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STUDY ON TRANSFORMATION OF ZERUMBONE WITH FATTY ACID HYDRAZIDES

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Abstract

Zerumbone was isolated from several plant species of the Zingiberaceae family that have shown many potential biological activities, such as antiproliferative, antioxidative, anti-inflammatory, and anticancer activities. Due to these biological effects, many scientists have tried to synthesize zerumbone derivatives and evaluate their bioactivities. In this paper, we report the synthesis of nine new zerumbone derivatives by the condensation of zerumbone and zerumbone oxide with fatty acid hydrazides. The structure of these compounds has been confirmed by ^{1}H NMR, ^{13}C NMR and FT-ICR-MS spectroscopic data.

Keywords. Zerumbone, zerumbone oxide, fatty acid hydrazide, condensation.

1. INTRODUCTION

Zerumbone (2,6,9,9-tetramethyl-[2E, 6E, 10E] - cycloundeca-2,6,10-trien-1-on), a sesquiterpene extracted from well-known plant *Zingiber zerumbet* Smith, contributed widely in South East Asia [1]. Structurally, this sesquiterpen contains an *α,β*-unsaturated ketone group, an isolated double bond at position 6 and a gem dimethyl group at position 9. Recent studies showed that zerumbone inhibits effectively several human cancer cell lines such as colon [2, 3], breast [2] and leukemia cell lines [4,1]…. without any effect on normal cells [2].

In molecules, the *α,β*-unsaturated ketone group in zerumbone was reported to be the center of preferential activity towards thiol group in certain proteins due to a conjugated addition. In 2006, P. M. Giang and colleagues [5] studied the inhibition of NF-κB factor by zerumbone and pointed out that the *α,β*-unsaturated ketone group is the key to the activity of this compound. This conclusion was also agreed with the results of bioactivity comparison between zerumbone and zerumbol, a derivative of zerumbone and humulene, a hydrocarbon with a similar structure to zerumbone. Zerumbone showed high bioactivity while zerumbol and humulene weak or no activity [6]. Chemically, this group can be easily hybridized with other bioactive components containing amine group and the fatty acid hydrazides may be suitable for this purpose.

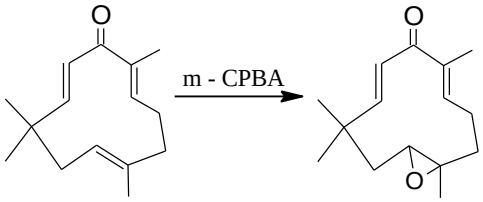
Organic hydrazide derivatives possess interesting biological activities such as antimicrobial [7], anticancer [8], anti-inflammatory [9], antivirus [10], and antimalarial activity [11]. So far, many studies on the synthesis of novel derivatives of zerumbone were reported, however no studies on the synthesis of novel zerumbone derivatives containing hydrazone-hydrazide linkage are available. In this paper, we present the synthesis of 9 new derivatives of zerumbone by the condensation reaction with fatty acid hydrazides.

2. EXPERIMENTAL

Zerumbone was extracted from stem and tuber of *Zingiber Zerumbet* Smith in Vietnam – Russia Tropical Centre. All chemicals and reaction solvents were purchased from Merck and Aldrich. Melting points were determined in open capillaries on Shimadzu Electrothermal IA 9200 apparatus and uncorrected. IR spectra were recorded on FT-IR IMPACT-410 using KBr discs. 1D- and 2D-NMR spectra were recorded on Bruker AVANCE 500 MHz spectrometer in DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (*J*) are expressed in hertz (Hz). Mass spectra were

recorded on FT-ICR-MS (Varian) model 910-MS TQFTMS-7 Tesla for all compounds to reconfirm the structure. Progress of the reaction was monitored by thin-layer chromatography (TLC) using precoated TLC sheets with ultraviolet (UV) fluorescent silica gel (Merck 60F254) and spots were visualized by UV lamp at 254 nm. Multiplicities are shown as follows: s (singlet), d (doublet), t(triplet), m (multiplet). Column chromatography was carried out using silica gel (40-230mesh). Solvents were commercially available materials of reagent grade.

