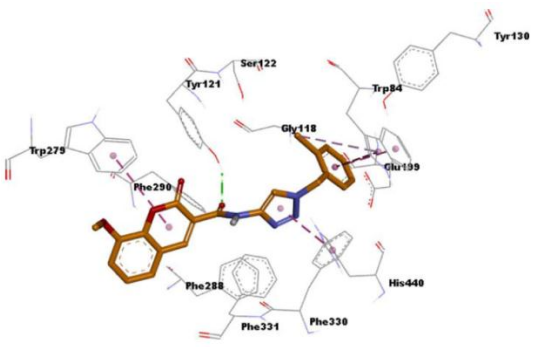


Figure 28 The most active compound (**86g**) in active site AcheE enzyme

Tacrine is the first drug applied for treatment of Alzheimer's disease by binding to CAS of AchE enzyme, but this drug is not selective inhibition of both hAChE and hBChE and have the side effect to the body as a toxicant in the liver. Recently, Wu designed and synthesized tacrine-quinolin-1,2,3-triazole derivatives which was found to be potent cholinesterase inhibitors (Wu et al., 2018). 1,2,3-Triazoles play a vital role in drug discovery, the structure of triazole possesses two H-bond acceptors capable to interact with biomolecules in the form of H-bonding, π-π stacking, and dipole interaction while quinoline derivatives can be binded to PAS exhibiting potent anti-Alzheimer activity. Therefore, combination of taccine, 1,2,3-triazole and quiniline would be interested for improving the activity.

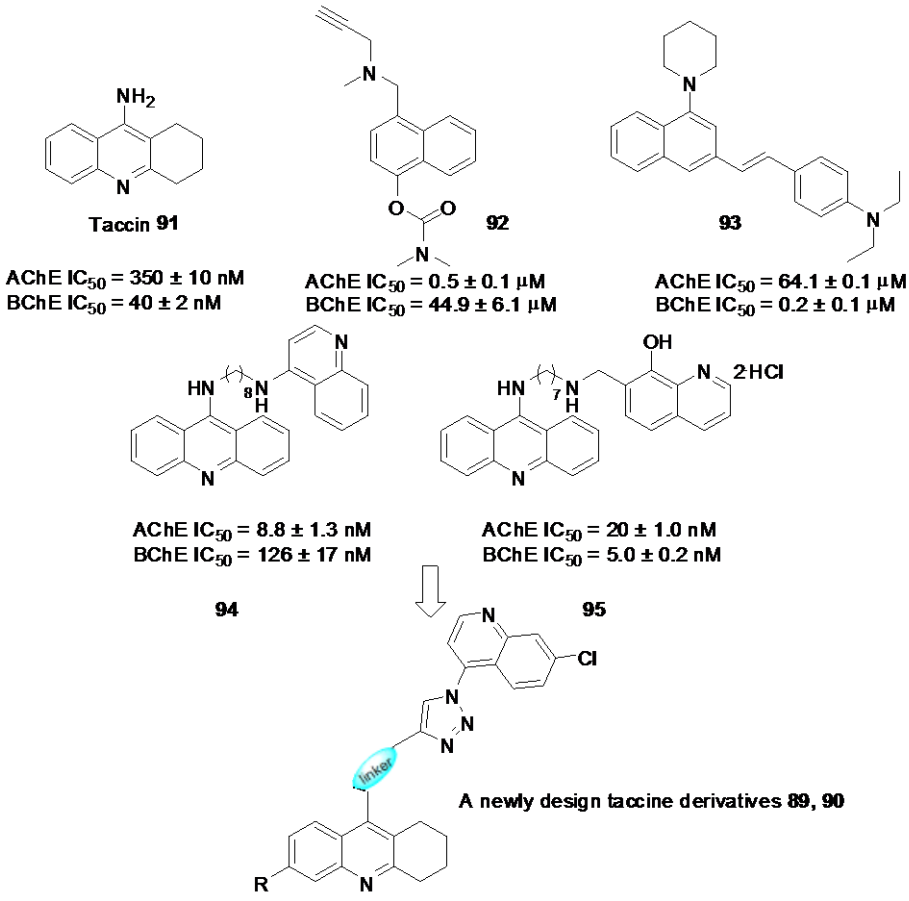
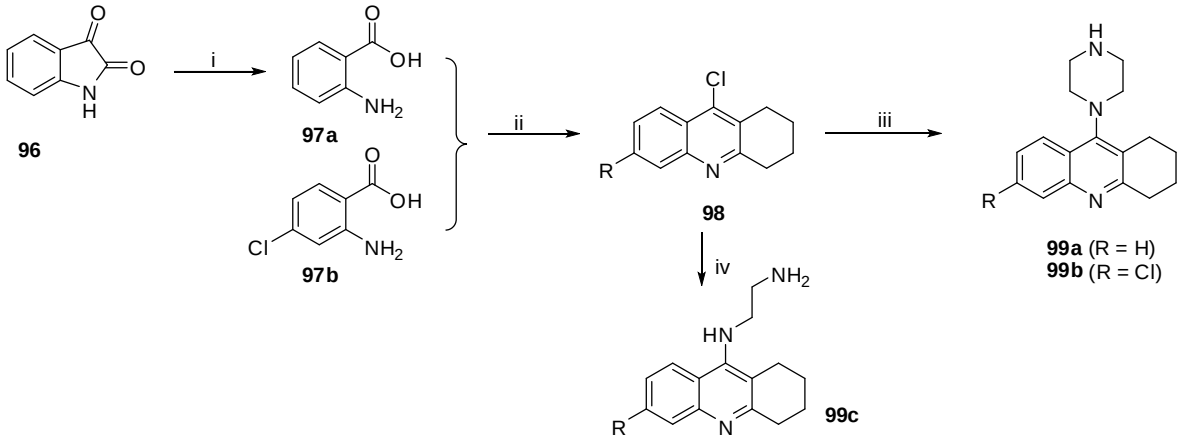


Figure 29 Tacrine and quinoline derivatives with favorable inhibitory activity, and the newly designed tacrine derivatives.

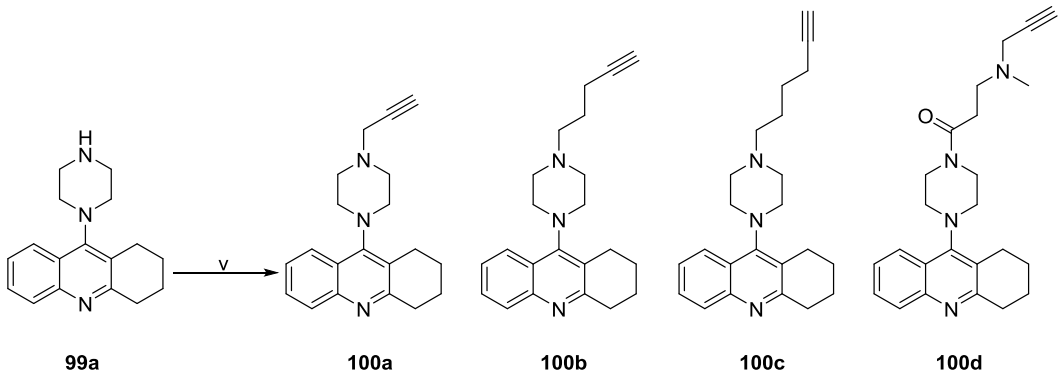
The synthesis of the target tacrine-1,2,3-triazole derivatives started from indoline-2,3-dione (**96**) as a starting material using sodium hydroxide and 30% hydrogen peroxide to provide 2-aminobenzoic acid (**97**) followed by cyclization and aromatization affording 9-chloro-1,2,3,4-tetrahydroacridine (**98**). Then, nucleophilic substitution with various alkynes gave the key intermediate compound (**100**). The azido moiety compound (**104**) was obtained via aromatic

