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New class of alkynyl glycoside analogues as tyrosinase inhibitors

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ABSTRACT

A new series of alkynyl glycoside analogues were designed and synthesized from cheap and a commercially available sugar by introduction of various alkynyl and alkyl groups at C-1 and C-6 positions of the sugar ring. The inhibitory abilities of alkynyl glycosides were investigated *in vitro* on mushroom tyrosinase for the catalysis of L-Tyrosine and L-DOPA as substrates and comparing with arbutin and kojic acid. Non-terminal alkyne compound **2d** showed excellent tyrosinase inhibitory activity (IC_{50} 54.0 μM) against L-Tyrosine comparable to arbutin (IC_{50} 1.46 mM) while **2b** exhibited potent activities (IC_{50} 34.3 μM) against L-DOPA higher than kojic acid (IC_{50} 0.11 mM) and arbutin (IC_{50} 13.3 mM). Kinetic studies revealed that compound **2d** was a non-competitive inhibitor with the best *Ki* value of 21 μM and formed an irreversible receptor complex with mushroom tyrosinase. The SARs results showed that the type of alkyne and alkyl groups at position C-6 on sugar and the stereoisomer played an important role in determining their inhibitory activities. The potent activity of alkynyl glycosides identified in this study highlight the importance of this scaffold and these compounds are very modestly potent to the development of new class for tyrosinase inhibitor.

Introduction

Tyrosinase or polyphenol oxidase (EC 1.14.18.1), is a multifunctional copper-containing enzyme widely distributed in nature. It is a well known catalyst in the transformation of L-tyrosine to melanin.[1] The process of melanin synthesis is of considerable importance in the coloring of skin, hair, eyes and in food browning.[2,3] On the other hand, the production of hyperpigmentation of melanin causes melasama, freckles and other dermatological disorders.[4] In addition, tyrosinase enzyme activity was found to be enhanced in the insect molting process[5] and influenced the neurodegeneration associated with Parkinson's disease.[6,7] Based on this problem, the development of tyrosinase inhibitors or skin whitening agents have become increasingly important in cosmetic, food and the medical industry. In the cosmetic industry, skin whitening products such as kojic acid[8] and arbutin[9] have been extremely important however these compounds display side effects such as skin toxicity and low clinical efficiency.[10,11] Moreover, arbutin is now prohibited for use in several countries. Therefore, the development of new non-toxic skin whitening agents is needed. In the past decade, the biological activities of glycosylated products have been increasingly used for the development of drug efficacy, pharmacokinetics and reduced side effects.[12,13] Currently, a large number of natural and synthetic tyrosinase inhibitors as a family of glycosides display potent inhibitory activity (Fig. 1).[14–19] The relationship between these sugars and bioactive aglycone has shed light on their biological significance, which could lead to the development of novel inhibitors based on the chemical properties of aglycone.

Acetylenic metabolites have been demonstrated to possess a number of interesting pharmacophore in nature with potent biological activities such as anticancer, antibacterial, anti-inflammatory, and other chemical and medicinal properties.[20–22] However, to our knowledge, the tyrosinase activity of acetylenic compounds have never been reported. In the present study, we designed and synthesized a series of alkynyl glycosides to investigate the influence of alkynyl groups on mushroom tyrosinase by modify at C-1 and C-6 positions of sugar and evaluate their bioactivity with L-Tyrosine (monophenolase activity) and L-DOPA (diphenolase activity) for develop to novel potent tyrosinase inhibitors.

The glycoside analogues (**1–9**) were synthesized by the strategic pathway shown in Schemes 1–3. The alkynyl *O*-glycoside derivatives (**1a-1d**) were prepared by Fischer glycosylation at the anomeric position of D-glucose with various carbon chain lengths of alkynyl alcohols (**a-d**) in the presence of sulphuric acid immobilized on silica gel (H_2SO_4–SiO_2)[23] (Scheme 1). *O*-Benzylation of D-glucose and alkynyl glycosides **1a-1d** with benzyl bromide under basic condition gave *O*-benzyl alkynyl glycosides **2a-2e**. Selective debenzylation at the C-6 position of compounds **2a-2e** with trimethylsilyl trifluoromethanesulfonate (TMSOTf), followed by *O*-acetylation using acetic anhydride provided compounds **3a-3e**. Removing of acetyl

