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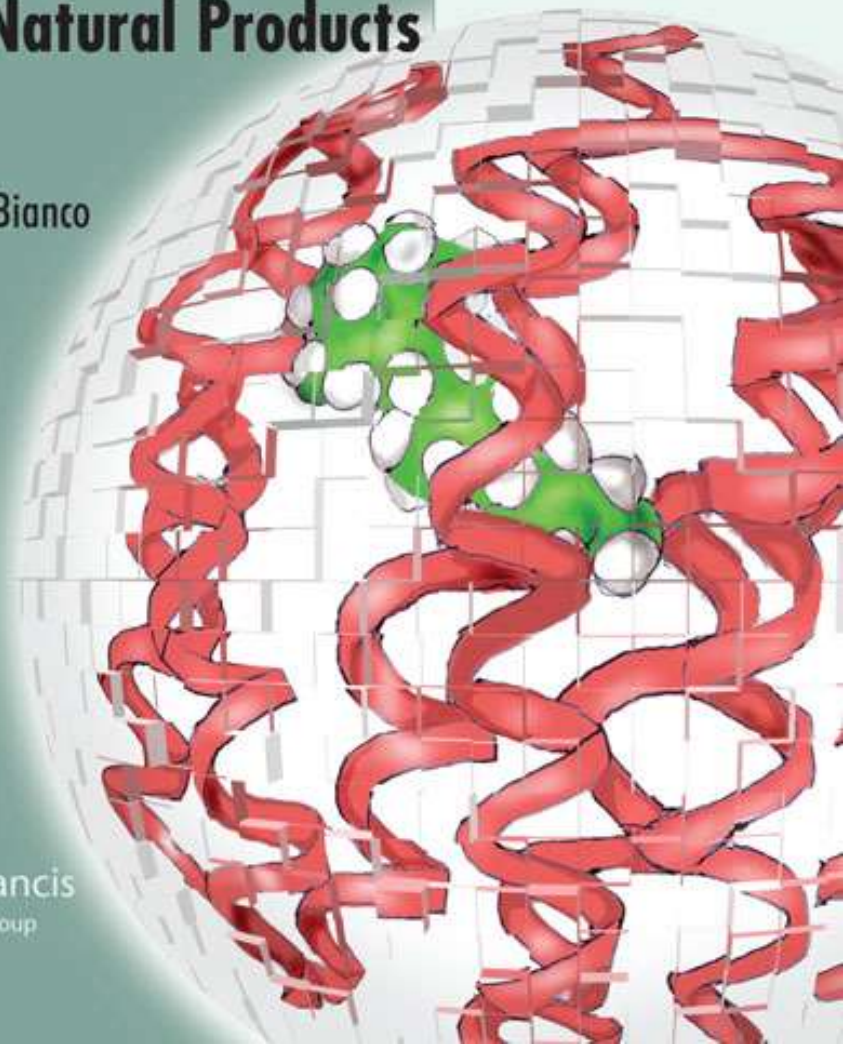

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A new pyrano coumarin from *Clausena excavata* roots displaying dual inhibition against α-glucosidase and free radical

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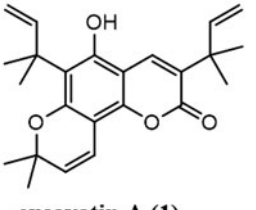
ABSTRACT

A new pyrano coumarin, identified as excavatin A (**1**) together with two known compounds nordentatin (**2**) and binorpocitrin (**3**) was isolated from the 95% EtOH extract of *Clausena excavata*. All structures were elucidated by using spectroscopy methods such as extensive NMR and HR-FAB-MS spectrometry. All the isolated compounds were tested on antidiabetes activity by using α-glucosidase inhibition assay and the antioxidant activity by DPPH assay. Compounds **1-3** showed antioxidant activity with IC_{50} values 0.286, 0.02, 0.278 mM. Among them, **2** exhibited inhibition activity against maltase (IC_{50} 5.45 μM) and sucrase (IC_{50} 43.57 μM). However, compounds (**1**) and (**3**) displayed inhibition on yeast α-glucosidase with IC_{50} values 1.92 and 5.58 mM.