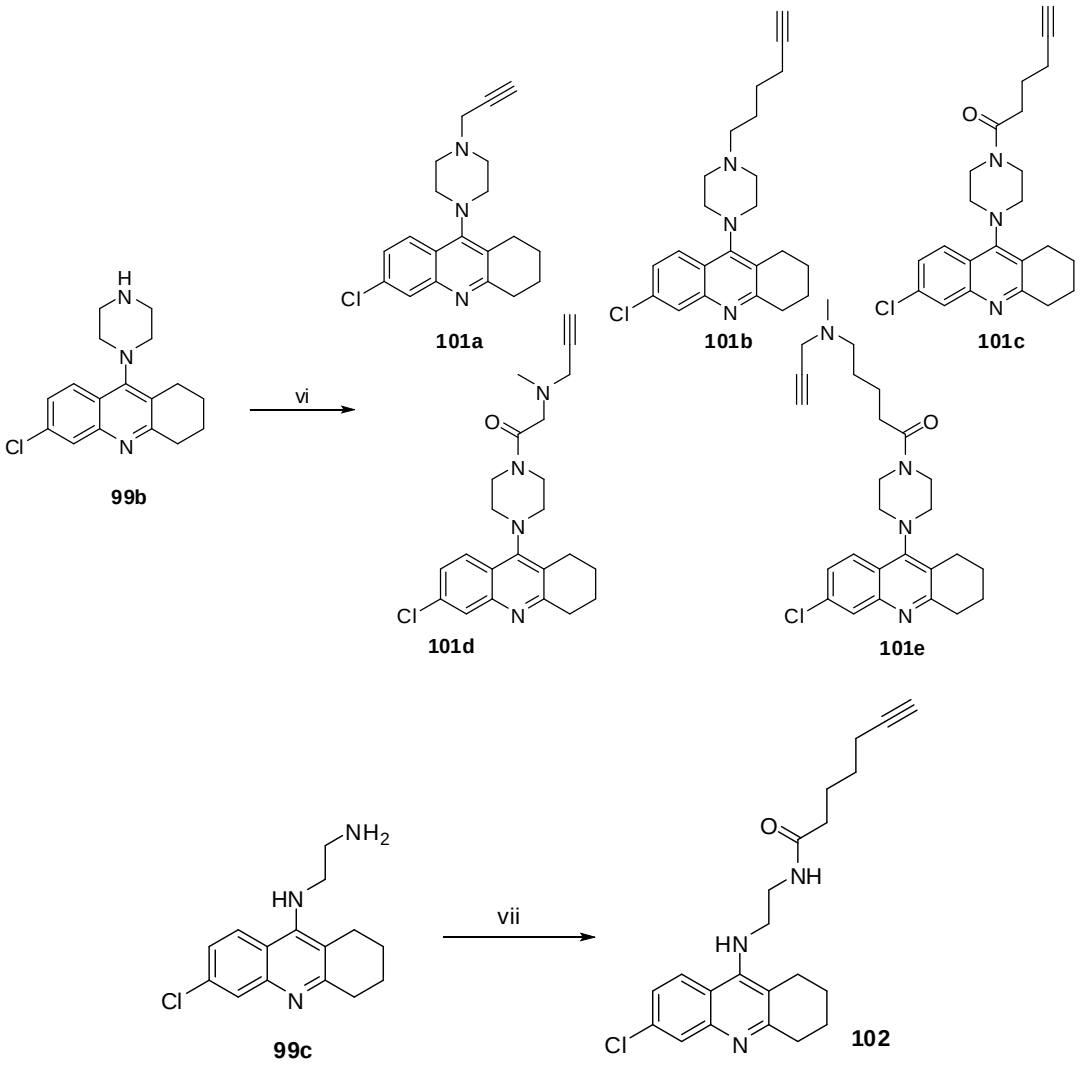
nucleophilic substitution of compound (**103**) with NaN_3. Finally, a novel tacrine-quinolin-1,2,3-triazole derivatives was synthesized by huisgen 1,3-dipolar cycloaddition reaction of azido quinoline and alkyne taccine compound.



Reagents and Conditions. (i) 30% H_2O_2, NaOH, 0 ^oC, 3 h; (ii) cyclohexanone, $POCl_3$, 100 ^oC, 3 h; (iii) piperazine, NaI, PhOH, 180 ^oC, 3 h; (iv) ethane-1,2-diamine, NaI, PhOH, 180 ^oC, 3 h.

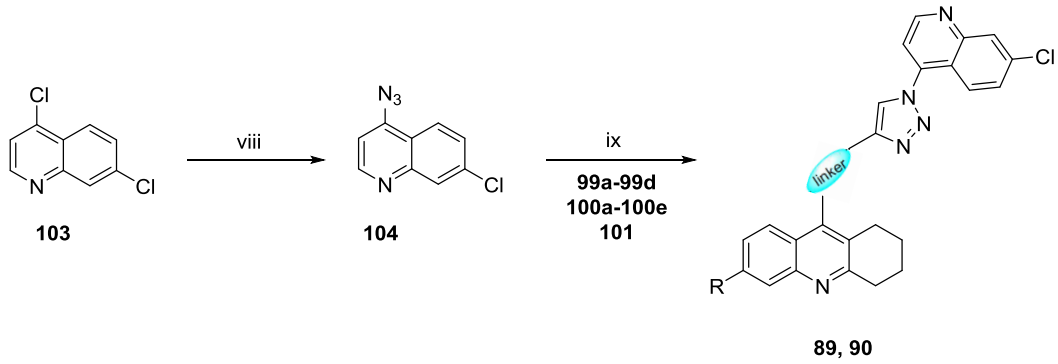
Figure 30 The synthetic route of intermediates (**99a**), (**99b**) and (**99c**)





Reagents and Conditions. (v) (**100a**) 3-bromoprop-1-yne, Et_3N, (**100b**) 5-chloropent-1-yne, K_2CO_3, (**100c**) 6-chlorohex-1-yne, K_2CO_3, (**100d**) hept-6-ynoic acid, EDCI, HOBt, Et_3N, (**100e**) 1) 4-chlorobutanoyl chloride, Et_3N, 2) N-methylprop-2-yn-1-amine, K_2CO_3 (vi) (**101a**) : 3-bromoprop-1-yne, Et_3N, (**101b**) 6-chlorohex-1-yne, K_2CO_3, (**101c**) hept-6-ynoic acid, EDCI, HOBt, Et_3N, (**101d**) 1) 2-chloroacetyl chloride, Et_3N 2) N-methylprop-2-yn-1-amine, K_2CO_3, (**101e**) 1) 5-bromopentanoyl chloride, Et_3N 2) N-methylprop-2-yn-1-amine, K_2CO_3, (vii) (**102**) 1) ethane-1,2-diamine, NaI, PhOH, 2) hept-6-ynoic acid, EDCI, HOBt, Et_3N.

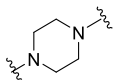
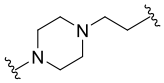
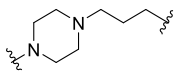
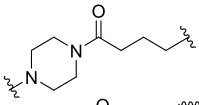
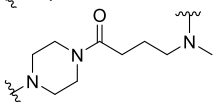
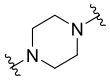
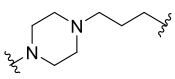
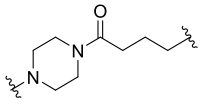
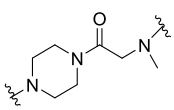
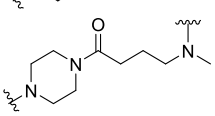
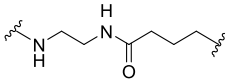
Figure 31 The synthetic route of intermediates (**100a-100d**), (**101a-101e**) and (**102**)



Reagents and Conditions. (viii) NaI, NaN_3, DMF/H_2O (v/v = 1:1), 80 ^oC, 8 h; (ix) Sodium ascorbate, $CuSO_4$, Et_3N, *n*-butanol/H_2O (v/v = 1:1).