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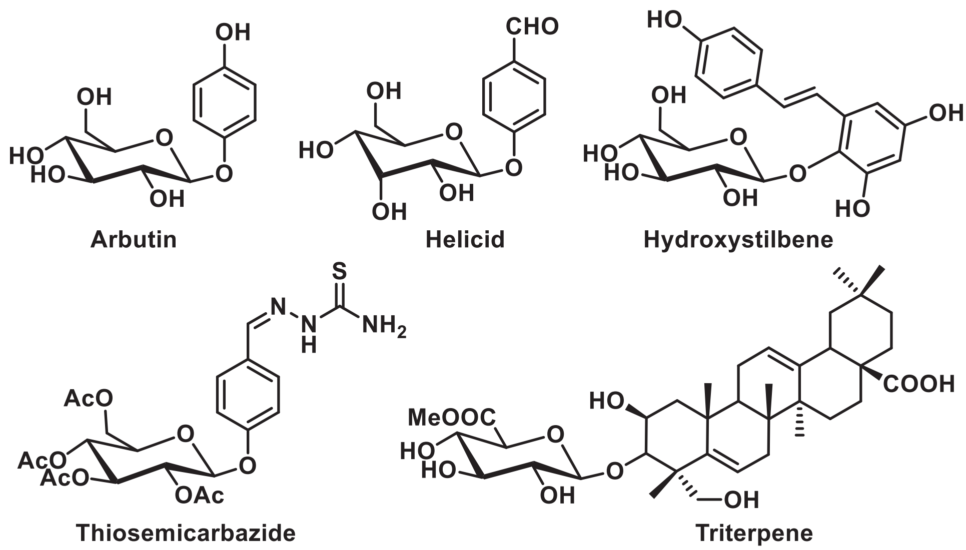
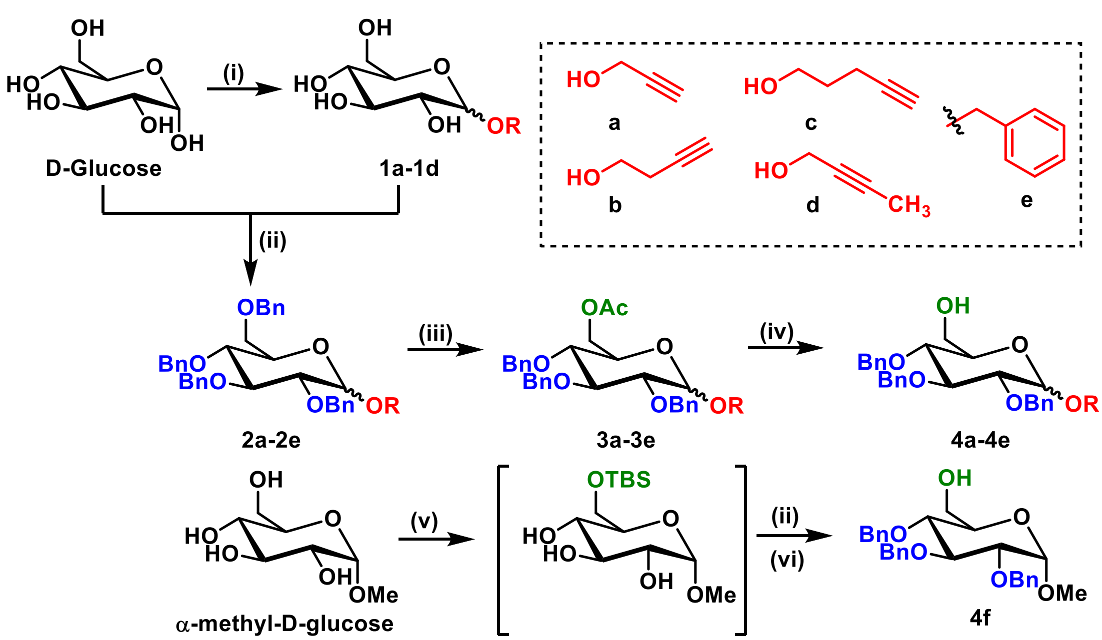


Fig. 1. Chemical structures of some known tyrosinase inhibitors.



Scheme 1. Synthesis of compounds **1–4**. Reagents and conditions: (i) H_2SO_4-SiO_2, acetylene alcohols (**a-d**), 60 °C, overnight, 60–78% (ii) NaH, BnBr, DMF, r.t., 3 h, 80–97% (iii) TMSOTf, Ac_2O, CH_3CN, 0 °C - r.t., 20 min., 64–88% (iv) NaOH, MeOH:H_2O, 0 °C - r.t., 30 min., 83–99% (v) TBSCl, pyridine, 0 °C - r.t., 1 h. (vi) HCOOH/H_2O (4:1), THF, 0 °C - r.t., 3 h, 61% (3 steps).

groups of **3a-3e** by treatment with sodium hydroxide furnished compounds **4a-4e**.

