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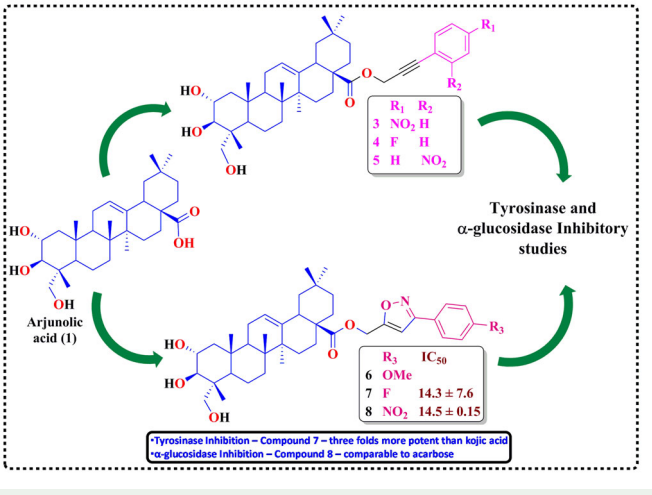
Design, synthesis of new phenyl acetylene and isoxazole analogues of arjunolic acid as potent tyrosinase and alpha glucosidase inhibitors

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ABSTRACT

A series of new phenyl acetylene and isoxazole analogues of arjunolic acid were designed, synthesized and evaluated (**3**–**8**) for their tyrosinase and alpha glucosidase inhibitory potential. All the tested analogues exhibited stronger inhibitory activity than the standard drug or parent compound. Of these, compound (**7**) displayed the most potent tyrosinase inhibitory action with IC_{50} (14.3 ± 7.6) of about three folds more than the standard drug, kojic acid (41.5 ± 1.0). Further, compound (**8**) (14.5 ± 0.15) possessed the potent alpha glucosidase inhibitory action with IC_{50} value comparable to that of standard, acarbose (10.4 ± 0.06). Henceforth, compounds (**7**) and (**8**) are promising candidates for further studies.



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1. Introduction

Arjunolic acid (**1**) is a pentacyclic cyclosqualenoid of oleanane triterpenoid, which possesses a lactonizable olefinic bond, carboxyl, three hydroxy functional groups, of which two constitute an alpha glycol system on the triterpenoid backbone, which are easily amenable to several types of structural modifications. This terrestrial triterpenoid acid was first isolated from the methanol extracts of the hardwoods of *Terminalia arjuna* in 1954 by King and coworkers (King et al. 1954). Since then, it was reported from several plant species, such as *T. catappa* (Diyabalanage et al. 1997; Ichoron et al. 2018), *Calotropis gigantean* (Huang et al. 2016), and *Combretum aculeatum* (Dawe et al. 2017).

Arjunolic acid was one of the active ingredients of nano preparation of Chinese medicine composition that found its application in the treatment of osteoarthritis and has the advantages of safety and strong targeting (Wang et al. 2018). Likewise, another invention has its application in anticancer drugs for improving the advanced-stage living standard of cancer patients was patented (Bai et al. 2019). It is applicable in inhibition of intestinal apoB48 secretion and synthesis in the manufacturing of medicines for resisting hyperlipidemia, cardiovascular, cerebrovascular, and atherosclerosis diseases (Yin et al. 2017). It is an active ingredient in several cosmetic formulations such as hair growth stimulator (Farwick et al. 2013) and anti-wrinkle (Koehler et al. 2015). It also found its application in the increase in the production of sebum, for oil secretion of the sebaceous gland (Inoue 2005).