2.1. Synthesis of zerumbone oxide

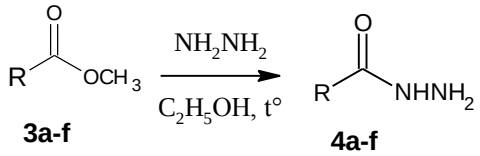


Scheme 1: Synthesis of zerumbone oxide **2**

To a solution of zerumbone (1.22 g, 5.6 mmol) in CH_2Cl_2 (20 ml) was dropwise added a solution of *m*-chloroperbenzoic acid (*m*CPBA) (1.27 g, 7 mmol) in CH_2Cl_2 (30 ml) at -5–0 ^oC. The mixture was stirred for 4 hours at room temperature, sodium carbonate solution 5 % was added (pH = 9) and the solution was extracted with dichloromethane (3×50 ml). The organic layers were combined, washed with water to pH = 7 and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford crude zerumbone oxide that was purified by column chromatography eluted with *n*-hexane:ethyl acetat (17:3).

Compound 2: mp = 97-98 ^oC. Yield 80 %. ***^{1}H NMR (DMSO – d_6) spectrum, δ_H (ppm)***: 6.08 (s, 2H, H-11, H-10), 6.11 (qd, 1H, *J* = 9.5 Hz, 1.5 Hz, H-3), 2.81 (1H, dd, *J* = 11, 1.5 Hz, H-7), 2.28-2.45 (2H, m, H-4), 2.1-2.15 (1H, m, H-5), 1.80 (1H, d, *J* = 14.0 Hz, H-8), 1.75 (3H, s, H-12), 1.41 (1H, dd,*J* = 14.0, 11.2 Hz, H-8), 1.27-1.33 (1H, m, H-5), 1.27 (3H, s, CH_3-14 or15), 1.15 (3H, s, CH_3-13), 1.03 (3H, s, CH_3-15 or14); ***^{13}C NMR spectrum (DMSO – d_6), δ (ppm)*:** 202.1 (C1), 159.16 (C10), 147.79 (C3), 138.59 (C2), 128.07 (C11), 61.43 (C7), 60.99 (C6), 42.07 (C8), 37.42 (C5), 35.65 (C9), 29.41 (CH_3-14 or15), 24.33 (C4), 23.61 (CH_3-15 or14), 15.4 (CH_3-13), 11.88 (CH_3-12); ***MS:*** m/z 257.06 ($[M+Na]^+$), base peak 100%, 235.08 ($[M+H]^+$).