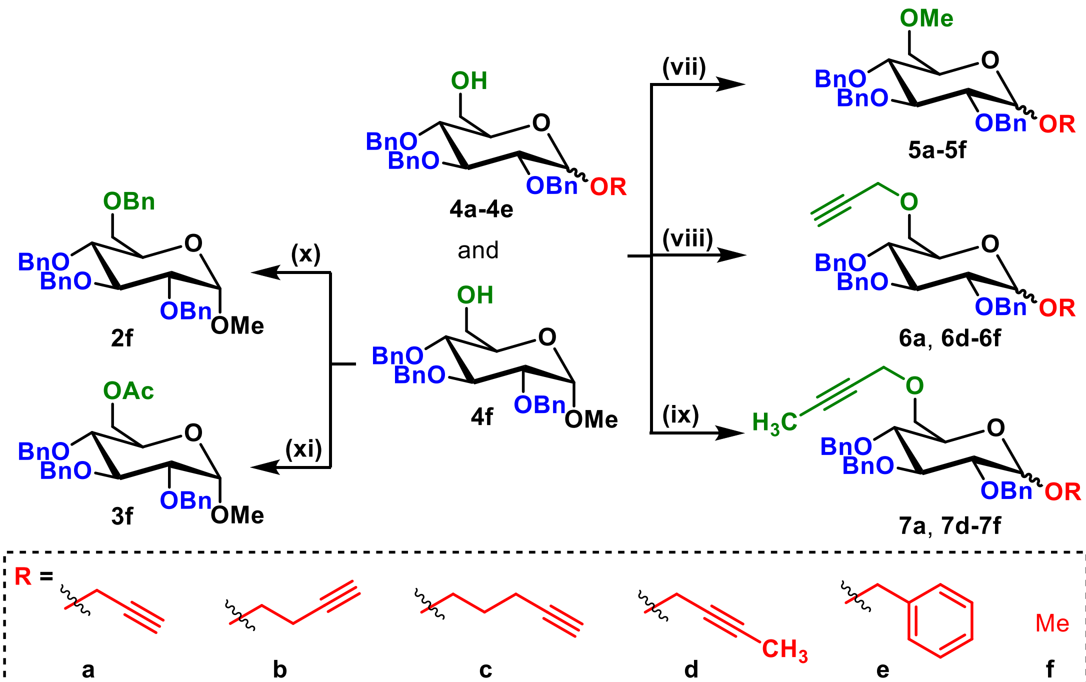
Compound **4f** was prepared by *O*-silylation at C-6 of α-methyl-D-glucose with TBSCl, followed by *O*-benzylation and removal of the silyl moiety under acidic conditions. Then, *O*-benzylation and *O*-acetylation at the C-6 position of **4f** gave products **2f** and **3f** respectively (Scheme 2). *O*-Methylation of compounds **4a-4f** with MeI gave products **5a-5f**. To study the structure activity relationship (SAR) of alkyne at C-6, *O*-glycoside analogues **6a, 6d-6f** and **7a, 7d-7f** were prepared from reactions of **4a, 4d-4f** with propargyl bromide and 1-bromo-2-butyne in the presence of sodium hydride as a base in DMF respectively.

In addition, to study the SAR at C-6, protection of diol at C-5 and C-6 of alkynyl glycosides **1a-1b, 1d** with benzaldehyde using $ZnCl_2$ as a catalyst gave benzylidene acetal compounds **8a-8b, 8d**, followed by *O*-benzylation with benzyl bromide, afforded the products **9a-9b, 9d**. All the synthesized compounds have been characterized by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.

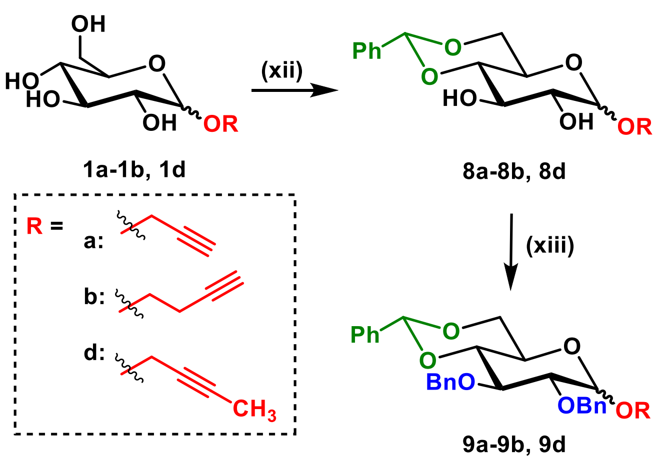
All alkynyl glycoside derivatives were evaluated *in vitro* on mushroom tyrosinase using arbutin and kojic acid as reference standard according to the procedures reported in literature.[24] The IC_{50} values was summarized in Table 1. In this study, two types of substrate were used to investigate the effect of competition against inhibitors catalyzed by tyrosinase.

