ABSTRACT
The phytochemical study on the dichloromethane extract of Neolamarckia cadamba (Roxb.) Bosser has afforded two indole alkaloids, (+)-neocadambine A (1) and (-)-nauclederine (2). Their structures were confirmed by extensive spectroscopic analysis and by comparing with the reported data. (+)-Neocadambine A (1) and (-)-nauclederine (2) exhibited potent inhibition activity of advanced glycation end products (AGEs) with IC\textsubscript{50} values of 1.2 and 0.95 mM, respectively, while the latter was almost two times more potent than the standard, aminoguanidine (1.8 mM). This is the first report on the compounds isolated from this plant with AGEs inhibition activity. In addition, (-)-nauclederine (2) was isolated for the first time in the genus of Neolamarckia. Complete \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR of compound 2 were also reported.

Keywords: Advanced glycation end products; indole alkaloid; (-)-nauclederine; (+)-neocadambine A; Neolamarckia cadamba

INTRODUCTION
Rubiaceae is one of the largest families of angiosperms and consists of approximately 600 genera and more than 10,000 species (Silva et al. 2010). The Rubiaceae family is characterized by the production of bioactive metabolites such as alkaloid as secondary metabolite with diverse
Examples of pharmacological properties exhibited by the metabolites of Rubiaceae plants are antimicrobial (Sultana et al. 2015), anti-diabetic (Habtemariam 2019) and anti-inflammatory activities (Qureshi et al. 2011).

*Neolamarckia cadamba* (Roxb.) Bosser, locally known as Laran, is a tree of moderate size found in Malaysia (Qureshi et al. 2011). *N. cadamba* is widely used in Indian traditional formulations in which the leaves decoction was consumed for the treatment of ulcers and wounds since many years ago (Verma et al. 2018). According to Pandey and Negi (2016), the fruit has a cooling effect and has been used for quenching thirst during high fever as prescribed by Charaka Samhita (Pandey & Negi 2016). Besides, the fruit of *N. cadamba* has also been used in different food preparations by tribal people (Pandey & Negi 2016).

Various extracts of *N. cadamba* such as ethanol and hydroethanolic extracts have beneficial effects in reducing the elevated blood glucose level of hyperglycemic mice (Ahmed et al. 2011; Alam et al. 2011). For example, an anti-diabetic study showed that the hydroethanolic fruit extract (400 mg/kg) had higher hypoglycemic activity than standard drug glibenclamide (0.6 mg/kg) in alloxan induced diabetic Swiss albino rats (Alam et al. 2011).

Maillard reaction which often known as nonenzymatic browning reaction is implicated in the development of pathophysiology in age-related diseases such as diabetes mellitus (Thorpe & Baynes 1996). Maillard reaction led to advanced glycation end products (AGEs) through a series of non-enzymatic, sequential and parallel reactions, which can be divided into two stages. The early glycation was reversible and involves the production of a Schiff base from the carbonyl group of a reducing sugar and the primary amino groups of a protein (lysine, arginine). The imine adduct undergoes rearrangement to form Amadori products such as HbA1c (glycated haemoglobin), which widely used as a diabetes control marker (Wolfenbuttel et al. 1996). During the late stage, complex irreversible oxidation, dehydrogenation and cyclization reactions lead to AGEs via intra- and intermolecular protein cross-linking (Boisard et al. 2014; Peyroux & Sternberg 2006; Poulsen et al. 2013; Reddy & Beyaz 2006).

AGE accumulation occurs in healthy person but the AGEs level is higher for those patients who have hyperglycemia and diabetes or in condition involving oxidative stress (Luevano-Contreras & Chapman-Novakofski 2010; Vlassara & Uribarri 2014). AGEs are associated with many pathogenic disorders such as pathogenesis of diabetes (Brownlee 2001; Singh et al. 2001; Wada & Yagihashi 2005), atherosclerosis (de Leeuw et al. 2005; Jandelevit-Dahm & Cooper 2008), neurological diseases such as Alzheimer’s disease (Takeuchi & Yamagishi 2008) or joint diseases (DeGroot 2004). AGEs are also responsible for aging, tissue and skin damages (Grillo & Colombatto 2008) as well as autoimmune diseases (Kurien et al. 2006). This consideration has driven the scientific community to identify and develop new AGE inhibitors that are able to prevent oxidation using free radical scavengers or transition metal chelators in order to trap reactive dicarbonyl species or to break AGE cross-linking (Elosta et al. 2012; Reddy & Beyaz 2006). By addressing to this issue, finding natural products possess anti-AGE properties with free of or fewer side effects are critically needed.