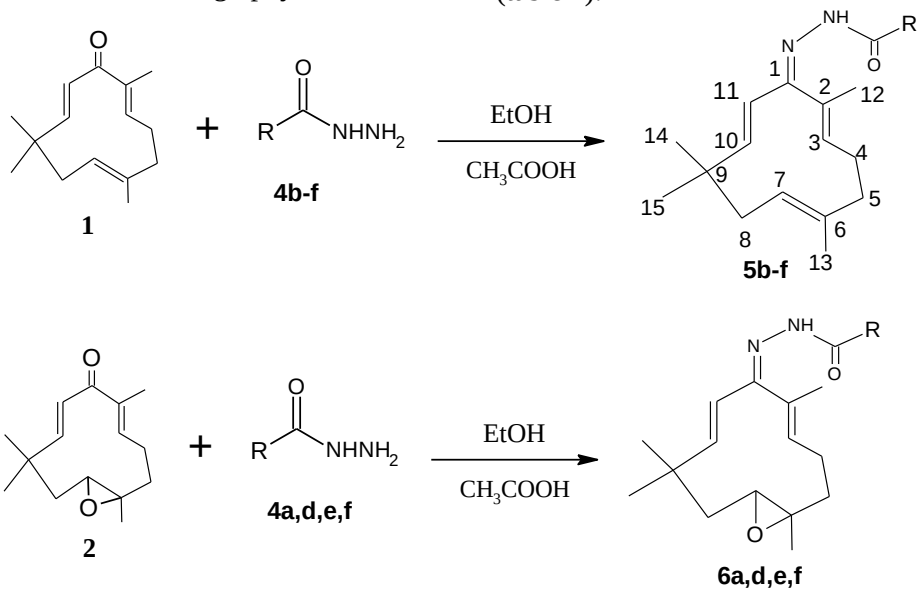
2.2. Synthesis of fatty acid hydrazides



R = $(CH_3)_2CH$ (**a**), $CH_3(CH_2)_3$ (**b**), $(CH_3)_2CHCH_2$ (**c**), $CH_3(CH_2)_4$ (**d**), $CH_3(CH_2)_6$ (**e**), $CH_3(CH_2)_4$ (**f**)

Scheme 2: Synthesis of fatty acid hydrazide **4a-f**

To a mixture of ester **3a-f** (10 mmol) in ethanol (15 ml) was added hydrazine hydrate solution 80% (6 ml). The reaction mixture was refluxed for 3-4 hours. The solvent was removed under reduced pressure to give crude **4a-f**. After recrystallization in ethanol, the purified **4a-f** was obtained as solids (table 1).



Scheme 3: Synthesis of hydrazone **5b-f** and **6a, 6d, 6e, 6f**

Table 1: Results of synthesis of fatty acid hydrazides **4a–f**

Symbol	Yield (%)	MP (^oC)	^1H NMR, ^{13}C NMR spectra, δ (ppm)
4a	73.2	97.0-99.0	1.16 (d, 6H, *J* = 7.0 Hz, H-2, H-3); 2.38 (quint, 1H, H-1); 7.43 (s, 1H, NH); 33.69 (C-1); 177.87 (C=O); 19.24; 19.29 (C-2 & C-3)
4b	78.2	53.0-56.0	0.92 (t, 3H, *J* = 7.5 Hz, H-4); 2.17 (t, 2H, *J* = 7.5 Hz, H-1); 1.62 (quint, 2H, *J* = 7.5 Hz, H-2); 1.35 (sextet, 2H, *J* = 7.5 Hz, H-3); 7.34 (s, 1H, NH); 34.16 (C-1); 174.13 (C=O); 27.51 (C-2); 22.28 (C-3); 13.63 (C-4).
4c	67.8	55.0-56.0	0.95 (d, 6H, *J* = 6.5 Hz, H-3, H-4); 2.03 (d, 2H, *J* = 7.5 Hz, H-1); 2.13 (m, 1H, H-2); 7.47 (s, 1H, NH).
4d	62.2	137.0-139.0	0.89 (t, 3H, *J* = 7.0 Hz, H-5); 2.27 (t, 2H, *J* = 7.5 Hz, H-1); 1.65 (quint, 2H, *J* = 7,5 Hz, H-2); 1,307 (m, 4H, H-3,4); 7.28 (s, 1H, NH); 33.43 (C-1); 169.6 (C=O); 30.83 (C-2); 24.6 (C-3); 21.8 (C-4); 13.35 (C-5).
4e	71.7	86.0-88.0	0.87 (m, 3H, H-7); 2.15 (t, 2H, *J* = 7.5 Hz, H-1); 1.58-1.68 (m, 2H, H-2); 1.21-1.34 (m, 8H, H-3,4,5,6); 7,1 (s, 1H, NH); 3.8 (s, 2H, NH_2); 34.54 (C-1); 174.11 (C=O); 31.62 (C-2); 29.2 (C-3); 28.92 (C-4); 25.48 (C-5); 22.55 (C-6); 14.0 (C-7).
4f	66.7	92.4-93.8	0.88 (t, 3H, *J* = 7.0 Hz, H-9); 2.15 (t, 2H, *J* = 7.5 Hz, H-1); 1.63 (quint, 2H, *J* = 7.5 Hz, H-2); 1.2-1.35 (m, 12H, H-3,4,5,6,7,8); 6.96 (s, 1H); 3.92 (s, 2H, NH_2); 34.57 (C-1); 174.09 (C=O); 31.83 (C-2); 29.4 (C-3); 29.28 (C-4); 29.26 (C-5); 29.23 (C-6); 25.49 (C-7); 22.63 (C-8); 14.06 (C-9).