Clausena excavata



excavatin A (1)

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Clausena excavata; pyrano coumarin; inhibition; α-glycosidase; antioxidant; IC50

1. Introduction

Diabetes mellitus (DM) is the common endocrinal disorder and rapidly increasing disease in the human population all over the world. The numbers concerning the

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prevalence of DM are alarming; about 415 million people worldwide are estimated to have diabetes, expected that the numbers will rise to 642 million or more diabetic patients in 2040 (Gothai et al. 2016). Diabetes Mellitus can be classified into clinical categories as: Type 1 Diabetes (T1DM), caused by β-cell destruction and usually leading to absolute insulin deficiency, Type 2 Diabetes (T2DM), due to a defect on the background of insulin resistance, and others such as gestational diabetes and specific types such as monogenic diabetes syndromes, exocrine pancreas diseases, and drug or chemical-induced diabetes (Deepak et al. 2014; Munhoz and Frode 2018). Although obesity and physical inactivity are known to be major risk factors for type 2 diabetes (T2DM), recent evidence suggests that oxidative stress may contribute to the pathogenesis of T2DM by increasing insulin resistance or impairing insulin secretion (Bajaj and Khan 2012). Various studies have shown that diabetes mellitus is associated with increased formation of free radicals and decreases antioxidant potential which, leads to disturbances in the balance between radical formation and protection against which ultimately results in oxidative damage of cell components such as proteins, lipids, and nucleic acids. An increased oxidative stress can be observed in both insulin-dependent (type 1) and non-insulin-dependent diabetes (type 2) (Sindhi et al. 2013). Type 2 diabetes is the predominant form of diabetes and accounts for at least 90% of all cases of diabetes. One of the established therapeutics to treat type 2 diabetes is to control blood glucose levels after eating. Decreased blood glucose levels after eating can be done with delaying the absorption of glucose by inhibiting the enzyme α-glucosidase activity (Cahyani and Purwaningsih 2015). In recent years, some of the standard synthetic drugs used for the treatment of diabetes lead to cause side effects like nausea, vomiting, abdominal pain, diarrhoea, head ache, abnormal weight gain, allergic reaction, low blood glucose, dark urine, fluid retention or swelling. Moreover, they are not safe for use during pregnancy. Active research has been performed on traditional available medicinal plants for discovery of new antidiabetic drug as an alternative for synthetic drugs (Abirami et al. 2014).

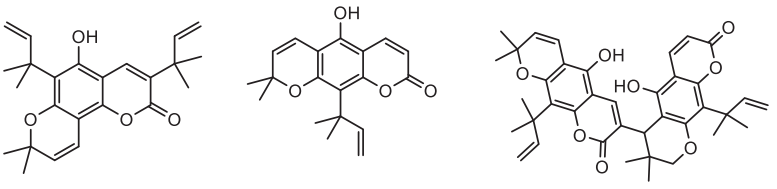
The genus *Clausena* belongs to the Rutaceae family, comprises of about 14 species of evergreen trees (Arbab et al. 2013). *C. excavata* is one the most well-known species in genus *Clausena,* is a shrub with strong and rather objectionable smell, found from the Himalayas and China to and throughout Southeast Asia (Taufiq-Yap et al. 2007). In Myanmar, it is locally known as 'Sat pu Kharyar', 'Taw Pyin Daw Thein'. People in Myanmar usually used this plant to treat headache, itching, flu, snake-bite detoxification. *Clausena spp.* is an abundant source of secondary metabolites, especially carbazole alkaloids, coumarins (furano and pyrano) and few lemonoids (Wu et al. 1999; Ito et al. 2000, Kumar et al. 2012; Liu et al. 2018). Many pharmacologically active compounds isolated from *Clausena* species have been used for the treatment of human diseases such as cardiovascular disease, anti-inflammatory, antioxidants, anti-snake venom, anticancer, anti-HIV, and antiplatelet (Auranwiwat et al. 2014; Arbab et al. 2015; Chakthong et al. 2016; Ma et al. 2017). In addition, *Clausena* species has been found to possess anti-diabetic activity (Damsud et al. 2017). The current research is conducted to isolate bioactive antidiabetic and antioxidant compounds from the roots of *C. excavata*. A new pyrano coumarin (**1**), excavatin A along with two pyrano coumarin, nordentatin (**2**), binorpocitrin (**3**) was isolated. Based on our knowledge, there was

not yet reported on α-glucosidase inhibitory activity and antioxidant activity of these isolated compounds. So we conducted to these bioactive compounds on α-glucosidase inhibition activity by using yeast and rat intestinal (maltase, sucrose) enzymes and antioxidant activity was performed by DPPH assay.