Our group has conducted an AGEs inhibitory assay on several plant extracts and the dichloromethane extract of the bark of *N. cadamba* displayed a strong anti-AGEs effect similar to the standard, aminoguanidine (0.15 mg/mL). This result has prompted us to conduct the present study. Hence, we shall report the isolation and elucidation of (+)-neocadambine A and (-)-nauclederine (2) together with their anti-AGEs activity. To the best of our knowledge, this is the first report on the anti-AGES effect of indole alkaloid extracted from *N. cadamba*.

**MATERIALS AND METHODS**

**GENERAL EXPERIMENTAL PROCEDURES**

The 1D-and 2D-NMR spectra were recorded deuterated methanol (CD$_3$OD) and deuterated pyridine (C$_6$D$_5$N) BRUKER Advance III 600 NMR spectrometers. Chemical shifts (δ$_n$ and δ$_e$) are expressed in ppm and J values in Hz. The HR-ESI-MS spectra were obtained from Agilent 6530 Accurate-Mass Q-TOF with electrospray ionization (ESI) (Santa Clara, CA, USA). Ultraviolet spectra were obtained in spectroscopic grade methanol with Shimadzu UV-250 UV-visible spectrometer. IR spectra were recorded on a Perkin Elmer Spectrum 1600 FTIR Spectrometer with spectroscopic grade chloroform as the solvent. A Jasco P-1020 polarimeter was used to record the optical rotation. Recycling High Performance Liquid Chromatography (RHPLC) with JAIGEL-ODS-AP, SP-120-15 reversed phase column was used for purification of compound. In the column chromatography, silica gel 60 F$_{254}$ was used for thin layer chromatography (TLC). Silica gel 60 F$_{254}$ plates backed by glass and aluminium were used for TLC. All solvents are AR grade except those used for bulk extraction.
PLANT MATERIAL
The bark of *N. cadamba* (Roxb.) Bosser was collected from Empangan Sg. Sunda Jeli, Kelantan, Malaysia. The voucher specimens (KL 5696) were deposited at the Herbarium of Department of Chemistry, Faculty of Science, Universiti Malaya, Kuala Lumpur, Malaysia.

EXTRACTION, FRACTIONATION, PURIFICATION AND ISOLATION OF COMPOUNDS
Dried and ground bark of the *N. cadamba* (1.8 kg) were defatted with hexane (10 L) for three days at room temperature. The hexane extract was filtered and dried using rotary evaporator. After that, the plant materials were moistened with ammonia solution and soaked for 4 h. The plant material was then re-extracted with dichloromethane (30 L) for three days. After the extract was filtered and dried using rotary evaporator, 17.5 g of dichloromethane extract was obtained. The plant materials were soaked again with methanol (28 L) for three days and the extract was dried using rotary evaporator. An amount of 70.0 g of methanol extract was obtained. The dichloromethane extract (1.75 g) was subjected to column chromatography over silica gel using dichloromethane and methanol solvent (100:0, 95:5, 90:10, 80:10 and 0:100) to obtain 5 fractions. Further purification of fraction 3 (20 mg/mL) using HPLC yielded alkaloid 1 (4.9 mg, flow rate 5 mL/min: isocratic: 100% MeOH, injection volume 3 mL). Alkaloid 2 (7.7 mg, MeOH-CHCl3; 100:0) was purified from fraction 3 by column chromatography C18.

(+)–Neocadambine A (1): yellow amorphous solid; +17.14° (c 0.07, MeOH); UV (MeOH) λ<sub>max</sub> 213, 227, 305 nm; 1H NMR and 13C NMR see Table 1; HRESIMS m/z 366.1466 [M + H]+ (calcd for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>) 366.1454.