2.3. Condensation reaction of zerumbone with fatty acid hydrazides

A mixture of zerumbone **1** (0.218 g, 1 mmol) and appropriate hydrazide (1.2 mmol) in ethanol (5 mL) was refluxed together in the presence of glacial acetic acid (4 ml) for 6-8 hours. The precipitate obtained was filtered off and purified by column chromatography using *n*-hexane:EtOAc (5:1) to give **5b-f**.

Spectral data of compounds 5b-f:

Compound 5b: mp (^oC) = 160.8-161.5; Yield 50 %. ***^1H NMR (DMSO – d_6). δ_H (ppm)***: 2.08-2.3 (m, 4H, H-4; H-5); 5.18 (t, 1H, *J* = 8.0 Hz; H-7); 5.45 (m, 1H, H-3); 5.4 (d, 1H, *J* = 16.5 Hz, H-10); 6.22 (dd, 1H, *J* = 16.5; 7.5 Hz, H-11); 1.79 (s, 3H, H-12); 1.44 (s, 3H, H-13); 1.0-1.2 (m, 6H, H-14; H-15); 2.22 (t. 2H. *J* = 7.5 Hz, H-1'); 1.52 (quint. 2H. *J* = 7.5 Hz, H-2'); 1.29 (sextet, 2H, *J* = 7.5 Hz, H-3'); 0.87(t, 3H, *J* = 7.5 Hz, H-4'); 9.78 (s, 68.5 %, NH); 9.69 (s, 31.5%, NH); ***^{13}C NMR ($CDCl_3$). δ (ppm)*:** 155.36 (C-1); 135.99 (C-2); 141.94 (C-3); 23.6 (C-4); 39.78 (C-5); 135.73 (C-6); 124.22 (C-7); 42.43 (C-8); 38.68 (C-9); 156.58 (C-10); 118.45 (C-11); 13.87 (C-12); 14.95 (C-13); 175.56 (C=O); 32.44 (C-1'); 26.86 (C-2'); 22.55 (C-3'); 13.87 (C-4'); ***MS**:* m/z 317.26 ($[M+H]^+$, base peak 100 %).

Compound 5c: mp (^oC) = 164.5-165; Yield 34%. ***^1H NMR (DMSO – d_6). δ_H (ppm)***: 2.08-2.3 (m. 4H, H-4; H-5); 5.18 (t, 1H, *J* = 8.0 Hz; H-7); 5.4-5.47 (m, 1H, H-3); 5.4 (d, 1H, *J* = 16.5 Hz, H-10); 6.23 (dd, 1H, *J* = 16.5; 8.5 Hz. H-11); 1.8 (s, 3H, H-12); 1.44 (s, 3H, H-13); 1.0-1.23 (m, 6H, H-14; H-15); 2.35-2.45 (m, 1H, H-1'); 2.12 (d, 2H, *J* = 7.0 Hz. H-2'); 0.9 (d, 6H, *J* = 6.0 Hz, H-3'; H-4'); 9.76 (s. 60%. NH); 9.65 (s, 40 %, NH); ***^{13}C NMR ($CDCl_3$). δ (ppm)*:** 155.18 (C-1); 135.92 (C-2); 141.81 (C-3); 23.52 (C-4); 39.70 (C-5); 135.64 (C-6); 124.14 (C-7); 42.36 (C-8); 38.59 (C-9); 156.48 (C-10); 118.4 (C-11); 13.81 (C-12); 14.87 (C-13); 174.73 (C=O); 41.49 (C-1'); 25.34 (C-2'); 22.66 (C-3'; C-4'); ***MS**:* m/z 317.3 ($[M+H]^+$, base peak 100 %).