2. Results and discussion

The excavatin-A (**1**) was obtained as a colorless crystal with melting point 261–262 °C and it was assigned the molecular formula, $C_{24}H_{28}O_4$, as deduced from the positive HR-FAB-MS at m/z 381.2058 $[M^+H]^+$ (calcd for $C_{24}H_{28}O_4$, 381.2066). The IR spectrum indicated the presence of hydroxyl (3174 cm^{-1}), conjugated lactone (1670 cm^{-1}) and aromatic (1608, 1591, 1469 cm^{-1}) groups. The UV spectrum showed absorption maxima at 335, 278 and 227 nm due to 7-oxygenated coumarin.

The ^{1}H NMR spectrum (Table S1) displayed the presence of pyrone substituted coumarin was revealed by the aromatic singlet proton at δ_H 7.90 (1H, s, H-4). The existence of olefinic protons of chromene ring was indicated by two peaks at δ_H 6.56(1H, d, $J = 9.9$Hz, H-9) and δ_H 5.66 (1H, d, $J = 9.9$Hz, H-10) respectively. The existence of two pairs of exomethylene protons was displayed at δ_H 6.18 (1H, dd, $J = 16.5$, 10.6 Hz,H-2′) and 5.08(1H, dd, $J = 16.5$, 1.2 Hz,H-3′a), 5.06(1H, dd, $J = 1.2$, 10.6 Hz, H-3′a) and another attached to C-6 was revealed 1,1-dimethyl group at δ_H 6.29 (1H, dd, $J = 17.4$, 10.6 Hz,H-2″), 4.92 (1H, dd, $J = 17.4$, 1.1 Hz,H-3a″) 4.85 (1H, dd, $J = 10.6$, 1.2 Hz,H-3b″). At the aliphatic regions 3 pairs of 1,1 dimethyl group showed three singlets at δ_H 1.42 (s, 6H, H-11a, H-11b), 1.47 (s, 6H, H- 1a′ and 1b′), 1.63 (s, 6H, H- 1a″ and 1b″) (Table S1). The ^{13}C-NMR spectrum of compound (**1**) indicated the presence of one cyclic lactone carbonyl carbon, five sp^2 and three sp^3 quaternary carbons, five methane carbons, two exomethylene carbons and six methyl carbons (Table S1). The 2 D NMR, DQF-COSY spectrum displayed the adjacent proton-proton correlation of three sets of proton pairs δ_H 6.56(H-9) and δ_H 5.66 (H-10), δ_H 6.18 (1H, dd, $J = 16.5$, 10.6 Hz, H-2′) and 5.08(H-3′a), 5.06(H-3′a), δ_H 6.29 (H-2″) and 4.92 (H-3a″) 4.85 (H-3b″) (figure S1). The inter-correlation of basic coumarin with chromene ring and two prenyl groups were confirmed by ^{1}H-^{13}C long range coupling of HMBC spectrum (Figure S6). The HMBC spectrum of compound (**1**) showed some correlation between H-4/C-1′, C-2, C-3, C-5, C-8a. It was revealed that the pyrone substituted coumarin with the position of H-4 proton and the prenyl group that attached to C-3 carbon of pyrone ring. Another prenyl group proton H-1a″, 1b″/C-1″, C-2″, C-6 revealed the attachment of prenyl to C-6 position of core coumarin. ^{1}H-NMR and ^{13}C-NMR of compound (**1**) is similar with clausarin that chromene ring was attached to core coumarin linearly. But in the HMBC spectrum of compound (**1**) strong correlation between H-9 (δ 6.56) to C-8 (δ 106.0),C-8a(δ 146.5) and C-7(δ 154.9) by HMBC spectrum (Figure S6) (Figure S1) showed that chromene ring was angularly connected to core coumarin (Takemura et al. 1996). Moreover, clausarin has to showed correlation between H-11(δ 6.56Hz) with C-6(115.4Hz). The correlation was not found in compound (**1**) (Table S1, figure S6). So it is showed that the structure is more reliable to compound (**1**). The NOESY spectrum of (**1**) showed the cross-peak of H-4 proton with 1,1dimethyl protons H-1a′ and 1b′ and exomethylene protons H-1′. Another cross peak displayed H-10 to H-9,



1 2 3

Figure 1. Structures of isolated compounds from *C. excavata*.

Table 1. α-glucosidase inhibitory activities of isolated compounds **(1-3)**.