Figure 32 The synthetic route of tacrine-1,2,3-triazole derivatives (**89, 90**).

Table 1 Inhibition activity of Tacrine derivatives for electrophorus electricus AChE and horse serum BChE

Compound	R	linker	Inhibition (%) at 100 μM		IC_{50} (μM)	
			AChE	BChE	AChE	BChE
89a	H		39.32	38.56	-	-
89b	H		78.69	91.80	4.89	3.61
89c	H		69.31	55.64	10	66.68
89d	H		65.69	46.37	11.07	>100
89e	H		47.56	57.90	>100	61.13
90a	Cl		30.38	22.12	-	-
90b	Cl		66.02	46.68	19.59	>100
90c	Cl		64.19	49.28	18.66	>100
90d	Cl		41.47	27.97	-	-
90e	Cl		42.31	39.04	-	-
90f	Cl		49.37	82.73	>100	6.06
Tacrine			86.22	99.63	0.316	0.066

All the synthetic compounds were evaluated for inhibitory activities of AChE and BChE. Among all of compounds, **90b** showed the most potent inhibitory activity against AChE and BChE with 78.69% and 91.80% inhibition at 100 μM. Moreover, compound **90f** showed selectivity toward BChE with 82.73% inhibition more than twice of AChE 49.37%. All of the synthetic compounds showed less inhibition activity than reference drug tacrine.

Chapter 2: Results and Discussions

Alzheimer's disease (AD) is the most common form of dementia preferably in the elderly. The aggregation of amyloid-beta (Aβ) peptides that build up of amyloid plaques and neurofibrillary tangles between the nerve cell are the primary cause of the Alzheimer's disease (AD). In this work, we focus on structure modification of genipin and screening for their inhibitory activity toward the self-induced Aβ aggregation. The synthesis of genipin analogues was designed to modify at C-10 position of genipin to triazole and acetylation of hydroxyl group at C-1 position. The new triazolylgenipin analogues will be synthesized *via* six or seven steps including silylation, acetylation, mesylation, azidation and Huisgen 1,3-dipolar cycloaddition reaction, respectively. All of the new triazolylgenipin analogues were study inhibitory the self-induced Aβ aggregation by induced apoptotic cell death as a promoting oxidative damage including superoxide and hydrogen peroxide after apoptosis in the cell and treats with new triazolylgenipin analogues for reduced levels of apoptosis, we believe the new products can be utilized for therapeutic purposes.

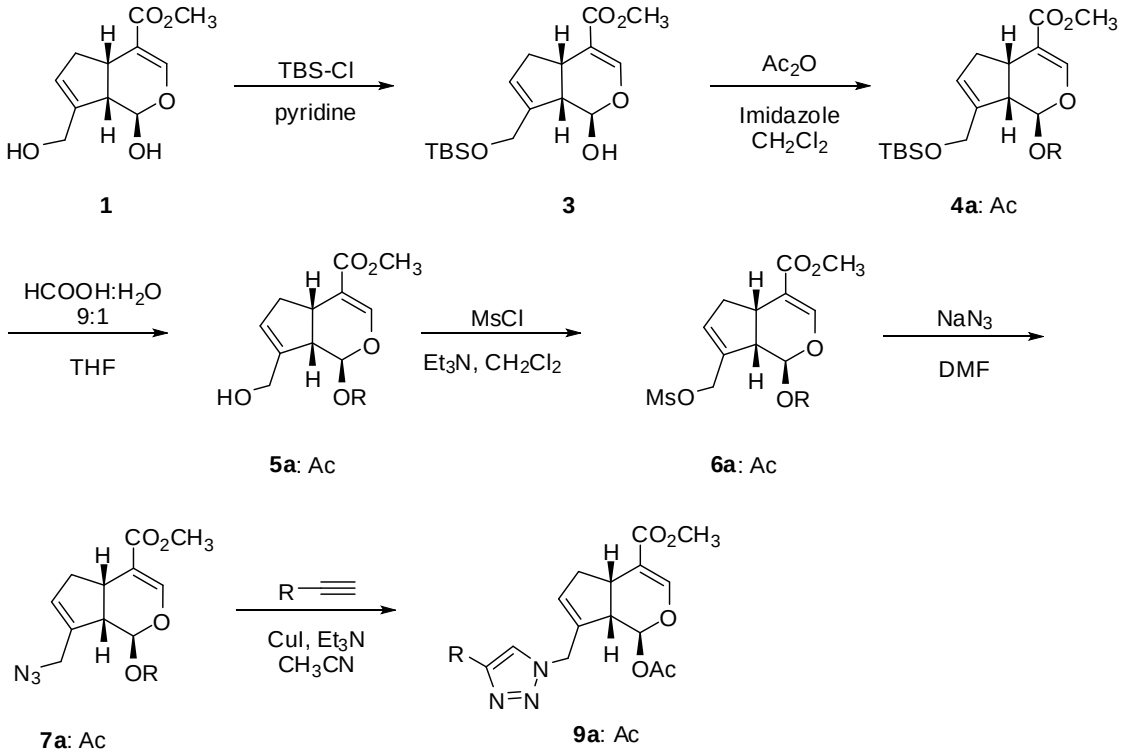
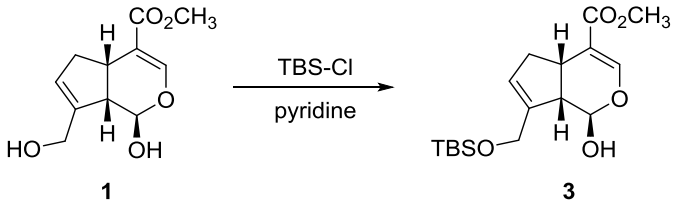


Figure 38 Synthesis of 10-triazolylgenipin (**9a**)

Synthesis of 10-TBS genipin analogue (3).

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 the reaction completed, the mixture was diluted with EtOAc (30 mL) subsequent quenched with cold saturated $CuSO_4 \cdot 5H_2O/NaHCO_3$, extracted with EtOAc and washed with brine, dried over with anhydrous Na_2SO_4, filtered, and evaporated in *vacuo* to obtain the crude product of 10-TBS genipin analogues (**3**).

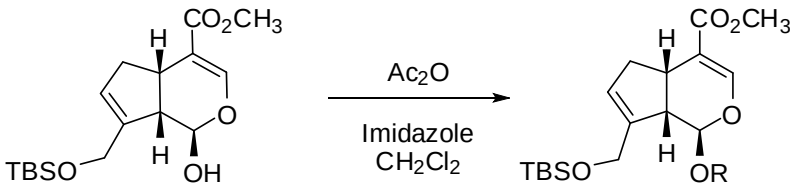


1 **3**

Figure 4 Synthesis of 10-TBS genipin analogue (**3**).

Acetylation reaction at C-1 position of 10-TBS genipin analogue (3).

To a solution of crude product 10-TBS genipin (**3**) (8.85 mmol) in CH_2Cl_2 (20 mL), imidazole (1.8 g, 26.55 mmol) was added and stirred for 10 min, then acetic anhydried (2.5 mL, 26.55 mmol) or tert-butyldiphenylsilyl chloride (6.9 mL, 26.55 mmol) was added. The solution mixture was stirred at room temperature for 1 hour. After TLC showed the reaction complete conversion, the reaction mixture was diluted with CH_2Cl_2 (10 mL), The reaction mixture was quenched with cold saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with brine, then dried over with Na_2SO_4 anhydrous, and concentrated in vacuo to obtain crude product 1-acetyl-10-TBS genipin (**4a**).