Compound 5d: mp (^oC) = 150.0-151.7; Yield 30%. ***^1H NMR (DMSO – d_6). δ_H (ppm)***: 2.05-2.35 (m. 4H, H-4; H-5); 5.18 (t, 1H, *J* = 8.0 Hz; H-7); 5.45 (m, 1H, H-3); 5.4 (d, 1H. *J* = 16 Hz. H-10); 6.23 (dd, 1H, *J* = 16.5; 6.5 Hz. H-11); 1.79 (s. 3H. H-12); 1.43 (s, 3H, H-13); 1.17 (s. 3H, H-14 or H-15); 1.07 (s, 3H, H-14 or H-15); 2.21 (t, 2H. *J* = 7.25 Hz. H-1'); 1.54 (m, 2H, H-2'); 1.25-1.31 (m. 4H. H-3'; H-4'); 0.86 (t, 3H, *J* = 6.5 Hz, H-5'); 9.79 (s. 69 %. NH); 9.7 (s. 31 %. NH); ***^{13}C NMR ($CDCl_3$). δ***

(ppm)*:** 155.36 (C-1); 136.01 (C-2); 141.96 (C-3); 23.61 (C-4); 39.8 (C-5); 135.75 (C-6); 124.24 (C-7); 42.46 (C-8); 38.71 (C-9); 156.62 (C-10); 118.41 (C-11); 13.87 (C-12); 14.95 (C-13); 175.57 (C=O); 32.73 (C-1'); 31.65 (C-2'); 24.44 (C-3'); 22.44 (C-4'); 13.97 (C-5'). ***MS: m/z 331.1 ($[M+H]^+$, base peak 100 %).

Compound 5e: mp (^oC) = 117.0-118.5; Yield 30 %. ***^{1}H NMR (DMSO – d_6). δ_H (ppm)***: 2.08-2.35 (m, 4H, H-4; H-5); 5.18 (t, 1H, *J* = 8.0 Hz; H-7); 5.45 (m, 1H, H-3); 5.4 (d, 1H, *J* = 16 Hz, H-10); 6.23 (dd, 1H, *J* = 16.5; 7.5 Hz. H-11); 1.79 (s, 3H, H-12); 1.43 (s, 3H, H-13); 1.17 (s, 3H, H-14 or H-15); 1.06 (m, 3H, H-14 or H-15); 2.21 (t, 2H, *J* = 7.25 Hz. H-1'); 1.45-1.58 (m, 2H, H-2'); 1.2-1.3 (m, 8H, H-3'; H-4'; H-5'; H-6'); 0.85 (t, 3H, *J* = 7.0 Hz. H-7'); 9.78 (s. 69 %. NH); 9.69 (s, 31 %, NH); ***^{13}C NMR ($CDCl_3$). δ (ppm)*:*** 155.35 (C-1); 135.99 (C-2); 141.96 (C-3); 23.6 (C-4); 39.78 (C-5); 135.74 (C-6); 124.21 (C-7); 42.43 (C-8); 38.70 (C-9); 156.61 (C-10); 118.42 (C-11); 13.88 (C-12); 14.95 (C-13); 175.56 (C=O); 32.76 (C-1'); 31.72 (C-2'); 29.4 (C-3'); 29.05 (C-4'); 24.75 (C-5'); 22.64 (C-6'); 14.1 (C-7'); ***MS:*** m/z 359.2 ($[M+H]^+$, base peak 100 %).

Compound 5f: mp (^oC) = 126.5-128; Yield 45%. ***^{1}H NMR (DMSO – d_6). δ_H (ppm)***: 2.08-2.3 (m. 4H, H-4; H-5); 5.18 (t, 1H, *J* = 8.0 Hz; H-7); 5.45 (m, 1H, H-3); 5.4 (d, 1H, *J* = 16 Hz, H-10); 6.23 (dd. 1H. *J* = 16.25; 7.5 Hz, H-11); 1.79 (s, 3H, H-12); 1.43 (s, 3H, H-13); 1.0-1.28 (m, 6H, H-14; H-15); 2.21 (t, 2H, *J* = 7.5 Hz. H-1'); 1.45-1.57 (m, 2H, H-2'); 1.25-1.3 (m, 12H, H-3'; H-4'; H-5'; H-6', H-7'; H-8'); 0.85 (t. 3H. *J* = 6.75 Hz; H-9'); 9.77 (s. 60 %. NH); 9.68 (s, 41 %. NH); ***^{13}C NMR ($CDCl_3$). δ (ppm)*:*** 155.16 (C-1); 135.68 (C-2); 142.15 (C-3); 23.4 (C-4); 39.52 (C-5); 135.54 (C-6); 124.01 (C-7); 42.17 (C-8); 38.42 (C-9); 156.64 (C-10); 118.14 (C-11); 13.81 (C-12); 14.67 (C-13); 176.11 (C=O); 32.47 (C-1'); 31.65 (C-2'); 29.23 (C-3'); 29.15 (C-4'); 29.1 (C-5'); 29.05 (C-6'); 24.57 (C-7'); 22.44 (C-8'); 13.59 (C-9'); ***MS:*** m/z 387.2 ($[M+H]^+$, base peak 100 %).