	α-Glucosidase			
Compound	Baker's yeast IC_{50} (mM)	Maltase IC_{50} (μM)*	Sucrase IC_{50} (μM)*	DPPH IC_{50} (mM)
1	1.92	NI	NI	0.286
2	37.62	5.45	43.57	0.02
3	5.58	NI	NI	0.278
Acarbose	0.1030	2.35	15.48	—
Ascorbic acid	—	—	—	0.0118

*Nonlinear regression analyzes were evaluated by SigmaPlot 12.5.

H-11a, H-11b and H2″ to H-1a″, H-1b″, H-3″. Hence the structure of compound (**1**) was unambiguously elucidated to be 5-hydroxy-8,8-dimethyl-3,6-bis(2-methylbut-3-en-2-yl)-2H,8H-pyrano[2,3-f]chromen-2-one (Figure 1).

By analysis of the physicochemical properties, NMR, and MS data, and comparison with those reported in the literature, the two known compounds were identified as pyrano coumarin, namely, nordentatin (**2**) and binorpocitrin (**3**) (Sripisut et al. 2012). All compounds were further evaluated for their inhibitory effects against α-glucosidase such as baker's yeast and rat intestinal (maltase and sucrose) α-glucosidase and antioxidant activity were measured by DPPH assay (Table 1). All compounds **1-3** exhibited radical scavenging activity with IC_{50} values 0.286, 0.02, 0.278 mM and displayed against sucrase with IC_{50} values 1.92, 37.62 and 5.58 mM respectively. However, in maltase α- glucosidase assay nordentatin (**2**) showed inhibition 5.45 μM but compound **1** and **3** showed no inhibition.

3. Experimental

3.1. Plant material

The roots of *C. excavata* were collected from Pyin Ma Nar Township, Mandalay Division, Myanmar in October 2016. The plant materials were authenticated by Prof. Soe Myint Aye, botanist from Department of Botany, Mandalay University, Myanmar, where the voucher specimen (UM-22032018) was deposited.

3.2. Extraction and isolation

The dried roots (3.6 kg) were extracted successively with 95% EtOH (12.0 L) over a period of two weeks at room temperature. Removal of the solvent under reduce pressure gave 156 g of dark gummy extracts. The extract (100g) was partitioned three times using solvents; *n*-hex: methanol (1:1, v/v) successfully. Then methanol portion (80.4 g) was fractionationated by vacuum liquid chromatography over silica gel eluted

with different mixtures of *n*-hex: EtOAc by stepwise increasing gradient polarity gave a total of 7 combined fractions (MF-1 to -7) were obtained. Among them the pale yellow crystals were come out from the combine fraction MF-5. After washing with ethyl acetate the pure compound nordentatin (**2**, 2.1 g) was afforded. The sub fraction MF-2 was fractionated by silica gel column eluting with gradient polarity *n*-hex: EtOAc, (0-10% EtOAc) afforded new compound, excavatin A (**1**, 68 mg). The fraction MF-6 (25.6 g) was subjected to VLC chromatography with *n*-hex:EtOAc (EtOAc, 10-100%) with gradient polarity and afforded 23 subfraction and after combining same component fractions gave (MF-6.1 to 6.7). Fraction MF-6.2 (3.4 g) was subjected to silica gel column chromatography with three solvent system (*n*-hex:$CHCl_3$:EtOAc/100- 70: 5-20:5-20) afforded a total of 300 fractions. White amorphous solid was come out from 201-215 and yielded pure compound, binorponcitrin (**3**, 138 mg).

Excavatin A, colorless crystal, mp. 261-262 °C; UV (MeOH), λ_{max} (logε) 335 (1.23), 279 (2.08), 228 (1.53). FT-IR (KBr) cm^{-1}: 3174, 2968, 1670, 1608, 1591, 1570, 1465, 1379, 1340, 1186, 1147, 1026, 908, 891. ^{1}H NMR and ^{13}C NMR data see (Table S1), HR-FAB-MS (*m/z* [M^+] H^+) 381.2058, (calcd for $C_{24}H_{28}O_4$, 381.2066).