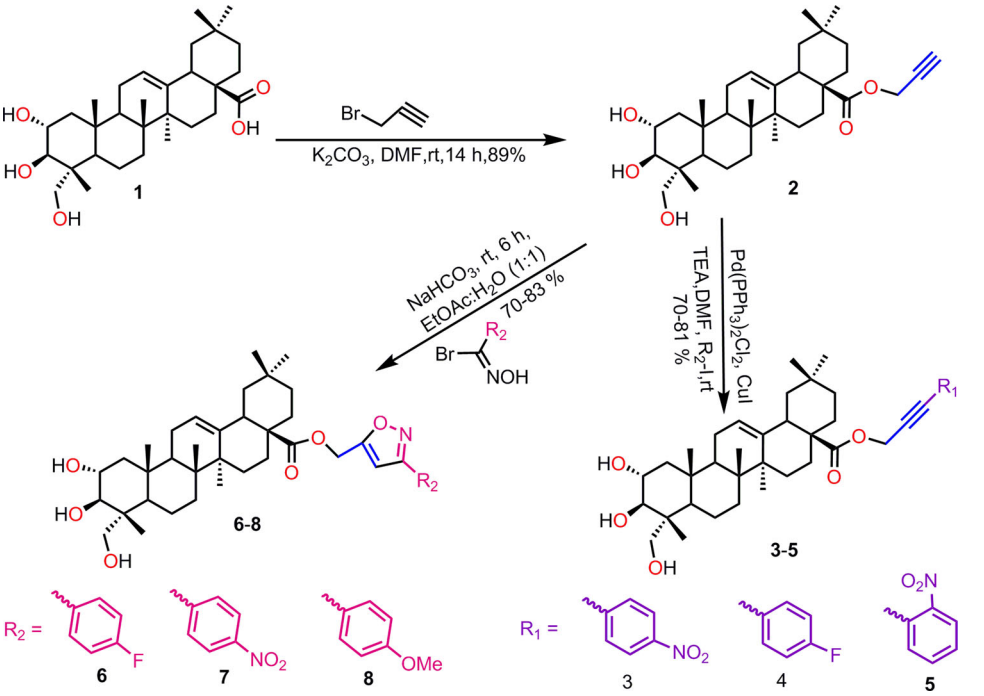
Tyrosinase is a copper containing enzyme that catalyses the production of melanin for protecting skin from UV radiation. The overproduction of melanin could be controlled by inhibition of the enzyme, tyrosinase. However, in cosmetic industry, kojic acid was used as tyrosinase inhibitor, which is associated with contact dermatitis side effects such as rashes, redness, itchiness, irritation, swollen skin etc (Seong et al. 2009; Cui et al. 2015). It is worth to evaluate the tyrosinase as well as AGH potential of arjunolic acid for the development of new products in cosmetics and diabetics with minimal side effects.

On the other hand, alpha-glucosidase inhibitory activity is an important assay for evaluation of potency of anti-diabetic drugs. Acarbose is the current gold standard alpha-glucosidase inhibitor used in treating type-2 diabetes. However, use of acarbose which is associated with many sides, and its prescription for patients with underlying ailments is discouraged (Clissold and Edwards 1988; Mertes 2001). Hence, there is a continual quest for safer yet highly active tyrosinase and α-glucosidase inhibitors. With the versatile biological activities and therapeutic potentials of arjunolic acid, it could represent a safe platform to tyrosinase, α-glucosidase inhibitors and other active therapeutic compounds. Hence, to explore the potential utility of arjunolic acid, we have undertaken the synthesis and biological evaluation of a number of new analogues.

2. Results and discussion

2.1. Chemistry

Arjunolic acid (**1**) was isolated from the chloroform extract of the stems of *X. granatum* as reported in our previous article (Olanipekun et al. 2020). It was obtained as



Scheme 1. Synthesis of new phenyl acetylene and isoxazole analogues of arjunolic acid.

colourless crystals after re-crystallization with acetone. The HRESIMS data of compound **1** revealed a quasimolecular ion [M^++H] peak at *m/z* 489.36100 (calc. mass of 489.35745) in accordance with the molecular formula $C_{30}H_{48}O_5$. Its ^{1}H NMR spectrum displayed the presence of six methyls at δ 0.69–1.18 ppm and one trisubstituted olefinic proton at δ (5.25, t, $J = 3.5$). Its ^{13}C NMR spectrum revealed thirty-carbon resonances. An acid carbonyl at δ 180.5 ppm, an olefinic carbon signals at δ 143.9 and 122.0 ppm, one oxymethylene at (δ 64.8 ppm) and two oxymethines at (δ 68.2 and 76.7 ppm). The location of oxymethylene and oxymethines were confirmed by DEPT-135 which revealed that the molecule possess; six methyls, ten methylenes, six methines and eight quaternary carbons. On comparison of the spectroscopic data of compound (**1**) with literature (Joseph et al. 2018), the structure was established as arjunolic acid (**1**).