2.4. Condensation reaction of zerumbone oxide with fatty acid hydrazides

A mixture of zerumbone oxide (0.234 g. 1 mmol) and appropriate hydrazide (1.2 mmol) in ethanol (5 ml) was refluxed together in the presence of glacial acetic acid (4 ml) for 8 hours. The precipitate obtained was filtered off and purified by column chromatography using *n*-hexane:EtOAc (5:1) to give **6a, 6d, 6e, 6f**.

Spectral data of compounds 6a, 6d, 6e, 6f:

Compound 6a: mp (^oC) = 218.5-219.7; Yield 45%. ***^{1}H NMR (DMSO–d_6). δ_H (ppm):*** 2.35 (m. 2H. H-4); 2.21 (d, 1H, *J* = 13.0 Hz, H-5); 1.24-1.3 (m. 1H. H-5); 1.9 (d, 1H, *J* = 13.5 Hz. H-8; 1.43 (dd. 1H. *J* = 13.5 Hz. H-8); 2.73 (d, 1H, *J* = 11.0 Hz, H-7); 5.67 (t, 1H, *J* = 5.5 Hz, H-3); 5.75 (d, 1H, *J* = 16.5 Hz, H-10); 6.1 (d, 1H, *J* = 16.5 Hz, H-11); 1.93 (s, 3H, H-12); 1.16 (s, 3H, H-13); 1.33 (s, 3H, H-14 or H-15); 1.09 (s. 3H. H-14 or H-15); 3.4 (septet. 1H, *J* = 7.0 Hz. H-1'); 1.2 (d. 3H. *J* = 7.0 Hz. H-2' or H-3'); 1.18 (d, 3H, *J* = 7.0 Hz. H-2' or H-3'); 8.27 (s, 1H, NH); ***^{13}C NMR (DMSO – d_6). δ (ppm):*** 152.86 (C-1); 136.91 (C-2); 139.14 (C-3); 23.51 (C-4); 37.39 (C-5); 60.62 (C-6); 61.86 (C-7); 41.55 (C-8); 35.53 (C-9); 154.75 (C-10); 118.17 (C-11); 13.02 (C-12); 14.43 (C-13); 29.34 (C-14 or C-15); 22.22 (C-14 or C-15); 178.19 (C=O); 29.42 (C-1'); 17.67 (C-2' or C-3'); 17.58 (C-2' or C-3'); ***MS:*** m/z 319.24 ($[M+H]^+$, base peak 100 %).