Inhibitory effects of alkynyl O-glycoside derivatives on mushroom tyrosinase with L-Tyrosine as substrate

The results indicated that α-propargyl *O*-glycoside compound $\mathbf{2a}_\alpha$ and β-isomer $\mathbf{2a}_\beta$ showed diferent activity (Table 1). β-propargyl *O*-glycoside showed strong tyrosinase inhibitory activity with an IC_{50} value of 94.7 μM while α-isomer showed weαk activity. Interestingly, the mixture of both isomers (**2a**) exhibited potent activity (81.9 μM), and the activity was slightly reduced when the chain length of alkyne increased to butynyl **2b** (IC_{50} = 150 μM) and pentynyl **2c**



Scheme 2. Synthesis of compounds **5–7**. Reagents and conditions: (vii) NaH, MeI, DMF, r.t., 30 min., 70–93% (viii) NaH, propargyl bromide, DMF, r.t., 30 min., 93–98% (ix) NaH, 1-bromo-2-butyne, DMF, r.t., 30 min., 93–97% (x) NaH, BnBr, DMF, r.t., 30 min., 98% (xi) NaH, Ac_2O, DMF, r.t., 30 min., 85%.



Scheme 3. Synthesis of compounds **8–9**. Reagents and conditions: (xii) $ZnCl_2$, benzaldehyde, r.t., overnight, 65–82% (xiii) NaH, BnBr, DMF, r.t., 1 h, 90–95%.

(IC_{50} = 105 μM). Non-terminal alkyne compound **2d** showed the strongest inhibitory activity (IC_{50} = 54.0 μM), indicating that the electron density of the alkynyl moiety greatly influenced the inhibitory behavior against tyrosinase. A comparison of the IC_{50} values of stereoisomers of compound **2d** found that mixtures of isomers exhibited more potent activity than single isomers, suggesting a synergistic effect. The IC_{50} values of benzyl glycoside **2e** and alpha methoxyl glycoside **2f** showed weak inhibitory activitities. This data suggested that the type of alkynyl moiety at C-1 plays a significant role in enabling the binding with the active site of tyrosinase. Replacement of the benzyl group at the C-6 position of glycoside with acetoxyl (**3d**), hydroxyl (**4d**), methoxyl (**5d**), alkyne (**6d,7d**) and benzylidene acetal (**9d**) led to a decrease in inhibitory activity, demonstrating that the benzyl group at C-6 of **2d** displayed a very important role in determining inhibitory behavior. According on the results in Table 1, several synthetic glycoside derivatives showed tyrosinase inhibitory activity greater than arbutin a whitening agent used in the cosmetic industry.

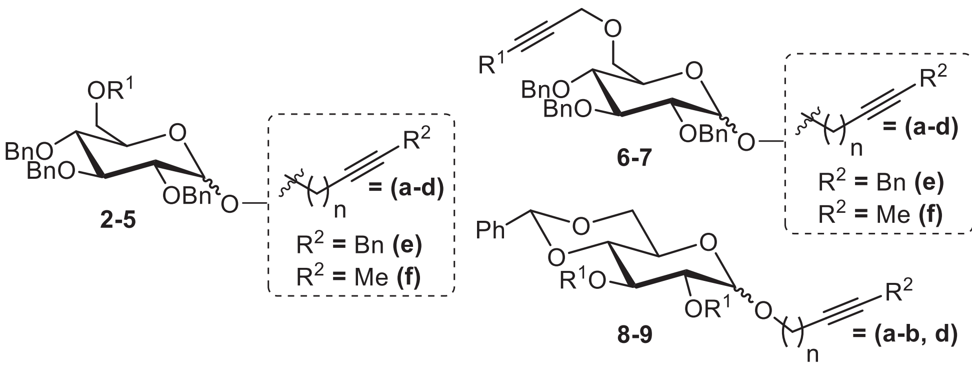
Inhibitory effects of alkynyl glycoside derivatives on mushroom tyrosinase with L-DOPA as substrate

The alkynyl *O*-glycosides **2b** and **2d** showed excellent tyrosinase inhibitory activity with IC_{50} values of 34.7 and 70.7 μM respectively, which exhibited stronger activity than kojic acid and arbutin. Changing the benzyl group at the C-6 position of **2d** to hydroxyl, **4d** exhibited slightly lower inhibition (IC_{50} = 80.4 μM). In contrast, when the C-6 position of **2d** was replaced with methoxyl, **5d** showed strong inhibitory potency with an IC_{50} value of 45.4 μM. The results suggested that with an alkynyl moiety at the C-1 and the benzyl group at C-6 position of sugar, a significant increasing in activity was increased by interacting with the active site of tyrosinase and L-DOPA as substrate.

