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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

N^2-Methylaurantiamide acetate: a new dipeptide from *Mimusops elengi* L. flowers

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Abstract

Mimusops elengi L. belonging to the *Sapotaceae* family is used in various folk systems of medicine in South and Southeast Asia. This study aims to identify the potential constituents responsible for anticancer activity of *M. elengi* flowers. The EtOAc fraction of *M. elengi* flowers methanolic extract possessed cytotoxicity and gave an intensive apoptotic response on human leukemia HL-60 cells. A new dipeptide N^2-methylaurantiamide acetate was isolated from the fraction along with two peptide derivatives and four phenolic compounds. Among the peptide constituents, N^2-methylaurantiamide acetate showed significant inhibition of cell proliferation and possible induction of apoptotic cell death. Molecular docking analysis demonstrated that N^2-methylaurantiamide acetate could fit tightly into the BH3-binding groove of anti-apoptotic protein Bcl-2. Our results provide further compelling evidence and enhance the ethnopharmacological value of *M. elengi*.

Keywords *Mimusops elengi* L · N^2-Methylaurantiamide acetate · Anticancer activity · Apoptosis · Bcl-2 protein

Introduction

For the past 3000 years, a large number of plants are used in healthcare practices (De Smet 1997; Tariq 2004). Natural products play a central role as the source of innovative therapeutic agents for treating various diseases and disorders for a long time (Koehn and Carter 2005; Mishra and Tiwari, 2011; Butler et al. 2014). Over 60% of anticancer drugs in clinical use originate from natural products (Newman and Cragg, 2012). Various folk systems of medicine using medicinal plants have held paramount potential in cancer therapeutics (Graham et al. 2009; Wang et al. 2013). Phytochemicals will continue to be important for anticancer drug discovery (Balunas and Kinghorn, 2005; Itokawa et al. 2008).

Mimusops elengi L. is a large evergreen tree belonging to the *Sapotaceae* family. It is native in south India but distributed across the tropics including Indonesia, Malaysia, Myanmar, Thailand, Sri Lanka, and Australia. Locally, it has been called as '*Molsari*' and '*Bakul*' in India, '*Tanjung*' in Indonesia, and '*Kha-yay*' in Myanmar. In the Unani and Āyurveda traditional systems of medicine, *M. elengi*. is in common usage in many regions of India (Gami et al. 2012; Kadam et al. 2012; Rani and Rahman, 2017). Based on the ethnopharmacological background, the barks are beneficial in empirical treatment for biliousness and dental ailments, and the flowers are used to cure blood and liver diseases. The seeds are reputed as a conventional laxative. In the Jamu system in Indonesia, *M. elengi* is utilized to treat hypertension, ulcers, and tumors (Ong and Nordiana, 1999). Previously, several reports revealed that *M. elengi* possessed a range of biological properties that include antioxidant, anticancer, antibacterial, and hypotensive activities

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(Dar et al. 1999; Shahwar and Raza, 2012; Amir et al. 2013; Kumar et al. 2016). Pentacyclic triterpenoids (mimusopgenone and mimugenone) and triterpenoid saponins (mimusopsides A and B, mimusopin, mimusopsin, and mimusin) were discovered from the seeds of *M. elengi* (Sen et al. 1995; Sahu et al. 1995; Sahu 1996; Lavaud et al. 1996; Sahu et al. 1997). Aromatic glycosides (elengiosides A and B) were isolated from its flowers (Morikawa et al. 2018).

Natural product fragments are extensively present in anticancer molecules such as etoposide, teniposide, vinorelbine, and topotecane, making them ideal candidates for cancer chemoprevention or associated agents in clinical treatment. Within the scope of our ongoing program aimed at the systematic chemical analysis of Indonesian folk medicine with a biologically interesting profile (Efdi et al. 2012; Anwar et al. 2017; Efdi et al. 2017; Pardede et al. 2018), we explored the anticancer constituents from *M. elengi* flowers.