The synthesis of the derivatives of (**1**) was achieved via two steps as shown in Scheme 1. First, the carboxylic acid group of (**1**) was esterified with propargyl bromide to obtain propargyl arjunolic ester (**2**). Then (**2**) served as precursor to the phenyl acetylene (**3**–**5**) and isoxazole (**6**–**8**) analogues via Sonogashira coupling and Click-type reaction respectively (Figure 1). The new isoxazole analogues were obtained by the reaction of (**2**) with bromoaldoximes. The bromoaldoximes were in turn prepared by one pot reaction of hydroxylamine hydrochloride with substituted benzaldehydes, and then the crude product obtained was reacted with NBS (Gundoju et al. 2018). The new phenyl acetylene analogues were synthesized by Sonogashira coupling (**2**) with the substituted aryl iodides in the presence of palladium (Sonogashira et al. 1975).

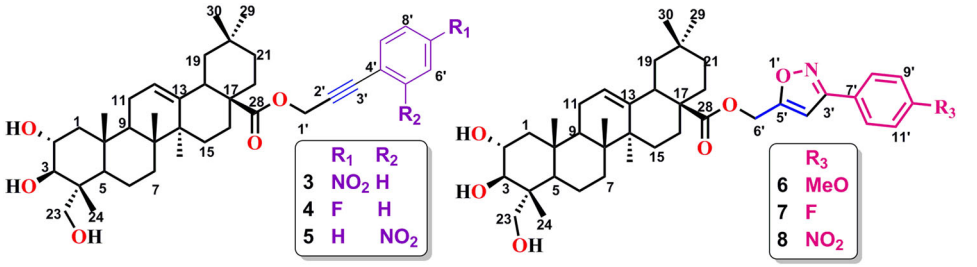


Figure 1. The Structures of new synthesized phenyl acetylene and isoxazole analogues of arjunolic acid (3-8).

2.2. α-Glucosidase inhibitory activity

Table S1 shows the results of the alpha-glucosidase inhibitory activities of compounds **1**, **3**–**8** in comparison with acarbose. Arjunolic acid (**1**) with IC_{50} value far higher than 600 μM displayed very low inhibitory activity. The poor inhibitory activity obtained for arjunolic acid agrees with the report of Dawe et al. (2018) who obtained similar results when arjunolic acid and asiatic acid were tested against α-glucosidase enzyme from yeast. The results in Table S1 also showed that the isoxazole analogues (**6**–**8**) displayed strong inhibitory activity against the α-glucosidase enzyme compared to the phenyl acetylene counterparts. Among the isoxazole derivatives, compound (**8**) was the most active molecule with IC_{50} of 14.5 ± 0.15. Nevertheless, isoxazole molecules displayed significant inhibition of the enzyme comparable to that of acarbose. Compound (**4**) displayed the strongest inhibitory activity among the phenyl acetylene analogues. Interestingly, all the derivatives showed stronger inhibitory action than the starting material, that is, arjunolic acid (> 600).

2.3. Tyrosinase inhibitory activity

Table S2 shows the results of the tyrosinase inhibitory activities of compounds **1**, **3**–**8** in comparison with kojic acid. The results revealed that all the derivatives showed stronger tyrosinase inhibitory activity than arjunolic acid (**1**). The isoxazole analogues displayed more than three folds potency than the starting material, arjunolic acid (**1**). These compounds showed a stronger tyrosinase inhibitory activity than the positive control, kojic acid (41.5 ± 1.0) in more than one fold. This revealed that the potency of the tested compounds is dependent on their functionalities. The decreasing order of the tyrosinase inhibitory activity of the compounds is; **7** > **8** > **6** > **4** > **5** > **3** > **1**.

3. Conclusion

In summary, six new derivatives of (**1**) comprising: three phenyl acetylene (**3** − **5**) and three isoxazole moieties (**6**–**8**) were synthesized in good to excellent yields. The parent compound (**1**) and its analogues (**3**–**8**) were evaluated for alpha glucosidase and tyrosinase inhibitory activity. The derivatives exhibited more than two folds higher alpha glucosidase and tyrosinase inhibitory activity than the parent compound (**1**). The

isoxazole analogues of arjunolic acid showed potent activity than the phenyl acetylene counterparts. Among the tested compounds, compound (**8**) (14.5 ± 0.15) possessed the potent alpha glucosidase inhibitory action, with IC_{50} value closest to that of the standard drug, acarbose (10.4 ± 0.06). Furthermore, compound (**7**) (14.3 ± 7.6) displayed the most potent tyrosinase inhibitory action with IC_{50} of about three folds than the positive control, kojic acid (41.5 ± 1.0).Therefore, compounds (**7**) and (**8**) are promising candidates for further studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

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