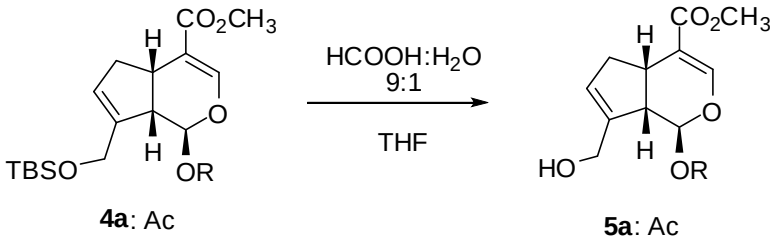


3 **4a**: Ac

Figure 5 The synthesis of 1-acetyl-10-TBS genipin (**4a**)

The desilylation at C-10 position of 1-acetyl-10-TBS genipin (4a)

To a stirred solution of 1-acetyl-10-TBS genipin (**4a**) (8.85 mmol) in THF (20 mL) was added dropwise of $HCOOH/H_2O$ (9:1) (40 mL) at 0^oC and stirred for 6 hours. After TLC showed the reaction complete conversion, the reaction mixture was diluted with EtOAc (30 mL) and quenched with cold saturated $NaHCO_3$ the mixture was extracted with EtOAc and washed with H_2O and brine, follow by dried over with Na_2SO_4 anhydrous, and concentrated in vacuo to obtain crude product of 1-acetylgenipin (**5**a).

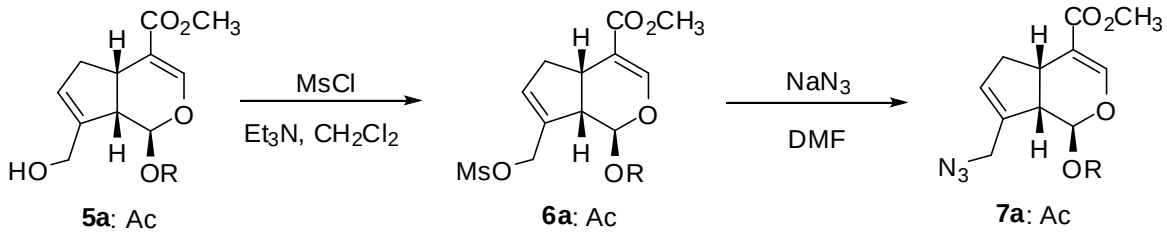


4a: Ac **5a**: Ac

Figure 6 The synthesis of 1-acetylgenipin (**5a**).

The synthesis of 10-azido-1-acetylgenipin (7a) and 10-azido-1-TBDPS-genipin (7b).

To a solution of crude product of 1-acetylgenipin (**5**a) (8.85 mmol) in CH_2Cl_2 (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 reaction mixture at 0^oC and stirred at room temperature. After TLC showed the reaction complete conversion, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched with cooled NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 and washed with water and then dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo* to obtain the mesylate crude product (**6a**, **6b**). The mesylate of crude product (**6a**, **6b**) was dissolved in DMF (30 mL) and NaN_3 (863 mg, 13.28 mmol) was added at 0 ^oC. The reaction was stirred at room temperature and continued stirring for 30 min. After TLC showed the reaction complete conversion, the reaction mixture was diluted with EtOAc (30 mL). and quenched with cooled water. The reaction mixture extracted with EtOAc, washed with brine then dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc/n-hexane) to afford 10-azido-1-acetylgenipin (**7a**).



5a: Ac **6a**: Ac **7a**: Ac

Figure 7 The synthesis of 10-azido-1-acetylgenipin (**7a**).

The synthesis of 10-triazolylgenipin product (9a).

To the solution of 10-azido-1-acetylygenipin (**7a**) (100 mg, 0.3413 mmol) (100 mg, 0.3980 mmol) in CH_3CN (1.0 mL) was added CuI (20 mol %), Et_3N (0.5 equiv) and alkyne (1.5 equiv). The reaction mixture stirred at room temperature until the reaction completed conversion. The reaction mixture was diluted with EtOAc (2 mL) and quenched with cooled water and extracted with EtOAc (3x30 mL). The organic phase was collected, dried with Na_2SO_4 anhydrous, filtered and evaporated in *vacuo*. The crude product was purified by column chromatography to obtain 10-triazolylgenipin product (**9a**).

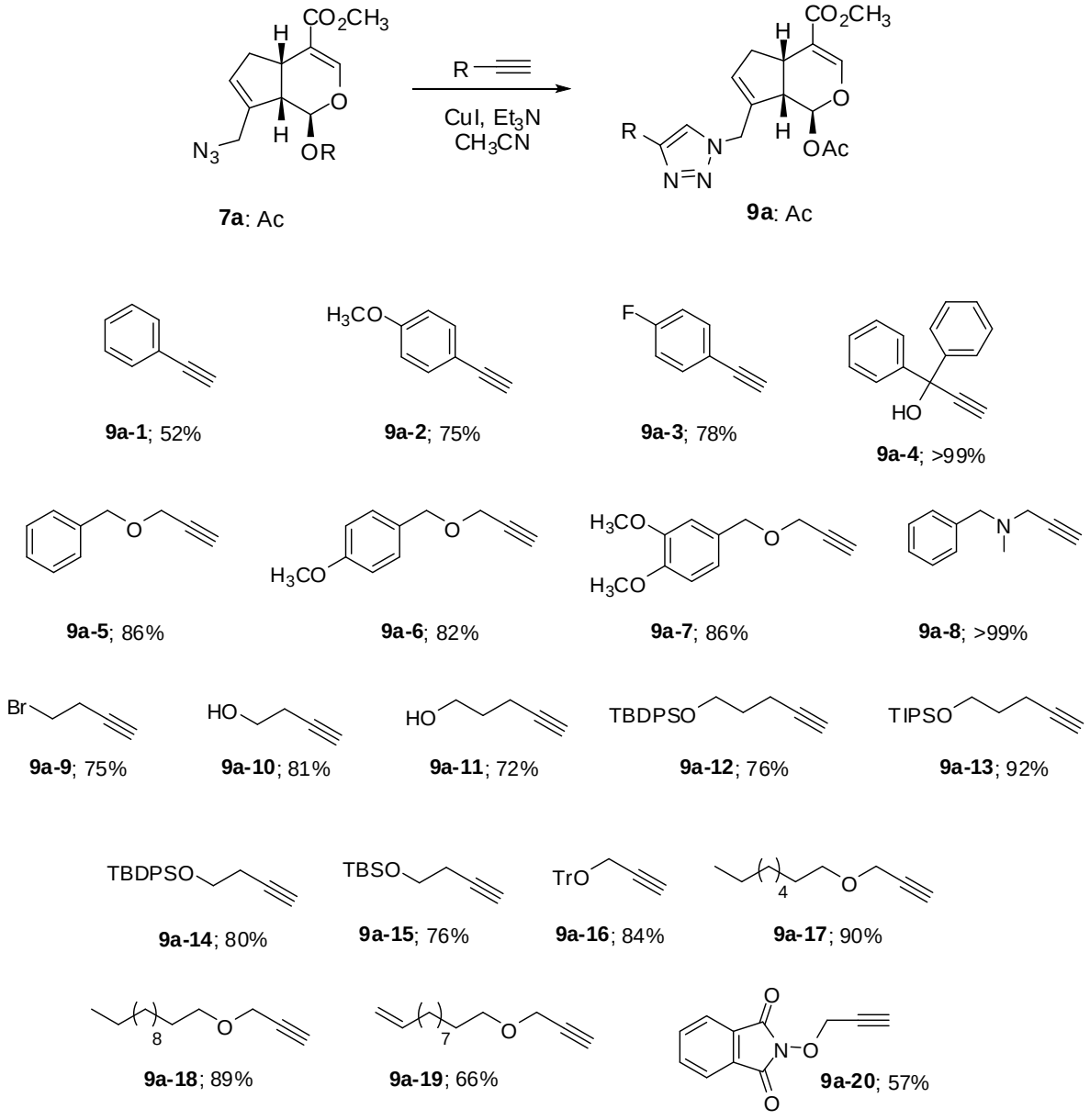


Figure 8 The synthesis of 10-triazolylgenipin product (**9a**)

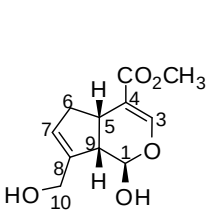
The neuroprotective effects of new triazolylgenipin analogues on the Aβ1-42-induced decrease in cell viability in PC12 cells

The investigated the effects of H_2O_2 on Aβ1–42-induced cell death in PC12 cells. The results showed that Aβ1–42 induced the death of approximately 50% of the cells compared with the control group. New triazolylgenipin analogues were found to attenuate the cytotoxicity of Aβ1–42 and significantly increased cell viability in a concentration-dependent manner.