4. Conclusion

In summary, three compounds were isolated from Myanmar medicinal plant *C. excavata* including a new pyrone substituted coumarin (**1**) together with two known bioactive compounds (**2-3**). The examination of all isolated compounds was done on antidiabetes activity by using α-glucosidase inhibition assay and the antioxidant activity was conducted by DPPH assay. Of isolated compounds, **2** exhibited inhibition activity against maltase (IC_{50} 5.45 μM) and sucrase (IC_{50} 43.57 μM) respectively. However, compounds (**1**) and (**3**) displayed inhibition on yeast α-glucosidase with IC_{50} values 1.92, and 5.58 mM. Moreover, all isolated compounds showed high antioxidant activity with IC_{50} values values 0.286, 0.02, 0.278 mM respectively. According recent study, isolated components from root of *C. excavata* can be candidate of natural antidiabetes and antioxidant.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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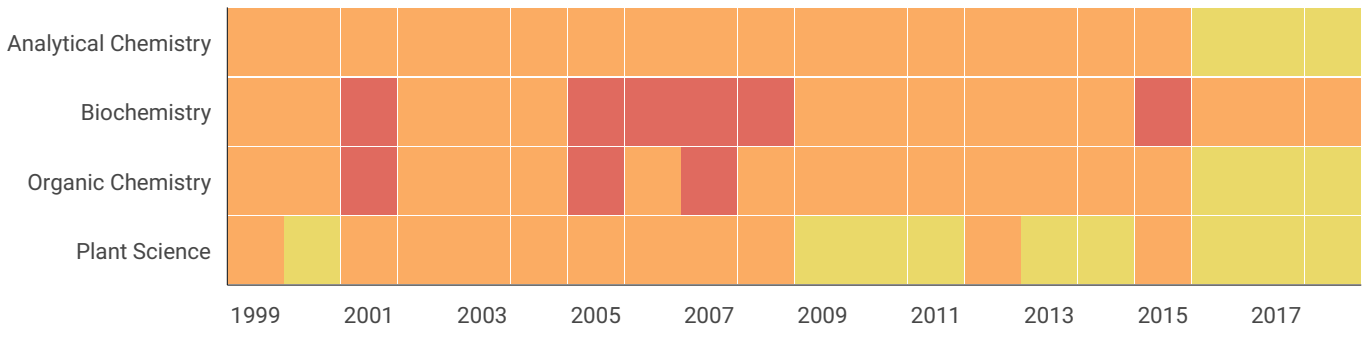

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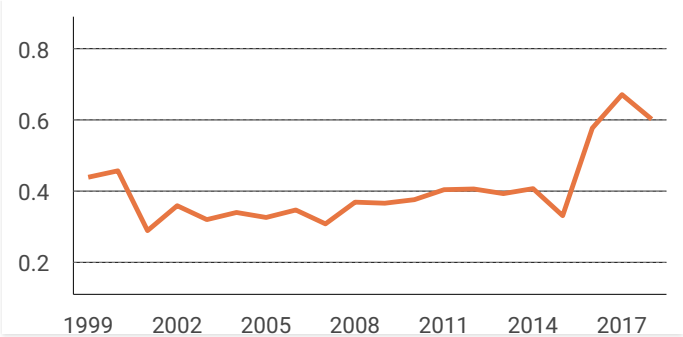