(-)–Nauclederine (2): yellow amorphous solid; -6.67° (c 0.06, MeOH); UV (MeOH) λ<sub>max</sub> 214, 244, 291, 313 nm; 1H NMR and 13C NMR see Table 2; HRESIMS m/z 322.1546 [M + H]+ (calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>) 322.1556.

ADVANCED GLYCATION END PRODUCTS (AGES)
INHIBITORY ACTIVITY
IC<sub>50</sub> values were determined as described by Derbré et al. (2010) and Séro et al. (2013). Briefly, bovine serum albumin (BSA) (10 mg/mL) was incubated with D-ribose (0.5 M) together with the tested compound (3 µM to 3 mM) or extract (1 µg to 1 mg) in 50 mM phosphate buffer at pH 7.4 (NaN<sub>4</sub>, 0.02%). Solutions were incubated in 96-well microtiter plates at 37 °C for 24 h in a closed system before AGE fluorescence measurement. Fluorescence resulting from the incubation, under the same BSA (10 mg/mL) and tested compound (3 µM to 3 mM) or extract (1 µg to 1 mg) conditions, was subtracted for each measurement. A control (i.e. no inhibition of AGE formation) consists of wells with BSA (10 mg/mL) and D-ribose (0.5 M). A blank control (i.e. 100% inhibition of AGE formation) consists in wells with only BSA in buffer (10 mg/mL). The final assay volume was 100 µL. Pentosidine-like (λ<sub>exc</sub> 355 nm, λ<sub>em</sub> 385 nm) AGE fluorescence was measured using a microplate spectrofluorometer. Aminoguanidine was used as a standard. In this type of automation, a single analysis is sufficient for an accurate IC<sub>50</sub> determination (Derbré et al. 2010; Séro et al. 2013). The percentage of AGE formation for each compound or extract concentration was calculated as follows: Dose-effect curves are best fitted with a sigmoidal dose response equation using Sigma Plot 12.0 software which enables calculation of the IC<sub>50</sub> values.

RESULTS AND DISCUSSION
Compound 1 was isolated as a yellowish amorphous solid with the molecular formula of C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>, as determined by molecular ion peak positive-mode HR-ESI-MS which showed a pseudomolecular ion peak [M+H]+ at m/z 366.1466 (calcd. 366.1454). The UV spectrum showed absorption bands at 313, 291, 244, and 214 nm. The IR spectrum exhibited absorption at 313, 291, 244, and 214 nm. The IR spectrum exhibited absorption at 1642 cm<sup>-1</sup> indicating the presence of lactam carbonyl functionality (Hu et al. 2009). Thorough analysis of all spectra data (Table 1) and comparison with literature data (Yuan et al. 2020) led to the conclusion that compound 1 has the similar structure with neocadambine A (Figure 1). However, the optical rotation signs of compound 1 is positive which is opposite to the sign in neocadambine A. This difference implied that compound 1 is the enantiomer of neocadambine A. Hence, the relative configuration of C-19 in compound 1 will be the opposite of that in neocadambine A. The connectivity between all the carbons and protons were established thorough analysis of COSY, HSQC and HMBC spectra (Table 1, Figure 2). H-19 in compound 1 appeared as doublet of doublet with coupling constant of 7.0 and 4.0 Hz, respectively. Besides, neocadambine A was reported...
with negative optical rotation while compound 1 is with positive optical rotation. Hence, compound 1 is named as (+)-neocadambine.