Materials and methods

General

All solvents and reagents were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan) and used without further purification. IR spectra were recorded on a PerkinElmer FT-IR/FIR Spectrometer 400. HRESIMS (High-resolution electrospray ionization mass spectrometry) spectra were obtained using the Waters UPLC-MS system (Aquity UPLC XevoQTof). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded with a JEOL ECX 400 spectrometer with tetramethylsilane as an internal standard. Silica gel column chromatography (CC) was performed on silica gel (Wakogel 60 N, 38–100 µm, FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan). Thin-layer chromatography (TLC) spots on plates precoated with Silica gel 70F$_{254}$ TLC Plate-wako (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) were detected with a UV lamp (254 nm). Fractionations for all CCs were based on TLC analyses. The HPLC (SHIMADZU Co., Ltd.) column was a Wakosil-II 5C18HG Prep (φ 20 mm × 250 mm), and a flow rate of 4.0 ml/min and UV detection (254 nm) were employed.

Plant material

Dried flowers of *Mimusops elengi* L. were purchased commercially from the herbal medicine market in Yangon, Myanmar in 2015 and identified by Dr. Nyunt Phay (Rector, Pathein University, Pathein, Myanmar). The voucher specimen (MY-42) has been deposited in College of Science and Technology, Nihon University.

Extraction and isolation

Using 200 liter round bottom tank, crushed *M. elengi* flowers (20 kg) were immersed in MeOH (100 L) for 24 h at room temperature with stationary standing. The solvent of MeOH extract was removed under reduced pressure. Subsequently, the MeOH extract was suspended in water, delipidated using *n*-hexane, and partitioned with EtOAc (76 g) and *n*-BuOH (138 g). The EtOAc-soluble fraction (76 g) was concentrated and then applied on silica gel (150 g) CC eluted using a step-gradient system ($CHCl_3$/EtOAc = 4/1 → 1/1 → 1/4 → EtOAc/MeOH = 10/1 → 4/1), to give eight fractions (Fr.1–Fr.8). The Fr.1 (8.5 g) was washed with acetone, and insoluble matter was separated carefully. The insoluble matter was dried. The dried matter (420 mg) was further purified by RP (reverse-phase)-HPLC with 70% MeCN elution to yield compounds **1**–**3**.

Spectral data of a new compound

N^2-Methylaurantiamide acetate (**1**): White powder. IR (film): ν_{max} 3117, 1701, 1634, 1514 cm^{-1}. HRESIMS: *m/z* 481.2102 $[M+Na]^+$ (calcd. for $C_{28}H_{30}N_2O_4Na$, 481.2103). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.03 (15 H, m, 3Ar), 6.79 (1 H, br d, J = 9.2 Hz, NH), 5.33 (1H, dd, J = 10.1 and 6.9 Hz, H-2), 4.60–4.50 (1H, m, H-2'), 4.20–4.06 (2H, m, H-1), 3.27 (1 H, dd, J = 15.6 and 6.9 Hz, H-3α), 3.07 (1H, dd, J = 15.1 and 10.6 Hz, H-3β), 2.93 (1H, dd, J = 14.2 and 5.5 Hz, H-3'α), 2.73 (1H, dd, J = 14.2 and 9.6 Hz, H-3'β), 2.45 (3H, s, NMe), 2.10 (3 H, s, OAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4 (OBz), 171.0 (OAc), 169.7 (C-1'), 137.3 (Ar), 137.1 (Ar), 135.1 (Ar), 130.5 (Ar), 129.0 (2C, Ar), 128.9 (2C, Ar), 128.7 (2C, Ar), 128.6 (2C, Ar), 128.4 (2C, Ar), 127.6 (2C, Ar), 126.8 (Ar), 126.7 (Ar), 65.7 (C-1), 57.6 (C-2), 48.9 (C-2'), 37.7 (C-3'), 33.6 (NMe), 33.3 (C-3), 21.0 (OAc).

CCK-8 assay

HL-60 cells (DS Pharma Biomedical Co., Ltd., Osaka, Japan) were cultured in RPMI 1640 media (Wako Pure Chemical Industries, Ltd., Osaka, Japan) supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 1% antibiotics, penicillin-streptomycin (Gibco®, Life Technologies, Thermo Fisher Scientific Inc., MA, USA). Cells were maintained at 37 °C under a humidified atmosphere of 5% CO_2. Cell counting kit-8 (CCK-8) was purchased from Dojindo Molecular Technologies, Inc. (Kumamoto, Japan). HL-60 cells (2×10^4 cells/mL, 100 µL) were seeded in 96-well plates. After 24-h incubation, each solution (2 µL) of test compounds (2.5 mM solution for 50 µM, 1.25 mM solution for 25 µM and 0.625 mM solution for 12.5 µM) in DMSO was added into the culture. Following 48-h

incubation, CCK-8 solution (10 µL) was added, and the plates were incubated for an additional 3 h. Visible absorption (490 nm) was measured using a microplate reader (E_{max} precision microplate reader, Molecular Devices Japan, Tokyo, Japan) (Anwar et al. 2017).