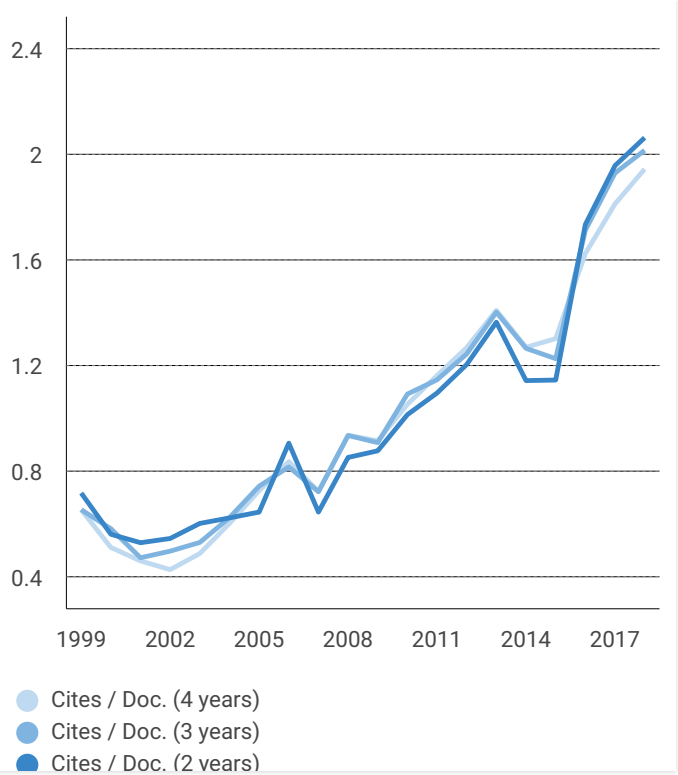

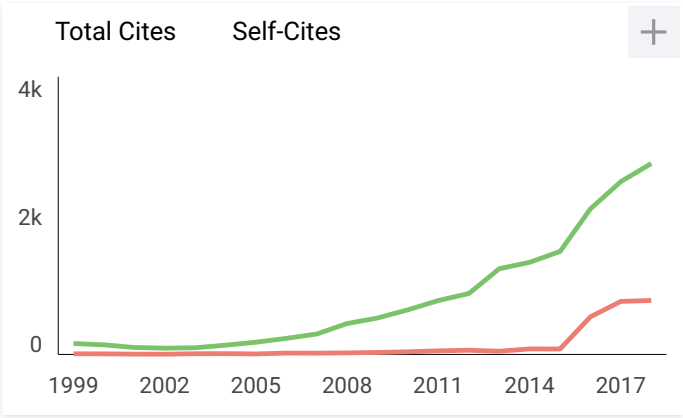

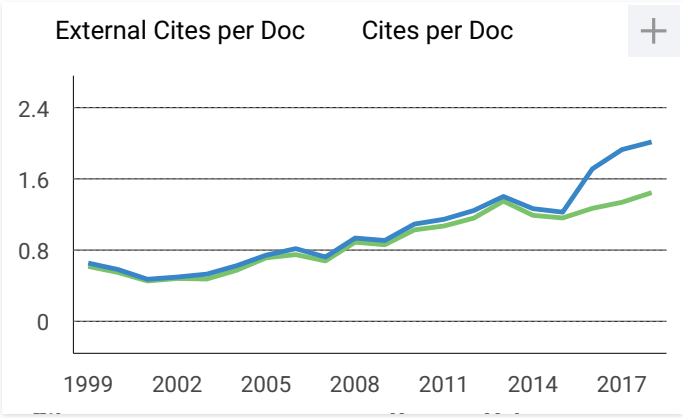

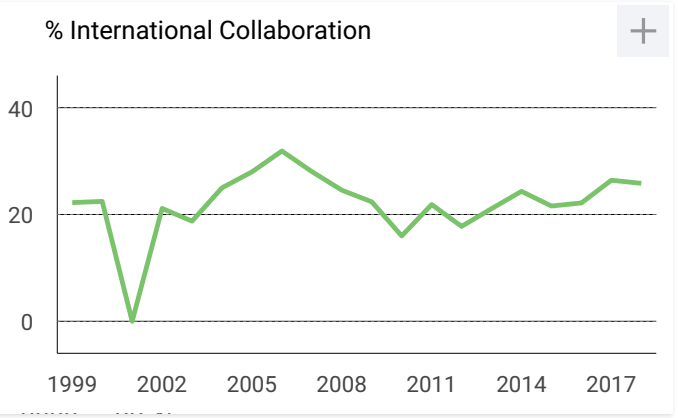

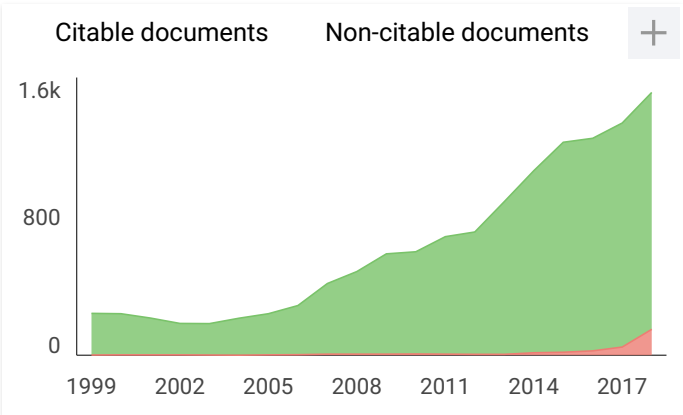

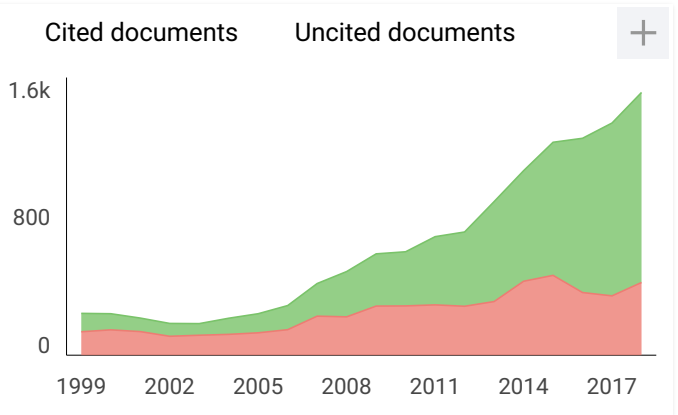

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E. Tramontano - Italy
B. M. Trost - USA
R. Verpoorte - Netherlands
W. Voelter - Germany
H. Wagner - Germany
P. G. Waterman - Australia
J. D. White - USA
K. R. Zeller - Germany

UNTUK INDONESIA ADIL & BERADAB

nanik siti aminah <nanik-s-a@fst.unair.ac.id>

Natural Product Research - Manuscript ID GNPL-2018-3087.R2

1 message

Natural Product Research <onbehalfof@manuscriptcentral.com> Mon, Feb 4, 2019 at 3:23 PM
Reply-To: alessandro.venditti@gmail.com
To: nanik-s-a@fst.unair.ac.id, naniksa2000@gmail.com
Cc: tin.myo.thant-2017@fst.unair.ac.id, nanik-s-a@fst.unair.ac.id, naniksa2000@gmail.com, alfinda-n-k@fst.unair.ac.id, rico.ramadhan@fst.unair.ac.id, preecha.p@chula.ac.th, ytakaya@meijo-u.ac.jp

*******This is an automated email generated by the Natural Product Research ScholarOne Manuscripts site*******

04-Feb-2019

Dear Dr Aminah:

Your manuscript entitled "A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical" has been successfully submitted online and is presently being given full consideration for publication in Natural Product Research.

Your manuscript ID is GNPL-2018-3087.R2.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://mc.manuscriptcentral.com/gnpl and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Centre after logging in to https://mc.manuscriptcentral.com/gnpl.

Thank you for submitting your manuscript to Natural Product Research.

Sincerely,
Natural Product Research Editorial Office

nanik siti aminah <nanik-s-a@fst.unair.ac.id>

GNPL-2018-3087.R2 Assigned to Editor

1 message

Natural Product Research <onbehalfof@manuscriptcentral.com> Wed, Feb 6, 2019 at 4:18 AM
Reply-To: alessandro.venditti@gmail.com
To: nanik-s-a@fst.unair.ac.id, naniksa2000@gmail.com

05-Feb-2019

Dear Dr Aminah,

This is a message to confirm that your revised manuscript GNPL-2018-3087.R2 "A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical" is being considered for publication in Natural Product Research and has been assigned to Professor Armandodoriano Bianco to serve as the editor.

