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Prediction Of Anticancer Activities Of Kaempferol-3-O-Methylether And Kaempferol-3-O-(2,4-O-Diacetyl-Alpha-L-Rhamnopyranoside) Isolating From Plant Rhizome Zingiber Zerumbet Sm Using QSDAR Models From ^{13}C-NMR and ^{15}O-NMR Simulation Spectra Data

Pham Van Tat[3]*, Bui Thi Phuong Thuy[1], Tran Duong[2], Phung Van Trung[4], Hoang Thi Kim Dung[4] and Pham Nu Ngoc Han[3]

[1]*Faculty of Chemistry, Hue University of Science, Viet Nam*

[2]*Faculty of Chemistry, Hue University of Education, Viet Nam*

[3]*Faculty of Science and Engineering, Hoa Sen University, Viet Nam*

[4]*Institute of Chemical Technology, Vietnam Academy of Science and Technology, Viet Nam*

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***Corresponding author:** Pham Van Tat, Faculty of Science and Engineering, Hoa Sen University, Ho Chi Minh City, Viet Nam; Email: vantat@gmail.com

Abstract

In this work, the quantitative spectrum data - activity relationship ($QSDAR_{MLR}$) models for a set of anticancer flavonoids were developed from the simulated-spectral data ^{13}C-NMR and ^{15}O-NMR. The quality of best model QSDARMLR resulting from the chemical-shift data of atoms O_1, O_{11}, C_2, C_3, C_6, C_7 và C_2' was shown in the values R^2_{train} of 0.9057 and R^2_{test} of 0.7137. The atomic sites C_3, C_6 and C_7 were used to design the new flavonoid derivatives. The neural network model $QSDAR_{ANN}$ I(7)-HL(9)-O(1) presented to be a better model in values R^2_{train} of 0.993 and R^2_{pred} of 0.971. The models $QSDAR_{MLR}$ and $QSDAR_{ANN}$ were explored to predict the anticancer activities of flavonoids in test group and two new compounds kaempferol-3-O-methylether and kaempferol-3-O-(2,4-O-diacetyl-alpha-L-rhamnopyranoside) isolating from *Rhizome Zingiber Zerumbet* Sm in Viet Nam [1]. The predicted activities resulting from those models turn out to be good agreement with experimental data.

Keywords: $QSDAR_{MLR}$ and $QSDAR_{ANN}$ Model; Anticancer Activities Hela Cell Line

Abbrevations: QSDAR: Quantitative Structure Activity Relationship; NMR: Nuclear Magnetic Resonance; LOO: Leave-One-Out

Introduction

Natural products from plants are of interest in searching for new anti-cancer drugs and can have a direct effect on HeLa cell line and reduce side effects. Recently, we have isolated a few flavonoids from *Rhizome Zingiber Zerumbet* Sm and tested *in vitro* activities pointed out the relatively strong impacts for cancer cells HeLa [1,2]. Flavonoids are polyphenolic compounds in most plants [3-5]. The flavonoids from *Rhizome Zingiber Zerumbet* Sm were also tested the biological activities in some different cancer cells [6]. The flavonoids presented their activities and role of food within flavonoids in the cancer inhibition are widely studied [7-10]. The derivatives flavonoids are present in all parts of high plants and are found in many everyday vegetables and fruits [1,2]. Flavonoids are known to be a group of compounds that have antioxidant effects or prevent the oxidation of free radicals produced during metabolism, such as OH •, ROO • ... [3,4]. Flavonoids in the natural foods have the potential to form complexes with metal ions, which act as catalysts that inhibit oxidative reactions. Therefore, flavonoids have the effect of protecting the body, preventing atherosclerosis, stroke, aging, liver degeneration, radiation damage and prevention:

osteoporosis, hypertension, cardiovascular, high cholesterol and some cancers [11,12].

The experimental results in this work have been studied the relationships between the structure and anti-cancer activity of flavonoids kaempferol-3-O-methylether and kaempferol-3-O-(2,4-O-diacetyl-alpha-L-rhamnopyranoside) isolating from *Rhizome Zingiber Zerumbet* Sm in Viet Nam using spectrum data ^{13}C-NMR and ^{15}O-NMR on atoms carbon and oxygen [1]. The statistical techniques were supported for building $QSDAR_{MLR}$ and $QSDAR_{ANN}$ model to predict the anticancer activities of these flavonoids [13-18]. In this work, we report the use of semi-empirical quantum calculations TNDO MO and construction of quantitative structure activity relationship (QSDAR) models for 32 flavone and isoflavone derivatives [19-22]. The anti-cancer activities GI_{50}/ μ M of flavonoids in test group and two new flavonoids kaempferol-3-O-methylether and kaempferol-3-O-(2,4-O-diacetyl-alpha-L-rhamnopyranoside) isolating from *Rhizome Zingiber Zerumbet* Sm in Viet Nam resulting from QSDAR models are compared with those from experimental data [1].