Hoechst 33342 staining

The cells (2×10^5 cells/mL) were seeded in 48-well plates. After incubation with samples for 48 h, Hoechst 33342 solution (Sigma-Aldrich, USA) was added to the culture medium at a 5 µg/mL concentration. After incubation for 30 min, the collected cells were washed with PBS and then observed under a fluorescence microscope (Axiovert 40, Carl Zeiss).

Computational studies

The crystallographic coordinate of the 2.05 Å human Bcl-2 structure co-crystallized with Navitoclax (PDB ID: 4LVT (Souers et al. 2013)) was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (http://www.rcsb.org). Initially, the 3D structure of Bcl-2 was cleaned and the binding sites were considered for further analysis. The conformation of N^2-methylaurantiamide acetate (**1**) was optimized by DFT, B3LYP, 3-21G* using Gaussian09W software. All simulations were performed using AutoDock Vina (Trott and Olson 2010). The Lamarckian genetic algorithm of the AutoDock Vina was performed with a maximum of 27,000 generations per iteration, a population size of 150 individuals, and a maximum of 2.5×10^6 energy evaluations per generation. Flexibility was allowed in the following active site: Phe101, Tyr105, Asp108, Phe109, Met112, Val130, Leu134, Arg143, and Ala146. The binding pattern and interactions of compound **1** were visualized using Discovery Studio ver. 4.5.

Results and discussion

Antileukemic activity of *M. elengi* fractions

Following delipidation using *n*-hexane, the MeOH extract of *M. elengi* flowers was fractionated with EtOAc and *n*-BuOH in that order at room temperature. Removal of the solvents under reduced pressure afforded each fraction (EtOAc: 76 g, *n*-BuOH: 138 g, H_2O residue: 147 g). Initially, these fractions were screened their in vitro antiproliferative effects on human leukemia HL-60 cells using the CCK-8 assay method (Anwar et al. 2017). The cells were treated with increasing concentrations (50 and 100 µg/mL) of each fraction for 48 h, with DMSO as control. As shown in Fig. 1, treatment of the EtOAc fraction remarkably inhibited cell proliferation. Even when the EtOAc fraction concentration was 50 µg/mL, HL-60 cell viability reached 21% (% of control). In contrast, cytotoxicity of the *n*-BuOH fraction and H_2O residue fraction were relatively poor in these concentrations. The cells were then stained with Hoechst 33342, and examined by fluorescence microscopy for topical morphological alternations. The microscopic images are shown in Fig. 2. The control cells had uniform round- or oval-shaped nuclei with evenly distributed chromatin. The EtOAc fraction-treated cells exhibited evident apoptosis characteristics that include cell shrinkage, nuclear fragmentation, and the formation of apoptotic bodies.

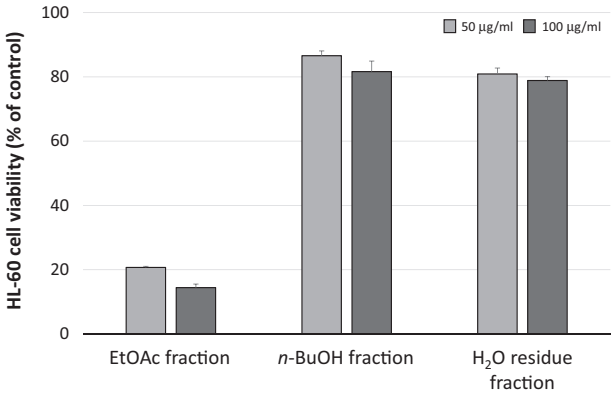

Fig. 1 Antiproliferative effects of EtOAc, *n*-BuOH, and H_2O residue fractions of the flowers of *Mimusops elengi* L. on human leukemia HL-60 cells (means ± SEMs, $n = 6$)