Once Professor Bianco is able to make a decision on your revised paper, we will contact you with a decision letter as soon as possible.

Thank you for revising your work and we look forward to bringing you a decision on your manuscript as soon as possible.

Best regards,
Dr Alessandro Venditti
Editorial Office | Natural Product Research
https://mc.manuscriptcentral.com/gnpl
alessandro.venditti@gmail.com

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nanik siti aminah <nanik-s-a@fst.unair.ac.id>

Natural Product Research - Decision on Manuscript ID GNPL-2018-3087.R1

2 messages

Natural Product Research <onbehalfof@manuscriptcentral.com> Thu, Jan 31, 2019 at 11:31 PM
Reply-To: armandodoriano.bianco@uniroma1.it
To: nanik-s-a@fst.unair.ac.id, naniksa2000@gmail.com

31-Jan-2019

Dear Dr Aminah,

Thank you for resubmitting your paper to Natural Product Research.

I am delighted to inform you that your paper has now been accepted by the Natural Product Research, subject to revision along the lines suggested below, and the reviewer comments at the end of this letter.

We will be in touch with you again with further details closer to the date of publication.

I would be grateful if you could now provide a final paper following (Journal) guidelines, with a Title page containing authors affiliation and e-mail address (page 1), followed by Abstract and Key Words (page 2), and full text, all in the same document. Only tables and figures are to be included as a separate document.
To provide your final version, please click on the link below:

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https://mc.manuscriptcentral.com/gnpl?URL_MASK=8843542762b542e78343e4c04eaaa453

This will direct you to the first page of your revised manuscript. This link will remain active until you have submitted your revised manuscript. If you begin a revision and intend to finish it at a later time, please note that your draft will appear in the “Revised Manuscripts in Draft” queue in your Author Centre.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we aim for the timely publication of manuscripts submitted to Natural Product Research, please upload your revised manuscript as soon as possible and before 02-Mar-2019.