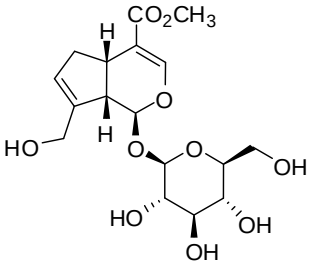
To confirm the protective effect of new triazolylgenipin analogues on the Aβ1-42-induced cell viability in PC12 cells. The cells were treated with H_2O_2 in the presence or absence of triazolylgenipin analogues. Our results showed that treatment with H_2O_2 decreased cell viability 50% and after treats with new triazolylgenipin analogues at concentrations of 0.075-10 µM significantly increased the cell viability. Interestingly 9 compounds (**9a-1**, **9a-3**, **9a-5**, **9a-6**, **9a-11**, **9a-12**, **9a-19**, **9a-25**, **9a-26**) increased cell viability levels up to 70%. The substitution of aromatic on the triazole ring showed good activity especially compound **9a-3** have the percentage of cell viability 75.9% at the low concentration 5 µM and substitution of the hydroxyl alkyl group **9a-11** and alkyl-TBDPS group **9a-12** on triazole ring showed 75.4% at 40 µM and 79.6% at 10 µM respectively. At the same time, long chain aliphatic C-11 prevented neuronal cell apoptosis 70% at 10 µM and substituted of phthalimide group compounds **9a-20** increase slightly of cell viability.

Chapter 3 Conclusion

In this project, we have modified the structure of genipin to study bioactivity against Alzheimer's disease.Genipin is an aglycone derived from an iridoid glycoside geniposide present in fruit of *Gardenia jasminoides*. Genipin (**1**) and geniposide (**2**) are the natural product found in gardenia fruit extract. Genipin can be prepared from geniposide (**2**) by hydrolysis at glycosidic bond using β-glucosidase enzyme. We focus on structure modification of genipin and screening for their inhibitory activity toward the self-induced Aβ aggregation.



Genipin (**1**)



Geniposide (**2**)

The synthesis of genipin analogues was designed to modify at C-10 position of genipin to triazole and acetylation of hydroxyl group at C-1 position. The new triazolylgenipin analogues will be synthesized *via* six steps including silylation, acetylation, mesylation, azidation and Huisgen 1,3-dipolar cycloaddition reaction, respectively.

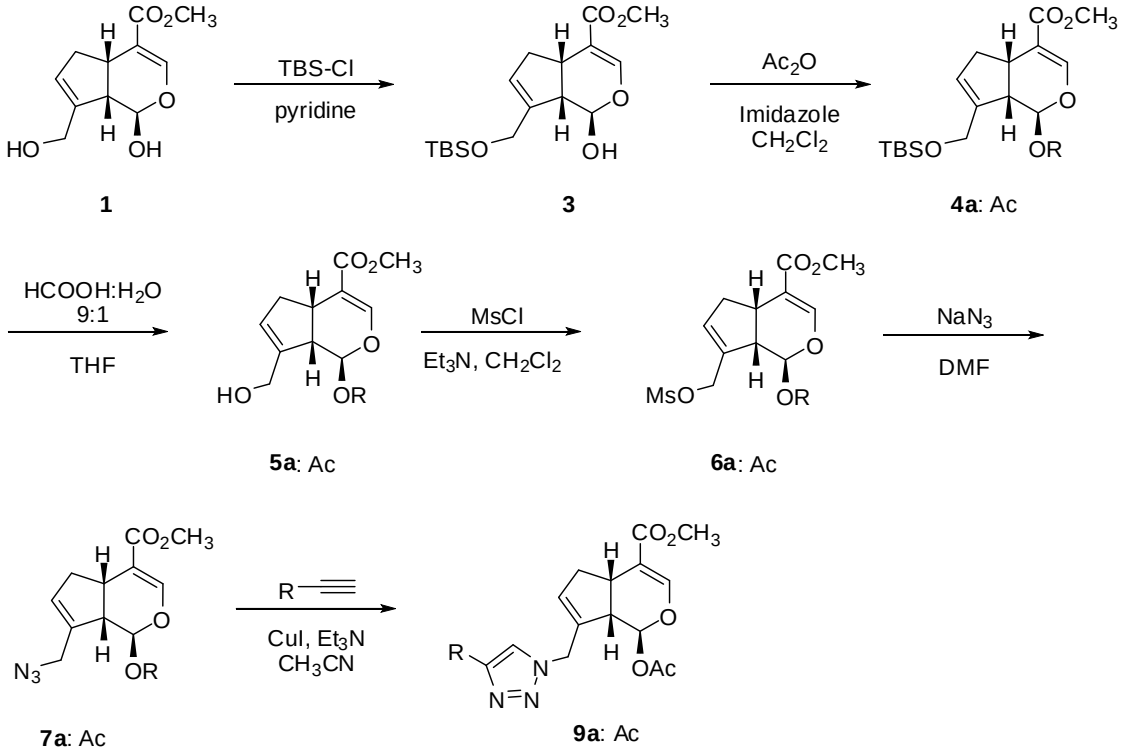


Figure 39 Synthesis of 10-triazolylgenipin (**9a**)

Twenty new analogues of genipin-triazole were synthesized in good to excellent yields. All the compounds were investigated the effects of H_2O_2 on Aβ1–42-induced cell death in PC12 cells. The results showed that Aβ1–42 induced the death of approximately 50% of the cells compared with the control group. New triazolylgenipin analogues were found to attenuate the cytotoxicity of Aβ1–42 and significantly increased cell viability in a concentration-dependent manner. Nine compounds (**9a-1**, **9a-3**, **9a-5**, **9a-6**, **9a-11**, **9a-12**, **9a-19**, **9a-25**, **9a-26**) increased cell viability levels up to 70%. These compounds may be considered as lead for further developing as anti-Alzheimer's agents.

Chapter 4 Experimental procedures

General Methods

All chemicals were purchased from commercial sources and used without further purification. Proton NMR spectra were recorded on a BRUKER AVANC (400 MHz). All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26). Data are reported as follows; chemical shift (multiplicity, integrate intensity or assignment, coupling constants in Hz, assignment). Carbon NMR spectra were recorded on a BRUKER AVANCE (100 MHz). All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to $CDCl_3$ (δ 77.0). High-resolution mass spectra (HRMS) data were obtained with a Finnigan MAT 95. Infrared spectra were determined on a PERKIN ELMER FT/IR-2000S spectrophotometer and are reported in wave number (cm^{-1}). Analytical thin-layer chromatrography (TLC) was conducted on precoated TLC plates; silica gel 60F-254 [E. Merck, Darmstadt, Germany]. Silica gel columns for open-column chromatrography utilized silica gel 60 [Grade 7734, 70-230 mesh, E. Merck, Darmstadt, Germany]. Melting points were recorded using GALLENKAMP Melting point apparatus Griffin.

Methodology for modification of genipin (1)

Genipin (**1**) is an iridoid compound showing many biological activities including anti-Alzheimer's activities. In this research, we focus on structure modification of genipin and screening for their inhibitory activity toward the self-induced Aβ aggregation. The synthesis of genipin analogues was designed to modify at C-10 position of genipin to triazole and acetylation at C-1 position. The new triazolylgenipin analogues will be synthesized *via* six or seven steps including silylation, acetylation, mesylation, azidation and Huisgen 1,3-dipolar cycloaddition reaction, respectively (Figure 33).