Isolation of Kaempferols From Plant

Chemicals and equipment: We used the chemicals and the equipments for isolating and purifying two flavonoids kaempferol-3-O-methylether and kaempferol-3-O-(2,4-O-Diacetyl-Alpha-L-Rhamnopyranoside) before determining the flavonoid structures by ^{1}H-NMR and ^{13}C-NMR spectrum [26]. The following materials are used to isolate the flavonoids as

a) Silica gel with the particle size in range 0.04 to 0.06 mm was used for ordinary and Rp18 phase chromatography.

b) Thin-layer chromatography was implemented by the thin plate DC-Alufolien F254 (Merck) for the ordinary phase and Rp18 F254s (Merck) for the reverse-phase chromatography.

c) Solvents used for the isolation processes: hexane, petroleum ether, chloroform, methanol, ethyl acetate, ethanol, acetone, distilled water.

d) UV handheld lamps, 254 and 365 nm UVITEC effect.

e) Vacuum Evaporators Buchi – 111 and Water Bath cooker JULABO 461.

f) Infrared heating equipment SCHOTT.

g) Chromatography column with diameter range 2 to 5.5 cm.

h) Analytical Balances AND HR 200.

Isolation process of kaempferols: To isolate and purify kaempferol compounds from plant *Rhizome Zingiber Zerumbet* Sm we used the techniques of thin-layer and column chromatography [22]. After isolating the compounds their structures were identified by the different spectrum as

i) Melting temperature carried out on Electrothermal IA 9000 series, using unadjusted capillary

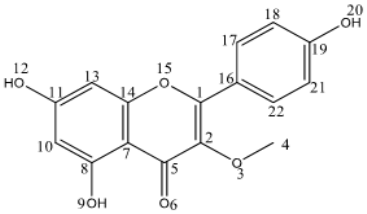
j) Column chromatography with silica gel for ordinary-phase, reverse-phase chromatography Rp 18 and sephadex techniques combined with thin-layer chromatography.

k) Substances were detected by ultraviolet light at wavelengths 254 nm and 365 nm or reagent used is liquid H_2SO_4/EtOH or $FeCl_3$/EtOH.

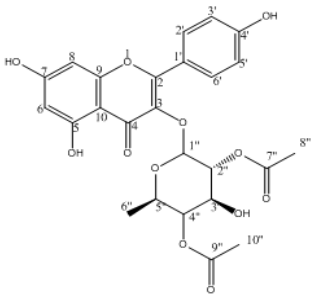
l) Nuclear magnetic resonance spectrum (NMR) ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) implemented on Bruker AM500 FT-NMR Spectrometer.

Prediction of biological activity for new substances: The predictability of the models $QSDAR_{MLR}$ and $QSDAR_{ANN}$ I(7)-HL(9)-O(1) [23] were evaluated carefully by the leave-one-out (LOO) technique using their predictive values R2pred [23,17,18,24-26]. The compounds of test group and two flavonoids kaempferols isolated from plant *Rhizome Zingiber Zerumbet* Sm were employed for evaluating predictability of these QSDAR models [1]. The predicted *in vitro* activities of new isolated kaempferols were compared to experimental *in vitro* activity on Hela cell line. The plant *Rhizome Zingiber Zerumbet* Sm and kaempferols are exhibited in Figure 1 [1].

a) Plant *Rhizome Zingiber Zerumbet* Sm [1]



b) kaempferol-3-O-methylether with $GI_{50,exp}$ (μM) = 15.37 ± 0.401



c) kaempferol-3-O-(2,4-O-diacetyl-alpha-L-rhamnopyranoside with $GI_{50,exp}$ (μM) = 38.86 ± 0.814

Figure 1: The structures of kaempferols isolating from *Rhizome Zingiber Zerumbet* Sm [1].

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Conclusion

The use of computational methods constructed successfully the $QSDAR_{MLR}$ and $QSDAR_{ANN}$ I(7)-HL(9)-O(1) model with relationships between the spectrum data ^{13}C-NMR and ^{15}O-NMR and anti-cancer activities GI_{50} (μ M) of flavonoids. These QSDAR models pointed out the important sites O_1, O_{11}, C_2, C_3, C_6, C_7 và C_2' on flavonoids which effect an *in vitro* activity on Hela cell line. The QSDAR models established in this work can be used for in vitro activity assessment of two kaempferols isolating from plant *Rhizome Zingiber Zerumbet* Sm [1]. This work established the different models QSDAR and isolated two flavonoids from plant *Rhizome Zingiber Zerumbet* Sm that may prove to be useful for guiding the rational search of new therapeutic agents for cancer diseases [1].

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