Compound 6d: mp (^oC) = 180.0-180.7; Yield 36 %. ***^{1}H NMR (DMSO – d_6). δ_H (ppm)***: 2.33-2.37 (m, 2H, H-4); 2.21 (t of d, 1H, *J* = 13.5; 3.5 Hz. H-5); 1.28-1.34 (m, 1H, H-5); 1.9 (d. 1H. *J* = 14.0 Hz. H-8; 1.43 (dd, 1H, *J* = 14.0; 11.0 Hz. H-8); 2.73 (d. 1H. *J* = 10.0 Hz, H-7); 5.67 (t, 1H, *J* = 6.0 Hz. H-3); 5.75 (d. 1H. *J* = 16.5 Hz, H-10); 6.08 (d, 1H, *J* = 16.5 Hz. H-11); 1.92 (s, 3H, H-12); 1.16 (s, 3H, H-13); 1.32 (s, 3H, H-14 or H-15); 1.08 (s, 3H, H-14 or H-15); 2.6-2.7 (m, 2H, H-1'); 1.66-1.72 (m, 2H, H-2'); 1.34-1.38 (m, 4H, H-3'; H-4'); 0.87-0.92 (m. 3H. H-5'); 8.61 (s, 1H, 43 %. NH); 8.29 (s. 1H. 57 %. NH); ***^{13}C NMR ($CDCl_3$). δ (ppm)***: 154.03 (C-1); 137.89 (C-2); 140.29 (C-3); 23.23 (C-4); 38.41 (C-5); 61.65 (C-6); 62.89 (C-7); 42.55 (C-8); 36.55 (C-9); 155.81 (C-10); 119.17 (C-11); 14.04 (C-12); 14.45 (C-13); 30.36 (C-14 or C-15); 22.44 (C-14 or C-15); 175.74 (C=O); 32.71 (C-1'); 31.64 (C-2'); 31.35 (C-3'); 24.54 (C-4'); 13.97 (C-5'). ***MS:*** m/z 347.27 ($[M+H]^+$, base peak 100 %).

Compound 6e: mp (^oC) = 155.1-155.6; Yield 32 %. ***^{1}H NMR (DMSO – d_6). δ_H (ppm)***: 2.33-2.37 (m, 2H, H-4); 2.22 (t of d. 1H. *J* = 13.0; 3.5 Hz, H-5); 1.26-1.32 (m, 1H, H-5); 1.91 (d, 1H, *J* = 14.0 Hz, H-8; 1.43 (dd, 1H, *J* = 14.0; 11.5 Hz, H-8); 2.74 (d, 1H, *J* = 9.5 Hz, H-7); 5.68 (t. 1H. *J* = 5.75 Hz, H-3); 5.75 (d, 1H, *J* = 16.5 Hz, H-10); 6.08 (d. 1H. *J* = 16.5 Hz, H-11); 1.93 (s, 3H, H-12); 1.17 (s, 3H, H-13); 1.33 (s, 3H, H-14 or H-15); 1.09 (s, 3H, H-14 orH-15); 2.62-2.71(m, 2H, H-1'); 1.67-1.72 (m. 2H. H-2'); 1.25-1.38 (m, 8H, H-3'; H-4'. H-5'; H-6'); 0.89 (t, 3H, *J* = 7.0 Hz. H-7'); 8.27 (s. 1H. NH); ***^{13}C NMR ($CDCl_3$). δ (ppm):*** 153.96 (C-1); 137.89 (C-2); 140.28 (C-3); 23.23 (C-4); 38.41 (C-5); 61.64 (C-6); 62.88 (C-7); 42.55 (C-8); 36.56 (C-9); 155.8 (C-10); 119.15 (C-11); 14.08 (C-12); 15.44 (C-13);

29.04 (C-14 or C-15); 22.68 (C-14 or C-15); 175.69 (C=O); 32.75 (C-1'); 31.72 (C-2'); 30.36 (C-3'); 29.4 (C-4'); 24.74 (C-5'); 24.54 (C-6'); 14.04 (C-7'); ***MS:*** m/z 375.3 ($[M+H]^+$, base peak 100 %).