The kinetic behaviour of the most active compounds **2d** and **7d** for the hydroxylation of L-Tyrosine (Fig. 2) and **2b** and **5d** for the oxidation of L-DOPA (Fig. 3) were investigated to determine the type of inhibition and inhibition constant (K_i) using Lineweaver–Burk plots. The results showed that the plots of 1/V versus 1/S gave straight lines with different slopes but same x-intercept points, which demonstrated that the V_{max} values increased while K_m remains unchanged. This behavior indicated that all of selected compounds were a non-competitive inhibitor of tyrosinase. The inhibition constant (K_i) of **2d** and **7d** were 21 and 32 μM with L-tyrosine as substrate, while for **2b** and **5d** were 49 and 52 μM with L-DOPA as substrate, respectively. This result suggested that compound **2d** had the most potent inhibitory effect (see Supporting data).

The inhibition mechanism of the inhibitors was determined by the relationship between enzyme activity versus the concentration of enzyme at different inhibitor concentrations as shown in Fig.4. The results of inhibitory effect of **2d** and **7d** on mushroom tyrosinase for the hydroxylation of L-tyrosine showed that when increasing the concentrations of enzyme at different concentrations of **2d**, a family of parallel straight lines with the same slopes was observed, indicating that **2d** was an irreversible inhibitor. In contrast, **7d** gave a family of straight lines with all passed through the origin, demonstrating that **7d** was a reversible inhibitor. The behavior of **2b** and **5d** gave the same result as **7d**, thus compounds **2b** and **5d** were reversible inhibitors on mushroom

Table 1
The inhibitory effects of alkynyl glycoside derivatives on mushroom tyrosinase activity.



compd.	R^1	R^2	n	IC_{50} (μM)		compd.	R^1	R^2	n	IC_{50} (μM)	
				Tyrosine	DOPA					Tyrosine	DOPA
2a	Bn	H	1	81.9 ± 0.14	> 500	**5c**	Me	H	3	> 500	> 500
2a$_{\alpha}$	Bn	H	1	> 500	> 500	**5d**	Me	Me	1	73.6 ± 0.10	45.4 ± 0.22
2a$_{\beta}$	Bn	H	1	94.7 ± 0.43	> 500	**5e**	Me	Bn	–	> 500	435 ± 0.58
2b	Bn	H	2	150 ± 0.41	34.3 ± 0.40	**5f**$_{\alpha}$	Me	Me	–	> 500	494 ± 1.8
2c	Bn	H	3	105 ± 0.21	> 500	**6a**	H	H	1	> 500	> 500
2d	Bn	Me	1	54.0 ± 0.10	70.7 ± 0.31	**6d**	H	Me	1	> 500	288 ± 1.2
2d$_{\alpha}$	Bn	Me	1	321 ± 0.67	> 500	**6e**	H	Bn	–	205 ± 0.22	> 500
2d$_{\beta}$	Bn	Me	1	179 ± 0.16	> 500	**6f**$_{\alpha}$	H	Me	–	> 500	> 500
2e	Bn	Bn	–	> 500	> 500	**7a**	Me	H	1	> 500	> 500
2f$_{\alpha}$	Bn	Me	–	191 ± 1.8	> 500	**7d**	Me	Me	1	72.0 ± 0.12	> 500
3a	Ac	H	1	461 ± 0.94	> 500	**7e**	Me	Bn	–	> 500	> 500
3b	Ac	H	2	268 ± 0.82	> 500	**7f**	Me	Me	–	274 ± 0.74	> 500
3c	Ac	H	3	208 ± 1.1	> 500	**8a**	H	H	1	> 500	> 500
3d	Ac	Me	1	219 ± 1.1	400 ± 0.35	**8b**	H	H	2	463 ± 2.7	207 ± 0.26
3e	Ac	Bn	–	273 ± 0.52	357 ± 1.9	**8d**	H	Me	1	> 500	> 500
3f$_{\alpha}$	Ac	Me	–	> 500	> 500	**9a**	Bn	H	1	> 500	383 ± 1.5
4a	H	H	1	> 500	> 500	**9a**$_{\alpha}$	Bn	H	1	> 500	431 ± 0.64
4b	H	H	2	> 500	> 500	**9a**$_{\beta}$	Bn	H	1	> 500	> 500
4c	H	H	3	> 500	> 500	**9b**	Bn	H	2	> 500	257 ± 0.26
4d	H	Me	1	> 500	80.4 ± 0.17	**9b**$_{\alpha}$	Bn	H	2	> 500	> 500
4e	H	Bn	–	> 500	> 500	**9b**$_{\beta}$	Bn	H	2	> 500	> 500
4f$_{\alpha}$	H	Me	–	> 500	> 500	**9d**	Bn	Me	1	> 500	> 500
5a	Me	H	1	> 500	> 500	**9d**$_{\alpha}$	Bn	Me	1	> 500	> 500
5b	Me	H	2	> 500	> 500	**9d**$_{\beta}$	Bn	Me	1	> 500	> 500
arbutin			1465 ± 3.3	13,282 ± 23.0							
Kojic acid			12.8 ± 0.15	107 ± 0.20							

tyrosinase for the oxidation of L-DOPA (Fig.5).