Characterization of constituents

To identify the potential compounds with respect to these properties, the EtOAc fraction of *M. elengi* flowers was separated by column chromatography (CC) using silica gel and RP-HPLC. Through several processes, three peptide derivatives and four phenolic constituents were isolated. Compound **1** was obtained as a white powder, and its molecular formula was established as $C_{28}H_{30}N_2O_4$ from HRESIMS for the peak at *m/z* 481.2102 $[M+Na]^+$ (calcd. for $C_{28}H_{30}N_2O_4Na$, 481.2103). The IR spectrum displayed absorptions at ν_{max} 3117 (NH), 1701 (COOR), 1634 (CONH), 1514 (benzene) cm^{-1}. Multiplet 15H observed at δ_H 7.45–7.03 in ^1H NMR and their respective carbons in ^{13}C NMR confirmed the presence of three single substituted phenyl rings. From any of these protons, the HMBC correlation to a carbonyl carbon at δ_C 173.4 was observed, indicating the existence of one benzoyl group. The occurrence of the *N*-benzoylphenylalanine fragment was deduced by HMBC correlations from a methylene [δ_H 3.27 (dd) and 3.07 (dd)] and a methine (δ_H 5.33). The CH_2 [δ_H 2.93 (dd)

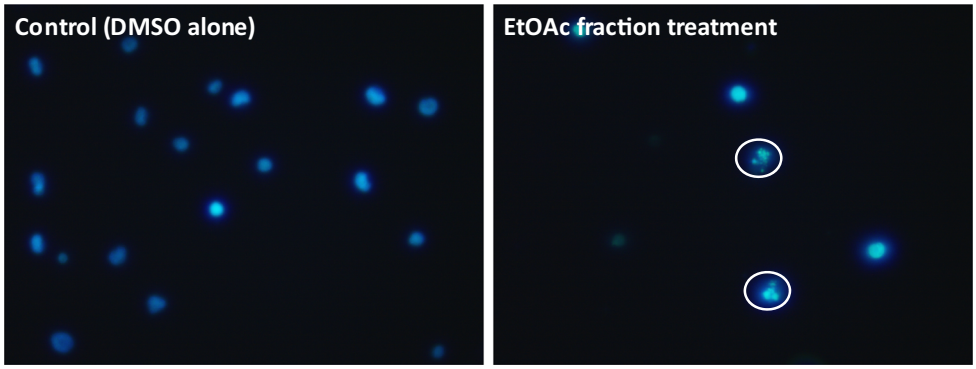

Fig. 2 Morphological changes of HL-60 cells induced by EtOAc fraction of the flowers of *Mimusops elengi* L. at a concentration of 100 µg/mL. Cells were treated with the fraction for 48 h, and were stained with Hoechst 33342

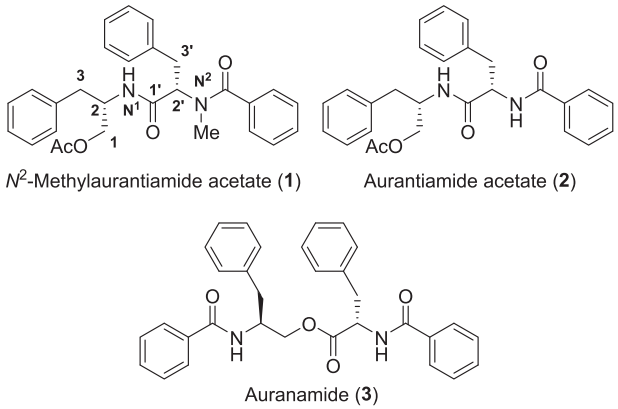

Fig. 3 Chemical structures of isolated peptide constituents

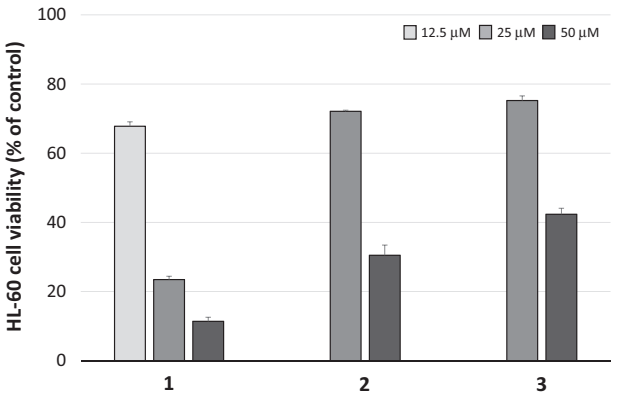

Fig. 4 Antiproliferative effects of isolated peptide constituents (**1**–**3**) on human leukemia HL-60 cells (means ± SEMs, $n = 3$)