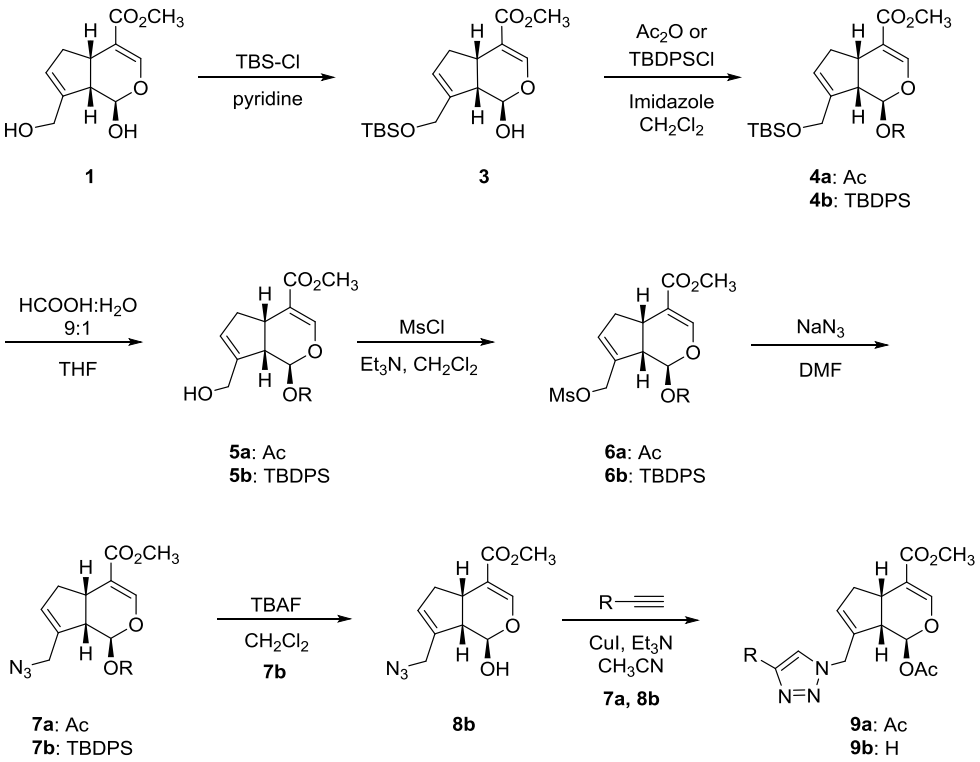


Figure 33 Synthesis of 10-triazolyl-1-methoxygenipin (**9a**, **9b**)

Synthesis of 10-TBS genipin analogue (3).

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 the reaction completed, the mixture was diluted with EtOAc (30 mL) subsequent quenched with cold saturated $CuSO_4 \cdot 5H_2O/NaHCO_3$, extracted with EtOAc and washed with brine, dried over with anhydrous Na_2SO_4, filtered, and evaporated in vacuo to obtain the crude product of 10-TBS genipin analogues (**3**).

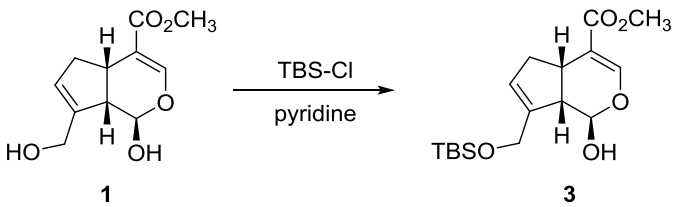
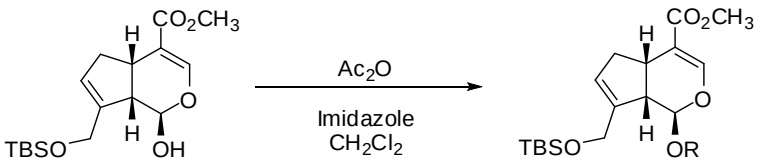


Figure 34 Synthesis of 10-TBS genipin analogue (**3**).

Acetylation reaction at C-1 position of 10-TBS genipin analogue (3).

To a solution of crude product 10-TBS genipin (**3**) (8.85 mmol) in CH_2Cl_2 (20 mL), imidazole (1.8 g, 26.55 mmol) was added and stirred for 10 min, then acetic anhydried (2.5 mL, 26.55 mmol) or tert-butyldiphenylsilyl chloride (6.9 mL, 26.55 mmol) was added. The solution mixture was stirred at room temperature for 1 hour. After TLC showed the reaction complete conversion, the reaction mixture was diluted with CH_2Cl_2 (10 mL), The reaction mixture was quenched with cold saturated $NaHCO_3$, extracted with CH_2Cl_2 and washed with brine, then dried over with Na_2SO_4 anhydrous, and concentrated in vacuo to obtain crude product 1-acetyl-10-TBS genipin (**4a**).

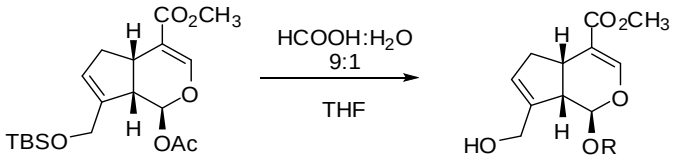


3 **4a**: R = Ac

Figure 35 The synthesis of 1-acetyl-10-TBS genipin (**4a**).

The desilylation at C-10 position of 1-acetyl-10-TBS genipin (4a)

To a stirred solution of 1-acetyl-10-TBS genipin (**4a**) (8.85 mmol) in THF (20 mL) was added dropwise of $HCOOH/H_2O$ (9:1) (40 mL) at 0 ^oC and stirred for 6 hours. After TLC showed the reaction complete conversion, the reaction mixture was diluted with EtOAc (30 mL) and quenched with cold saturated $NaHCO_3$ the mixture was extracted with EtOAc and washed with H_2O and brine, follow by dried over with Na_2SO_4 anhydrous, and concentrated in vacuo to obtain crude product of 1-acetylgenipin (**5a**).

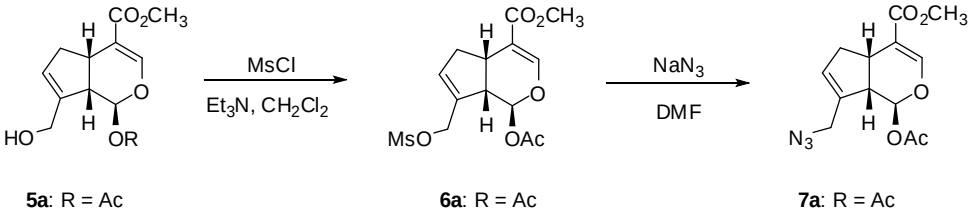


4 **5a**: R = Ac

Figure 36 The synthesis of 1-acetylgenipin (**5a**).

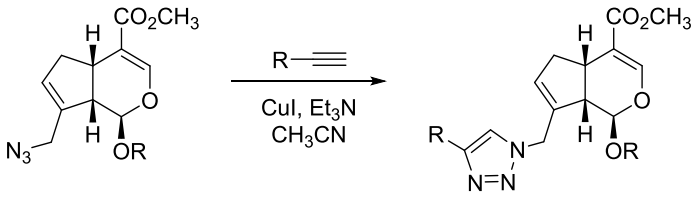
The synthesis of 10-azido-1-acetylgenipin (7a)

To a solution of crude product of 1-acetylgenipin (**5a**) (8.85 mmol) in CH_2Cl_2 (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 reaction mixture at 0^oC and stirred at room temperature. After TLC showed the reaction complete conversion, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched with cooled NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 and washed with water and then dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo* to obtain the mesylate crude product (**6a**). The mesylate of crude product (**6a**) was dissolved in DMF (30 mL) and NaN_3 (863 mg, 13.28 mmol) was added at 0 ^oC. The reaction was stirred at room temperature and continued stirring for 30 min. After TLC showed the reaction complete conversion, the reaction mixture was diluted with EtOAc (30 mL). and quenched with cooled water. The reaction mixture extracted with EtOAc, washed with brine then dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc/n-hexane) to afford 10-azido-1-acetylgenipin (**7a**).