To investigate the binding modes of the most inhibitor (**2d** and **2b**) with in the active site of tyrosinase, docking simulations were performed using Autodock 4.2 software[25] and the structure of mushroom tyrosinase was obtained from the Protein Data Bank (ID: 2Y9X)[26] as shown in Fig. 6. Interestingly, compound **2d** showed a good fit in the pocket site of the protein molecular surface and had a binding energy of −7.80 kcal/mol. The three hydrogen bond interactions was observed between all three oxygen groups of the **2d** and the His244 residue (bond distances: 1.8, 2.3 and 2.8 Å). In addition, the benzyl and alkyl

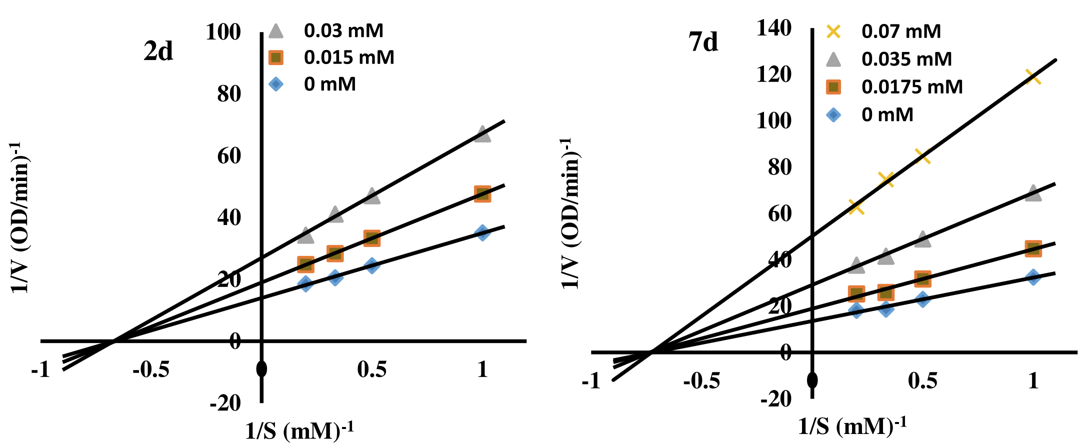


Fig. 2. Lineweaver-Burk plots for inhibition of selected compounds **2d** and **7d** against mushroom tyrosinase for the catalysis of L-Tyrosine.

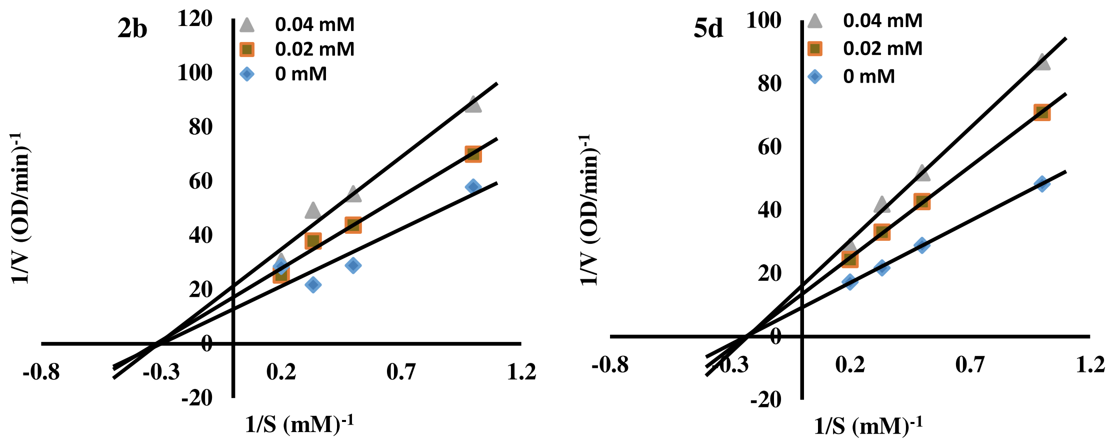


Fig. 3. Lineweaver-Burk plots for inhibition of selected compounds **2b** and **5d** against mushroom tyrosinase for the catalysis of L-DOPA.