Compound 2 was isolated as a yellowish amorphous solid. The molecular formula of C_{19}H_{19}N_{3}O_{2} was determined by positive HR-ESI-MS which showed a pseudomolecular ion peak [M+H]^+ at m/z 322.1546 (calculated 322.1556). The UV spectrum showed absorption at 305, 227, and 213 nm. In the IR spectrum, an absorption band of the NH stretching vibration was observed at 3250 cm⁻¹. The ¹H-NMR spectrum (Table 2) of this alkaloid showed the presence of indole moiety by exhibiting two doublets signals at δ_H 7.47 (1H, d, J = 7.7 Hz, H-10) and δ_H 7.20 (1H, d, J = 7.7 Hz, H-13) as well as two triplet of doublets signals at δ_H 7.00 (1H, td, J = 7.7, 1.1 Hz, H-11) and δ_H 7.04 (1H, td, J = 7.7, 1.1 Hz, H-12) in the aromatic region (Wang et al. 2015). Besides, three proton signals were observed in the deshielded region at δ_H 8.16 (1H, t, J = 2.0 Hz, H-16), δ_H 8.96 (1H, d, J = 2.0 Hz, H-18) and δ_H 8.55 (1H, d, J = 2.0 Hz, H-20). These three proton signals; H-16, H-18 and H-20 correlated with the carbon signals of δ_C 138.9, δ_C 149.5 and δ_C 154.3, respectively, in the HSQC spectrum, thus implying the presence of 3,5-disubstituted pyridine moiety. In addition, a singlet proton signal was observed at δ_H 3.90, corresponding to the methoxy group of C-22 (δ_C 53.1). The ¹³C-NMR (Table 2) and DEPT spectra showed nineteen carbon signals, i.e. one carbonyl carbon, six quaternary carbons, eight methines, three methylenes and one methyl. The HMBC spectrum (Figure 3) showed correlations of H-4 with C-2 and C-6, H-6 with C-4 and C-8, H-7 with C-2 and C-8 indicated that the azepane unit is fused to the indole ring through C-2 and C-8. Moreover, the methoxy proton, H_3-22 correlated with the carbonyl carbon of C-21 (δ_C 167.0) which can be observed in HMBC spectrum signifying the existence of methyl ester group. The linkage of this methyl ester group to the pyridine (ring D) through C-17 (δ_C 128.0) was
supported by the HMBC correlations of H-18 with C-17, H-16 and H-18 with C-21. Furthermore, correlations of H-4 with C-3 and C-15, H-3 with C-16 and C-20, H-20 with C-15, H-16 and H-20 with C-3 indicated that the pyridine unit was connected to the azepinoindole skeleton through C-3. From the analysis of the spectroscopic data obtained and by comparison with the limited reported data, the structure of (-)-nauclederine (2) was established. This compound was previously isolated from *Nauclea diderrichii* in 1971 and had been synthesized in 1976 (McLean et al. 1976; Murray et al. 1972). However, there is no thorough spectroscopic data being reported.

**TABLE 1.** ¹H-NMR (600 MHz) and ¹³C-NMR (150 MHz) of (+)-neocadambine A (1) in CD₅N

| Position | ¹H (δ, multiplicity, J in Hz) | ¹³C (δ) (ppm) | HMBC (H→C) |
|----------|-----------------------------|---------------|------------|
| NH-1     | 14.51 (s)                   | -             | -          |
| 2        | -                           | 128.2         | Quaternary |
| 3        | -                           | 170.6         | Quaternary |
| 5a       | 4.09-4.12 (m)               | 54.2          | Methylene  |
| 5b       | 4.20-4.23 (m)               |               |            |
| 6        | 3.10-3.16 (m)               | 20.2          | Methylene  |
| 7        | -                           | 124.5         | Quaternary |
| 8        | -                           | 124.7         | Quaternary |
| 9        | 7.55 (d, 7.9)               | 122.3         | Methine    |
| 10       | 7.14 (t, 7.9)               | 122.3         | Methine    |
| 11       | 7.42 (t, 7.9)               | 129.6         | Methine    |
| 12       | 8.19 (d, 7.9)               | 115.0         | Methine    |
| 13       | -                           | 143.2         | Quaternary |
| 15       | 8.94 (t, 1.9)               | 136.1         | Methine    |
| 16       | -                           | 126.6         | Quaternary |
| 17       | 9.39 (d, 1.9)               | 150.9         | Methine    |
| 18a      | 4.89 (dd, 13.8, 4.0)        | 62.3          | Methylene  |
| 18b      | 5.10-5.30 (overlapping signal) |           |            |
| 19       | 5.96 (dd, 7.0, 4.0)         | 69.9          | Methine    |
| 20       | -                           | 137.9         | Quaternary |
| 21       | 9.59 (d, 1.9)               | 153.4         | Methine    |
| 22       | -                           | 166.2         | Quaternary |
| 23-OCH₃  | 3.83 (s)                    | 52.6          | Methyl     |
TABLE 2. ¹H-NMR (600 MHz) and ¹³C-NMR (150 MHz) of (-)-nauclederine (2) in CD₃OD