Compound 6f: mp (^oC) = 128.3-129.0; Yield 40 %. ***^1H NMR (DMSO – d_6). δ_H (ppm)***: 2.33-2.37 (m. 2H. H-4); 2.22 (td, 1H, *J* = 13.5; 3.0 Hz. H-5); 1.25-1.3 (m, 1H, H-5); 1.91 (d, 1H, *J* = 14.0 Hz, H-8; 1.43 (dd, 1H, *J* = 14.0; 11.5 Hz. H-8); 2.73 (d, 1H, *J* = 11.0 Hz, H-7); 5.67 (t, 1H, *J* = 5.75 Hz, H-3); 5.75 (d, 1H, *J* = 16.5 Hz, H-10); 6.07 (d, 1H, *J* = 16.5 Hz. H-11); 1.92 (s, 3H, H-12); 1.16 (s, 3H, H-13); 1.32 (s, 3H, H-14 or H-15); 1.08 (s, 3H, H-14 or H-15); 2.62-2.7 (m, 2H, H-1'); 1.7 (quint, 2H, *J* = 7.5 Hz, H-2'); 1.25-1.38 (m, 12H, H-3'; H-4', H-5'; H-6'; H-7'; H-8'); 0.88 (t. 3H, *J* = 7.0 Hz; H-9'); 8.22 (s. 1H. NH); ***^{13}C NMR ($CDCl_3$). δ (ppm)*:*** 153.96 (C-1); 137.9 (C-2); 140.29 (C-3); 23.23 (C-4); 38.41 (C-5); 61.64 (C-6); 62.88 (C-7); 42.55 (C-8); 36.56 (C-9); 155.84 (C-10); 119.12 (C-11); 14.11 (C-12); 15.44 (C-13); 29.3 (C-14 or C-15); 22.68 (C-14 or C-15); 175.69 (C=O); 32.75 (C-1'); 31.9 (C-2'); 30.37 (C-3'); 29.4 (C-4'); 29.48 (C-5'); 29.39 (C-6'); 24.74 (C-7'); 24.54 (C-8'); 14.04 (C-9'); ***MS:*** m/z 403.33 ($[M+H]^+$, base peak 100 %).

3. RESULTS AND DISCUSSION

Derivatives **5b-f** and **6a, 6d, 6e, 6f** were prepared from zerumbone, zerumbone oxide and fatty acid hydrazides **4a-f** by condensation reaction to form hydrazone linkage. Firstly, zerumbone was oxidized to zerumbone oxide in 80 % yield by mCPBA at 0 ^oC in CH_2Cl_2 (scheme 1). Next, the hydrazides were synthesized in 60-75 % yields from esters of corresponding fatty acids with hydazine hydrate in ethanol (scheme 2). Finally, condensation reaction of hydrazides **4a-f** with zerumbone and zerumbone oxide was carried out in ethanol in presence of glacial acetic acid to afford **5b-f** and **6a, 6d, 6e, 6f** in 30-60 % yields, respectively (scheme 3). The structure of target compounds **5b-f** and **6a, 6d, 6e, 6f** was elucidated by spectra such as NMR and MS. In ^{1}H-NMR spectra of compounds **5b-f** and **6a, 6d, 6e, 6f**, the signal of protons in aliphatic hydrocarbon radicals of hydrazides appeared at 0.8-3.5 ppm and overlaped with those of zerumbone skeleton. The singlet signals arose at 8-10 ppm were assigned to the protons of NH group in **5b-f** and **6a, 6d, 6e, 6f**. The data in ^{1}H-NMR spectra of the synthesized hydrazone compounds also indicated that the signal of proton in NH group of some compounds **5b-f** and **6d** was separated into two singlets with a ratio of about 30:70 or 40:60. This can be explained by the configuration rotation around N-N linkage in solvent DMSO leading to the formation of two conformational isomers *syn* and *anti* or the formation of two geometric isomers *E* and *Z* of double bond C=N. And the two singlets ratio of proton in NH group was also the ratio of two isomers.

In comparison with the spectra of the zerumbone and zerumbone oxide, ^{13}C NMR spectra of hydrazone compounds showed the resonance signal C=N of hydrazone at 153 ppm and the resonance signal of C=O of hydrazide at about 175 ppm instead of the resonance signal of carbon ketone δ = 204 ppm. Futher, spectra also showed the resonant signals of the aliphatic carbon in hydrazides between 13-34 ppm.

Finally, the structure of hydrazones was reconfirmed by mass spectrometry. On the spectrum, we found the presence of molecular ion $[M+H]^+$ at 100 % intensity matching the results of theoretical calculations.

The structure of target compounds well agreed with ^{1}H-NMR, ^{13}C-NMR and MS data.

4. CONCLUSION

In this paper, 9 new compounds (**5b-f** and **6a, 6d, 6e, 6f**) were synthesized by condensation reaction of zerumbone and zerumbone oxide with 6 fatty acid hydrazides. The structures of products were elucidated by ^{1}H NMR, ^{13}C NMR and FT-ICR mass spectra.

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