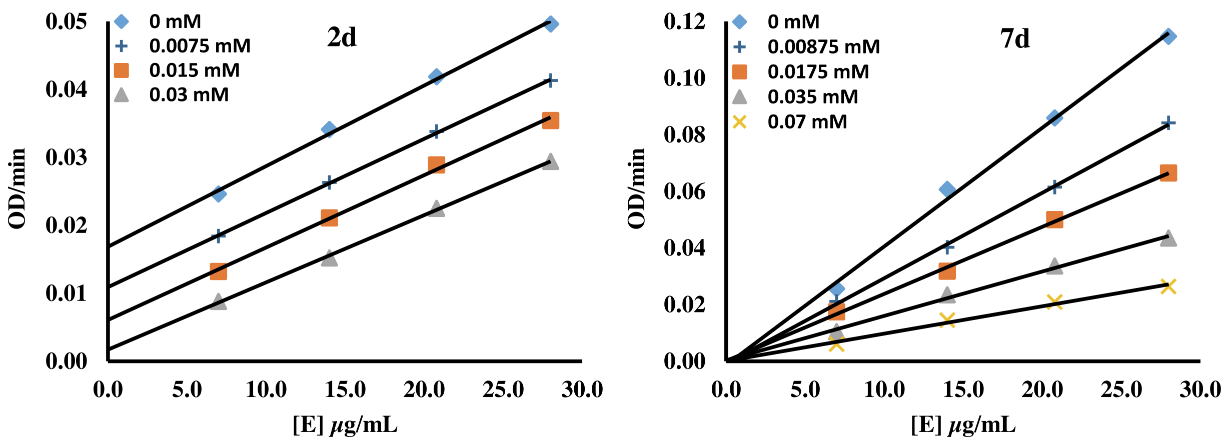


Fig. 4. The inhibitory effects of **2d** and **7d** on mushroom tyrosinase for the catalysis of L-Tyrosine.

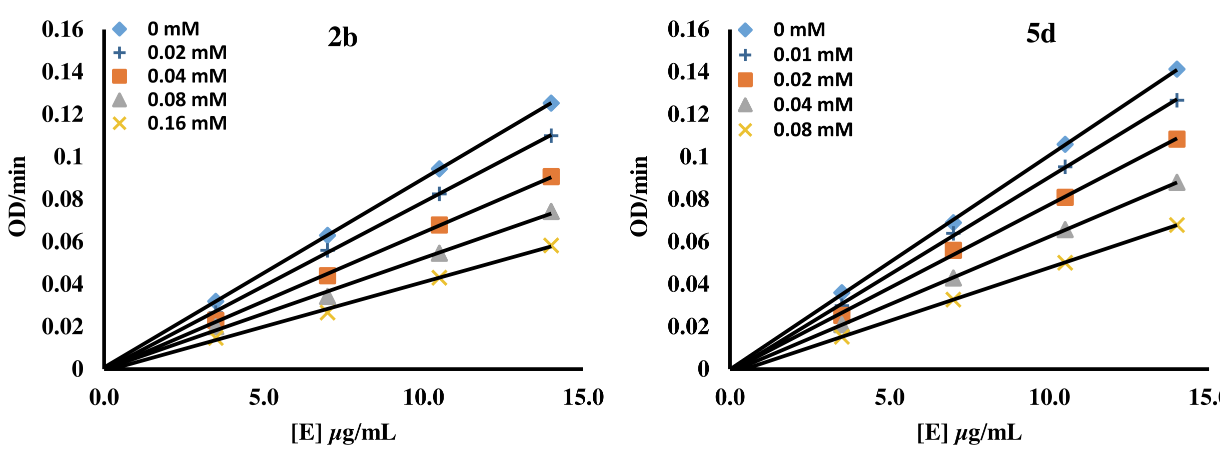


Fig. 5. The inhibitory effects of **2b** and **5d** on mushroom tyrosinase for the catalysis of L-DOPA.

group of the **2d** interacted with Val248, Asn281, His263 and His61 residues *via* π-alkyl interactions, while benzyl group interacted with Phe264 *via* π-π interactions. In the same way, the binding energy of **2b** was calculated as −7.12 kcal/mol and displayed hydrogen bond interaction with the Glu322 residue (bond distance: 3.5 Å). The alkynyl group of **2b** interacted with Val283 residues *via* π-alkyl interaction, while benzyl group was involved in the π-alkyl and π-π interaction with Val248 and Phe264, respectively. Thus, on the basis of the molecular docking results, we observe that the oxygen group was formed a strong hydrogen bond against tyrosinase. Moreover, the benzene ring and alkynyl group were important formed hydrophobic interactions with amino acid residues surrounding active site of tyrosinase.