and 2.73 (dd)]–C(N)H (δ_H 4.54)–CH_2 (δ_H 4.14) chain correlated to another phenyl ring and OAc (δ_H 2.10 and δ_C 171.0) in HMBC, suggesting the presence of the *O*-acetylphenylpropanolamine fragment. The HMBC correlations to a carbonyl carbon at δ_C 169.7 determined the basic framework of compound **1** as aurantiamide acetate (Lin 1987). A remaining 3H methyl proton at δ_H 2.45 did not have the HMQC correlation to any carbon, but had the HMBC correlation to the benzoyl carbonyl carbon. In other words, the methyl group was attached to a heteroatom close to the benzoyl group. These spectral studies led us to elucidate the structure of **1** as N^2-methylaurantiamide acetate which is a novel compound, depicted in Fig. 3. Compounds **2** and **3** were determined to be aurantiamide acetate and auranamide, respectively (Nwodo et al. 2014). Together with these peptide constituents, well-known phenolic compounds including quercetin (372 mg), p-hydroxybenzoic acid (156 mg), protocatechuic acid (721 mg), and gallic acid (345 mg) were identified.

In vitro anticancer activity of isolated compounds

As a crucial step for the structure-activity relationships, we evaluated the isolated peptide constituents for in vitro cytotoxicity against HL-60 cells. N^2-Methylaurantiamide acetate (**1**) displayed significant inhibition in a dose-dependent fashion, compared to aurantiamide acetate (**2**) and auranamide (**3**) in Fig. 4. The IC_{50} value of N^2-methylaurantiamide acetate (**1**) was 16.5 ± 1.1 µM. This data confirmed that *N*-methylation on the peptide linkage improves the anticancer potential of these compounds. Previous reports revealed that alkylation of nitrogen atoms in a peptide chain exists in naturally occurring peptides, which often show interesting biological activities. Actinomycin D (dactinomycin) produced by *Actinomyces antibioticus* is beneficial in the treatment of Wilms cancer, Ewing sarcoma, neuroblastomas, and trophoblastic tumors, primarily in children (Karpiński and Adamczak 2018). Cosmegen and Lyovac containing actinomycin D are available in the market. Synthadotin (ILX-651), derived from dolastatin 15 (found in *Dolabella auricularia*) showed promising results in phase II clinical trials of melanoma skin cancers (Liu and Rein 2010). *N*-Methylated analogues seem to be more effective anticancer agents than their intact counterparts.

Moreover, we observed morphological changes in the cells stained with Hoechst 33342. As shown in Fig. 5, while the nuclei of the cells were round in shape and stained

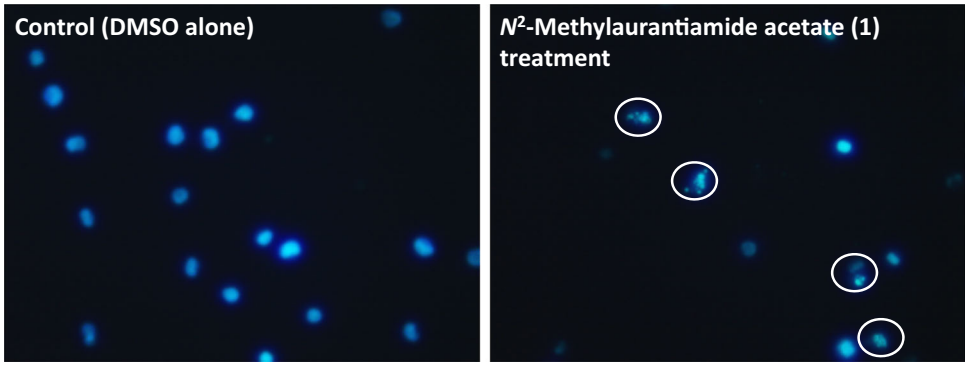

Fig. 5 Morphological changes of HL-60 cells induced by N^2-methylaurantiamide acetate (**1**) at a concentration of 50 µM. Cells were treated with the compound for 48 h, and were stained with Hoechst 33342