| Position | ¹H (δ) (multiplicity, J in Hz) | ¹³C (δ) (in ppm) | HMBC (H→C) |
|----------|-------------------------------|------------------|-------------|
| 2        | -                             | 136.4            | Quaternary  |
| 3        | 4.50 (dd, 4.9, 3.4)           | 46.5             | Methine     |
|          |                               |                  | C4, C8, C16, C20 |
| 4a       | 3.36 (dd, 13.7, 3.3)          | 56.2             | Methylene   |
|          |                               |                  | C2, C6, C15 |
| 4b       | 3.45 (dd, 13.7, 4.9)          |                  |             |
| 6a       | 2.98-3.02 (m)                 | 51.1             |             |
| 6b       | 3.27-3.30 (m)                 |                  |             |
| 7        | 3.05-3.09 (m)                 | 28.0             | Methylene   |
|          |                               |                  | C2, C6, C8, C9 |
| 8        | -                             | 114.4            |             |
| 9        | -                             | 130.2            |             |
| 10       | 7.47 (d, 7.7)                 | 119.0            | Methine     |
|          |                               |                  | C8, C12, C14 |
| 11       | 7.00 (d, 7.7, 1.1)            | 119.9            | Methine     |
|          |                               |                  | C9, C13     |
| 12       | 7.04 (d, 7.7, 1.1)            | 122.5            | Methine     |
|          |                               |                  | C10, C14    |
| 13       | 7.20 (d, 7.7)                 | 111.8            | Methine     |
|          |                               |                  | C9, C11     |
| 14       | -                             | 137.3            |             |
| 15       | -                             | 140.0            |             |
| 16       | 8.16 (t, 2.0)                 | 138.9            | Methine     |
|          |                               |                  | C3, C18, C20, C21 |
| 17       | -                             | 128.0            |             |
| 18       | 8.96 (d, 2.0)                 | 149.4            | Methine     |
|          |                               |                  | C16, C17, C20, C21 |
| 20       | 8.55 (d, 2.0)                 | 154.3            | Methine     |
|          |                               |                  | C3, C15, C17, C18 |
| 21       | -                             | 167.0            |             |
| 22       | 3.90 (s)                      | 53.1             | Methyl      |
|          |                               |                  | C21         |
Both compounds; (+)-neocadambine A (1) and (-)-nauclederine (2), have been tested for AGEs inhibitory effect and the IC\textsubscript{50} values calculated are 1.2 and 0.95 mM, respectively (Table 3). Interestingly, both compounds were more potent AGEs inhibitors as compared to the standard aminoguanidine (IC\textsubscript{50} = 1.8 mM). Therefore, from the above results, both alkaloids; (+)-neocadambine A (1) and (-)-nauclederine (2), can be potential lead compounds for the development of therapeutic agents for the prevention of AGEs formation.

TABLE 3. The IC\textsubscript{50} values of three different extracts of \textit{N. cadamba}, (+)-neocadambine A (1), (-)-nauclederine (2) and aminoguanidine (standard)

| Extracts/Compounds       | IC\textsubscript{50} (mg/mL) | IC\textsubscript{50} (mM) |
|-------------------------|-------------------------------|--------------------------|
| Hexane                  | > 1.0                         | -                        |
| Dichloromethane         | 0.15                          | -                        |
| Methanol                | > 1.0                         | -                        |
| (+)-Neocadambine A (1)  | -                             | 1.2                      |
| (-)-Nauclederine (2)    | -                             | 0.95                     |
| Aminoguanidine (standard)| 0.15                          | 1.8                      |

CONCLUSIONS
In conclusion, the current study has yielded two compounds; (+)-neocadambine A (1) and (-)-nauclederine (2) from the dichloromethane extract of the bark of \textit{N. cadamba} which demonstrated high potency in inhibiting AGEs formation. (-)-Nauclederine (2) exhibited twice the potency of aminoguanidine which is a prototype therapeutic agent for the prevention of the formation of AGEs.

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