In conclusion, a series of alkynyl *O*-glycoside derivatives were designed and synthesized and study as a new class of tyrosinase inhibitor for the first time. Several of the *O*-glycoside derivatives exhibited more potent tyrosinase inhibitory activities than arbutin a widely used tyrosinase inhibitor. In particularly, compound **2b** and **2d** showed the most potent activity with IC_{50} values of 34.3 and 54.0 μM, respectively. The structure activity relationships (SARs) suggested that the type of alkynyl moiety, benzyl group at C-6 position of the sugar and

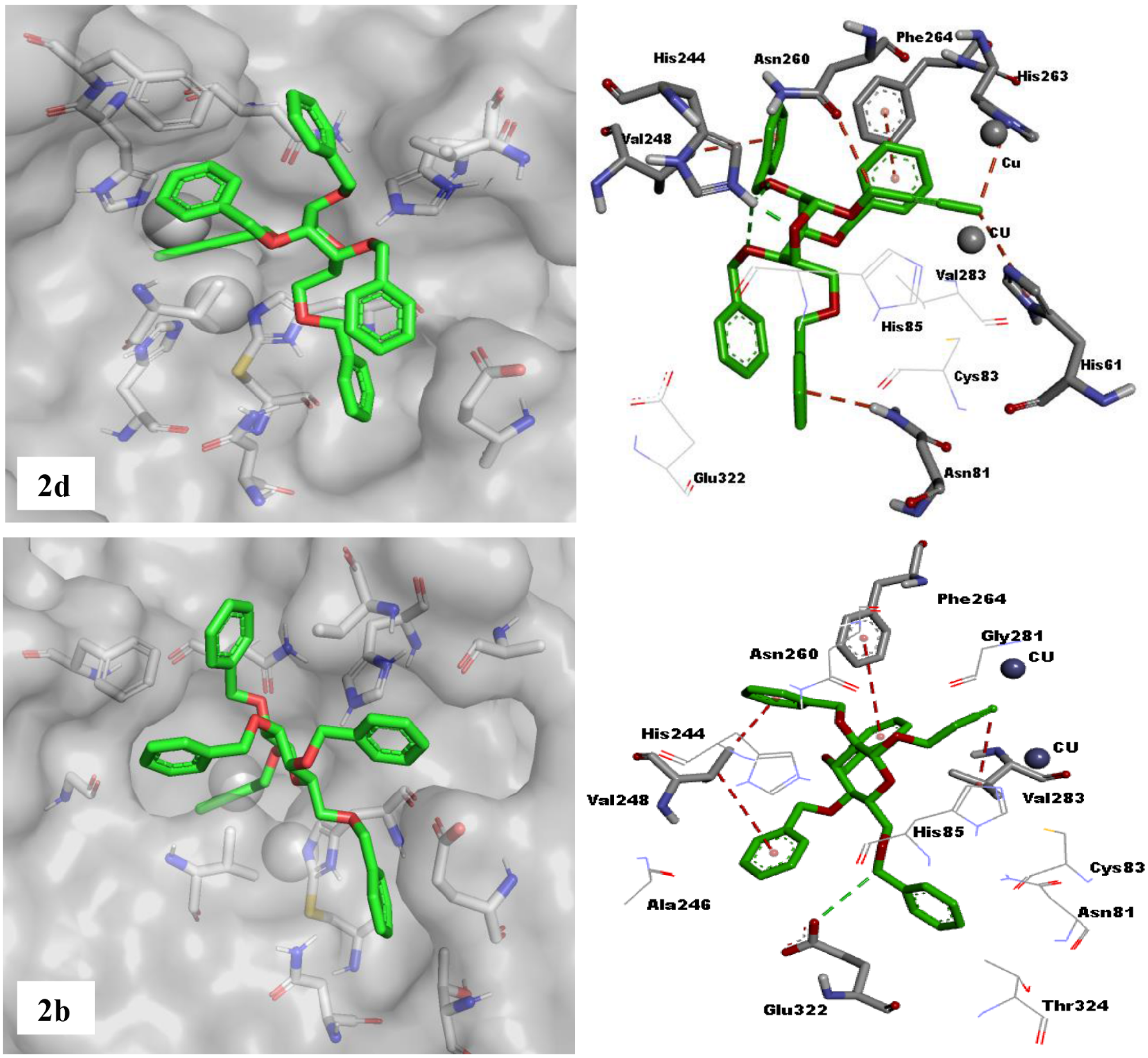


Fig. 6. Molecular docking results of **2d** and **2b** (Green) interacting with residues in the active site of tyrosinase (PDB code: 2Y9X). Hydrogen bonds and hydrophobic interactions were displayed as green and red dashed lines, respectively.

stereoisomers at C-1 played a very important role in the tyrosinase inhibition activity. Moreover, the kinetic analysis study indicated that **2d**, the most potent tyrosinase inhibitor was a non-competitive type inhibitor with a *Ki* value of 21 μM and formed an irreversible receptor complex against mushroom tyrosinase. Molecular docking showed a good fit in the cavity of tyrosinase and had a binding energy of −7.80 kcal/mol. These compounds will be of potential use for further development of drugs for the treatment of tyrosinase-related disorders.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127276.

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