5a: R = Ac **6a**: R = Ac **7a**: R = Ac

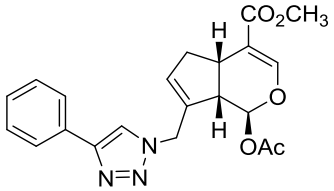
Figure 37 The synthesis of 10-azido-1-acetylgenipin (**7a**)



7a: R = Ac **9a:** R = Ac
8b: R = H **9b**: R = H

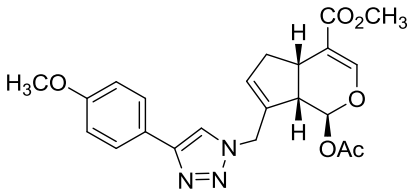
Figure 39 The synthesis of 10-triazolylgenipin product (**9a**, **9b**)

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-1)



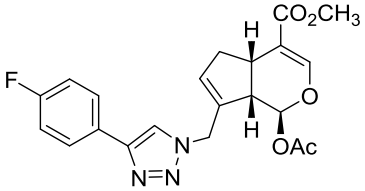
Following the general procedure, A, phenyl acethylene (51.0 µL) was used in click reaction. The reaction was stirred at room temperature for 2 hours. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-1**) as a white solid (63 mg, 52%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-2)



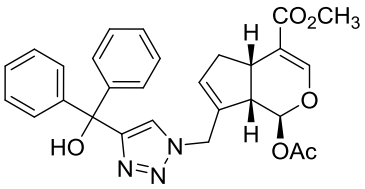
Following the general procedure, A, 4-methoxyphenyl acethylene (88.0 µL) was used in click reaction. The reaction was stirred at room temperature for 24 hours. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-2**) as a yellow oil (109.4 mg, 75%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-3)



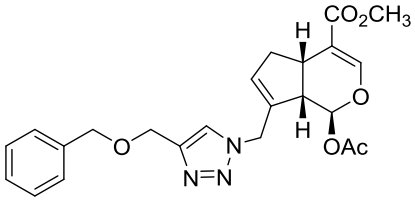
Following the general procedure, A, 4-fluorophenylacethylene (78.0 µL) was used in click reaction. The reaction was stirred at room temperature for 4 hours. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-3**) as a white solid (109.9 mg, 78%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-4)



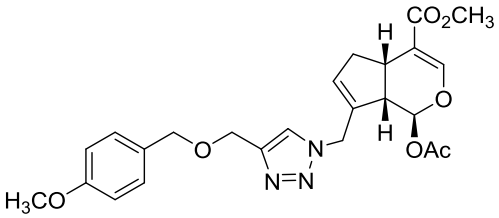
Following the general procedure, A, 1, 1-diphenyl-2-propyn-1-ol (141.0 mg) was used in click reaction. The reaction was stirred at room temperature for 4 hours. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-4**) as a white solid (171.6 mg, >99%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-5)



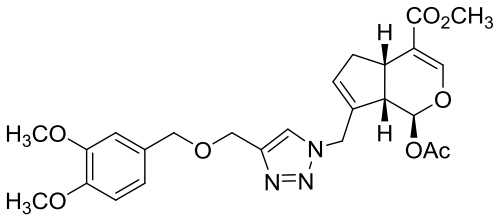
Following the general procedure, A, benzyl propagyl ether (100.0 mg) was used in click reaction. The reaction was stirred at room temperature for 1 hours. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-5**) as a yellow oil (129.3 mg, 86%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-6)



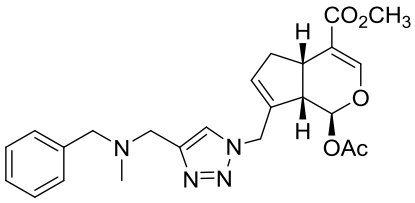
Following the general procedure, A, 4-methoxybenzyl propagyl ether (121.0 mg) was used in click reaction. The reaction was stirred at room temperature for 1 hours. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-6**) as a colorless oil (131.5 mg, 82%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-7)



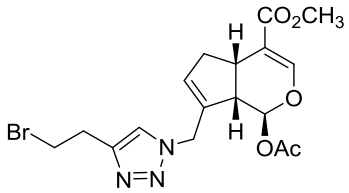
Following the general procedure, A, 3, 4-dimethoxybenzyl propagyl ether (141.0 mg) was used in click reaction. The reaction was stirred at room temperature for 10 min. The crude product was purified by silica gel column chromatography (SiO_2, 60% EtOAc/*n*-hexane-100% EtOAc) to afford triazole linked genipin (**9a-7**) as a colorless oil (122.5 mg, 72%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-8)



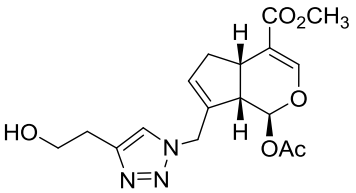
Following the general procedure, A, *N*-Methyl-*N*-propargylbenzylamine (128.0 µL) was used in click reaction. The reaction was stirred at room temperature for 30 min. The crude product was purified by silica gel column chromatography (SiO_2, 50% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-8**) as a yellow oil (162.7 mg, >99%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-9)



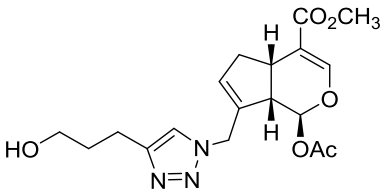
Following the general procedure, A, 4-bromo-1-butyne (64 µL) was used in click reaction. The reaction was stirred at room temperature for 30 min. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane-70% EtOAc/n-hexane) to afford triazole linked genipin (**9a-9**) as a yellow oil (109.1 mg, 75%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-10)



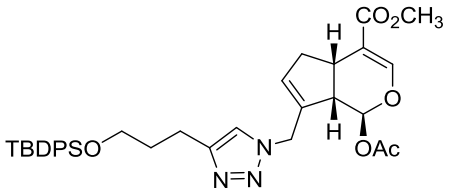
Following the general procedure, A, 3-butyn-1-ol (52 µL) was used in click reaction. The reaction was stirred at room temperature for 30 min. The crude product was purified by silica gel column chromatography (SiO_2, 100%EtOAc-5 MeOH/ EtOAc) to afford triazole linked genipin (**9a-10**) as a yellow oil (100.0 mg, 81%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-11)



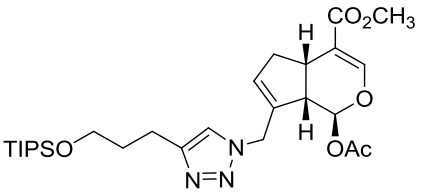
Following the general procedure, A, 4-pentyn-1-ol (64 µL) was used in click reaction. The reaction was stirred at room temperature for 30 min. The crude product was purified by silica gel column chromatography (SiO_2, 100%EtOAc-5 MeOH/ EtOAc) to afford triazole linked genipin (**9a-11**) as a yellow oil (92.3 mg, 72%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-12)



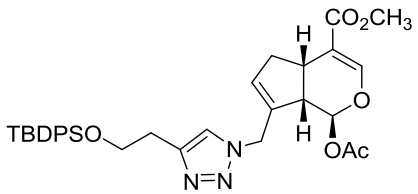
Following the general procedure, A, 4-pentyn-1-*tert*-butyldiphenylsilylether (274 mg) was used in click reaction. The reaction was stirred at room temperature for 1.5 hours. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-12**) as a yellow oil (160 mg, 76%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-13)