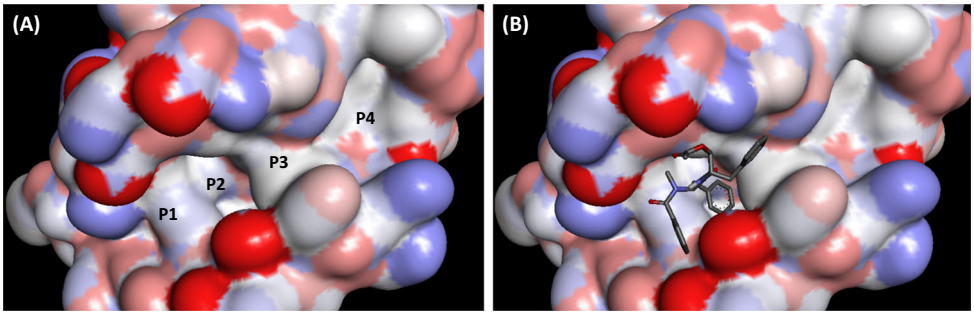

Fig. 6 Calculated binding mode of N^2-methylaurantiamide acetate (**1**) in Bcl-2 protein. **a** Binding groove of Bcl-2. **b** Surface view of Bcl-2 binding **1**

homogenously in the control without testing compound, those treated with N^2-methylaurantiamide acetate (**1**) caused chromatin compaction and nuclear fragmentation, both of which are signs of apoptotic appearance. This indicated that induction of apoptosis is likely to be the mechanism of N^2-methylaurantiamide acetate (**1**)-mediated inhibition of HL-60 cell proliferation.

Computational studies

The Bcl-2 family of proteins includes both anti- and pro-apoptotic proteins, and maintains the delicate balance between cell death and cell survival (Cory and Adams 2002; Ola et al. 2011). Cancer cells can evade death signal by overexpressing anti-apoptotic proteins, which suppress the function of pro-apoptotic activators (Lebedeva et al. 2000). Arguably, inhibition of Bcl-2 family of anti-apoptotic proteins is one of the most important targets for anticancer drug discovery (Delbridge et al. 2016). To estimate the detailed interactions, probable binding mode, and orientation of the ligand, molecular docking of N^2-methylaurantiamide acetate (**1**) with Bcl-2 protein (PDB ID: 4LVT (Souers et al. 2013)) was performed. The binding groove of Bcl-2 are shown in Fig. 6a with the four hydrophobic pockets labeled P1–P4. The visual inspection of the top scoring pose revealed that **1** favorably docked to the P1–P3 with free binding energy of ΔG −8.3 kcal/mol (Fig. 6b). Especially, **1** could go deeply into the P2 throughout the simulations. The intramolecular interactions between NMe···OAc···NH seem to fix the 3D conformation of **1**, leading to a tight-fit into the P2. This is

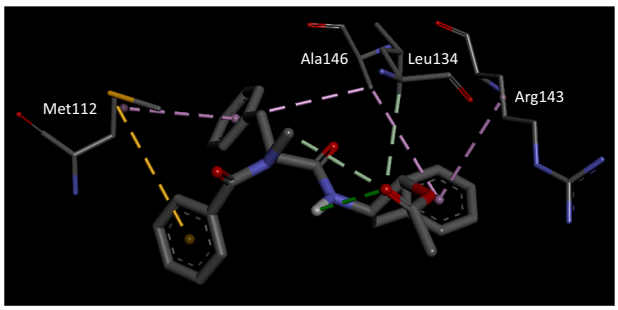

Fig. 7 Protein–ligand interactions of N^2-methylaurantiamide acetate (**1**) in Bcl-2 (hydrogen bond: green dotted line; non-classical hydrogen bond: pale green dotted line; π-alkyl interaction: pink dotted line, π-sulfur interaction: yellow dotted line)

the hydrophobic region occupied by the helical backbone of the BH3 peptide (Sattler et al. 1997; Lee et al. 2007). The benzene rings hydrophobically contacted with Met112, Arg143, and Ala146 (Fig. 7). In addition, a non-classical hydrogen bond (C–H···O interaction) between a carbonyl oxygen of OAc and Leu134 was observed. In brief, N^2-methylaurantiamide acetate (**1**) is able to inhibit the Bcl-2 protein by invading into the P1–P3 binding area.

Conclusion

Our phytochemical investigation of *M. elengi* flowers resulted in the discovery of a new modified dipeptide N^2-methylaurantiamide acetate (**1**). Furthermore, in vitro and *in*

silico anticancer studies presented the great potential into the development of *N*-methylated dipeptide derivatives as more appropriate drug candidates. Our findings also demonstrated the ethnopharmacological relevance of *M. elengi* as an affordable medicament for sustainable human healthcare.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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