Once again, thank you for submitting your manuscript to Natural Product Research and I look forward to receiving your revision.

Sincerely,
Professor Bianco
Editor-in-Chief, Natural Product Research
armandodoriano.bianco@uniroma1.it

Reviewer(s)' Comments to Author:

Editorial Office:

The figures/tables which will appear in the main document should be submitted in single copy as individual files provided with captions, and not embedded in the main document.

Reviewer: 1

Comments to the Author
It can be accepted for publishion in present form.

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nanik siti aminah <nanik-s-a@fst.unair.ac.id> Fri, Feb 1, 2019 at 3:40 AM
To: tin myo <tin.myo.thant-2017@fst.unair.ac.id>, ramadhan Rico <rico.ramadhan@fst.unair.ac.id>, alfinda novi kristanti <alfinda-n-k@fst.unair.ac.id>

---------- Forwarded message ---------
From: **Natural Product Research** <onbehalfof@manuscriptcentral.com>
Date: Thu, 31 Jan 2019, 23:31
Subject: Natural Product Research - Decision on Manuscript ID GNPL-2018-3087.R1
To: <nanik-s-a@fst.unair.ac.id>, <naniksa2000@gmail.com>

31-Jan-2019

Dear Dr Aminah,

Thank you for resubmitting your paper to Natural Product Research.

I am delighted to inform you that your paper has now been accepted by the Natural Product Research, subject to revision along the lines suggested below, and the reviewer comments at the end of this letter.

We will be in touch with you again with further details closer to the date of publication.

I would be grateful if you could now provide a final paper following (Journal) guidelines, with a Title page containing authors affiliation and e-mail address (page 1), followed by Abstract and Key Words (page 2), and full text, all in the same document. Only tables and figures are to be included as a separate document.
To provide your final version, please click on the link below:

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Sincerely,
Professor Bianco
Editor-in-Chief, Natural Product Research
armandodoriano.bianco@uniroma1.it

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Reviewer: 1

Comments to the Author
It can be accepted for publishion in present form.

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Manuscripts with Decisions

ACTION	STATUS	ID	TITLE	SUBMITTED	DECIS
	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Accept (20-Feb-2019) view decision letter	GNPL-2018-3087.R2	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical View Submission	04-Feb-2019	20-Feb
a revision has been submitted (GNPL-2018-3087.R2)	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Conditional Accept (31-Jan-2019) • a revision has been submitted view decision letter	GNPL-2018-3087.R1	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical View Submission	14-Jan-2019	31-Jan
a revision has been submitted (GNPL-2018-3087.R1)	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Major Revision (29-Dec-2018) • a revision has been submitted view decision letter	GNPL-2018-3087	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical View Submission	07-Dec-2018	29-Dec
a resubmission has been submitted (GNPL-2018-3087)	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Reject & Resubmit (05-Dec-2018) • a resubmission has been submitted view decision letter	GNPL-2018-2760	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-Glucosidase and free radical View Submission	08-Nov-2018	05-Dec

Author Dashboard

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	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Accept (20-Feb-2019) view decision letter	GNPL-2018-3087.R2	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical View Submission	04-Feb-2019	20-Feb
a revision has been submitted (GNPL-2018-3087.R2)	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Conditional Accept (31-Jan-2019) • a revision has been submitted view decision letter	GNPL-2018-3087.R1	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical View Submission	14-Jan-2019	31-Jan
a revision has been submitted (GNPL-2018-3087.R1)	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Major Revision (29-Dec-2018) • a revision has been submitted view decision letter	GNPL-2018-3087	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-glucosidase and free radical View Submission	07-Dec-2018	29-Dec
a resubmission has been submitted (GNPL-2018-3087)	EO: Bianco, Armandodoriano EO: Venditti, Alessandro • Reject & Resubmit (05-Dec-2018) • a resubmission has been submitted view decision letter	GNPL-2018-2760	A new pyrano coumarin from Clausena excavata roots displaying dual inhibition against α-Glucosidase and free radical View Submission	08-Nov-2018	05-Dec