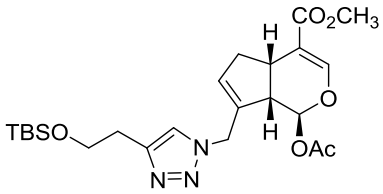
Following the general procedure, A, 4-pentyn-1-triisopropylsilylether (205 mg) was used in click reaction. The reaction was stirred at room temperature for 3 hours. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-13**) as a yellow oil (168.1 mg, 92%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-14)



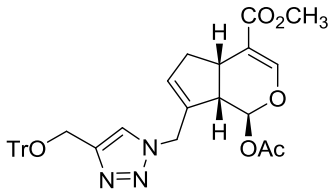
Following the general procedure, A, 4-butyn-1-*tert*-butyldiphenylsilylether (260 mg) was used in click reaction. The reaction was stirred at room temperature for 10 min. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane-50% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-14**) as a yellow oil (165.0 mg, 80%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-15)



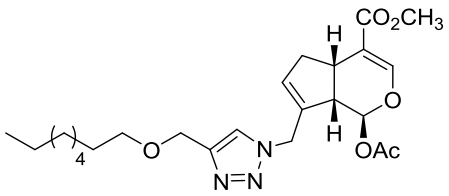
Following the general procedure, A, 4-butyn-1- *tert*-butylsilylether (126 mg) was used in click reaction. The reaction was stirred at room temperature for 30 min. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane-50% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-15**) as a yellow oil (123.2 mg, 76%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-16)



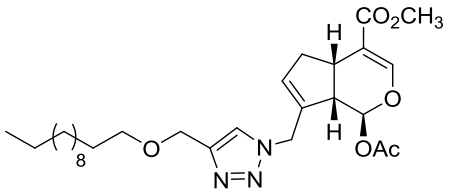
Following the general procedure, A, tri-phenylsilyl propagyl ether (147 mg) was used in click reaction. The reaction was stirred at room temperature for 5 min. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-16**) as a colorless oil (170.7 mg, 84%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-17)



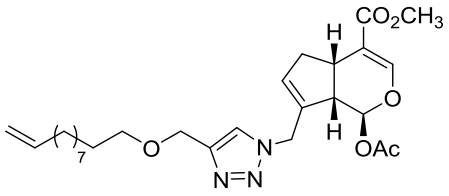
Following the general procedure, A, octyl propagyl ether (130 mg) was used in click reaction. The reaction was stirred at room temperature for 1 hour. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-17**) as a yellow oil (141.8 mg, 90%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-18)



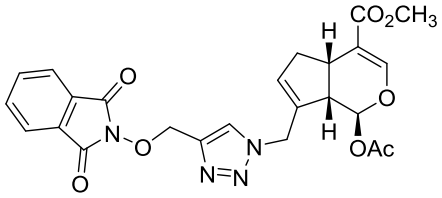
Following the general procedure, A, dodecyl propagyl ether (153 mg) was used in click reaction. The reaction was stirred at room temperature for 3 hours. The crude product was purified by silica gel column chromatography (SiO_2, 30% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-18**) as a yellow oil (158.0 mg, 89%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-19)



Following the general procedure, A, undecyl propagyl ether (142 mg) was used in click reaction. The reaction was stirred at room temperature for 30 min. The crude product was purified by silica gel column chromatography (SiO_2, 40% EtOAc/*n*-hexane) to afford triazole linked genipin (**9a-19**) as a white solid (112.6 mg, 66%).

Synthesis of 10-triazolyl-1-acetyl-genipin product (9a-20)



Following the general procedure, A, 2-prop-2-ynoxyisoindoline-1,3-dione (137 mg) was used in click reaction. The reaction was stirred at room temperature for 6.5 hours. The crude product was purified by silica gel column chromatography (SiO_2, 50% EtOAc/*n*-hexane-100%EtOAc) to afford triazole linked genipin (**9a-20**) as a white solid (95.5 mg, 57%).

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บทสรุปสำหรับผู้บริหาร
(Executive Summary)

ข้าพเจ้า ผศ. ดร. รุ่งนภา แซ่เอ็ง ได้รับทุนสนับสนุนโครงการวิจัย จากมหาวิทยาลัยบูรพา ประเภทงบประมาณเงินรายได้ จากเงินอุดหนุนรัฐบาล (งบประมาณแผ่นดิน) มหาวิทยาลัยบูรพา โครงการวิจัยเรื่อง “การปรับเปลี่ยน Geniposide จากสมุนไพรเพื่อศึกษาฤทธิ์ต้านอัลไซเมอร์” (Modification of Geniposidefrom natural product for study bioactivity against Alzheimer’s disease) รหัสโครงการ 2561A10802297 สัญญาเลขที่ 142/2561 ได้รับงบประมาณรวมทั้งสิ้น 455,000.00 บาท (สี่แสนห้าหมื่นห้าพันบาทถ้วน) ระยะเวลาดำเนินการ 1 ปี ตั้งแต่วันที่ 1 ตุลาคม 2560 ถึงวันที่ 31 มีนาคม 2562

บทคัดย่อ

Genipin เป็นสาร aglycone ที่มาจากสารอิริดอยด์ไกลโคไซด์ที่มีชื่อว่า geniposide สารธรรมชาติที่พบในผลของ *Gardenia jasminoides* ทีมวิจัยได้เน้นการปรับเปลี่ยนโครงสร้างของสาร genipin และตรวจสอบฤทธิ์ต้านอัลไซเมอร์ สารอนุพันธ์ใหม่ของ triazolylgenipin ได้ถูกวางแผนและสังเคราะห์ผ่านปฏิกิริยาเคมีหกขั้นตอน คือปฏิกิริยา silylation, acetylation, desilylation, mesylation, azidation และ Huisgen 1,3-dipolar cycloaddition ตามลำดับ ได้สารอนุพันธ์ใหม่ genipin-triazole จำนวน 20 อนุพันธ์ ด้วยร้อยละการเกิดผลิตภัณฑ์ที่ดีถึงดีมาก สารอนุพันธ์จำนวน 9 อนุพันธ์ แสดงฤทธิ์ต้านอัลไซเมอร์ที่ดี

Abstract

Genipin is an aglycone derived from an iridoid glycoside namely geniposide present in fruit of *Gardenia jasminoides*. We focus on structure modification of genipin and screening for their bioactivity against Alzheimer’s disease. The new triazolylgenipin analogues were designed and synthesized *via* six steps including silylation, acetylation, desilylation, mesylation, azidation and Huisgen 1,3-dipolar cycloaddition reaction, respectively. Twenty analogues of genipin-triazole were obtained in good to excellent yields. Nine compounds showed promising results of bioactivity against Alzheimer’s disease.

Output / Outcome

ผลงานที่กำลังจัดทำเพื่อส่งตีพิมพ์ในวารสารนานาชาติ จำนวน 1 เรื่อง

Silalai, P., Tocharus, J., Suksamrarn, A., & Saeeng, R. Synthesis and biologacal evaluation of genipin and its derivatives as potential anti-alzeimer agents (preparing manuscript).

สิทธิบัตรที่จะจัดทำ

สารอนุพันธ์ใหม่ triazole-genipin และฤทธิ์ต้านอัลไซเมอร์

การนำเสนอผลงานวิจัยแบบโปสเตอร์ในงานประชุมระดับนานาชาติ

1. Silalai, P., Tocharus, J., Suksamrarn, A., & Saeeng, R. Synthesis of 1-acetyl-10-triazolegenipin analogues from natural genipin and screening of neuroprotective activity, Scientific Frontiers in Natural Product Based Drugs Conference, July 6-7, 2017, Department of Pharmacology, National University of Singapore, Singapore

ได้รางวัล The best poster scientific presentation award

การผลิตบัณฑิต

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นางสาวปฐมาวดี ศิลาลาย