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Theoretical Studies of Quercetin and its Methylamine Derivatives

Faik Gokalp[a], Ramazan Erenler[b*]

[a]*Department of Mathematics and Science Education, Faculty of Education, Kırıkkale University, 71450 Kırıkkale, Turkey*
[b]*Department of Chemistry, Faculty of Arts and Sciences, Tokat Gaziosmanpasa University, 60240 Tokat, Turkey,*
**Corresponding author, email adress: ramazan.erenler@gop.edu.tr*

ABSTRACT: Quercetin is a significant natural product isolated from many plants reveals a large number of biological activities. Natural products are derivatized to enhance the pharmacological effects. Hence, quercetin was functionalized to display the most active compound theoretically. Moreover, this study will inspire to synthetic chemists for synthesis of active and targeted compound. The chemical properties of quercetin derivatives have been investigated the oretically. B3lyp/6-31+g(d,p) method was used for quantum calculations of these compounds. (2-(3,4-bis(aminomethyl) phenyl)-4-(1,3-diisopropylhexahydropyrimidin-5-yl)-4H-chromene-3,5,7-triyl) trimethanamine was found as the most stable. It can reach the each tissue of the body and has more advantageous than others in terms of the desired reaction. Due to the high polarity of 8-(aminomethyl)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one, it has a potency to dissolve in blood and to be used in pharmaceutical industry.

1. Introduction

Natural products play a significant role in drug discovery process since they exhibit many biological effects (Bayir et al., 2014; Erenler et al., 2018a; Erenler et al., 2016a; Erenler et al., 2015; Erenler et al., 2014; Genç et al., 2019; Guzel et al., 2017; Karan and Erenler, 2017; Karan and Erenler, 2018). Polyphenols, an extensive class of biologically active materials, are found in plants as secondary metabolites (Aksit et al., 2014; Demirtas et al., 2013; Elmastas et al., 2018; Elmastas et al., 2016; Erenler et al., 2018b). These compounds produce color and flavor to various parts of the plants and they play a significant role in resistance against different microbial pathogens, radiation and toxins. Flavonoids, most typical polyphenols reveal fascinating and beneficial medicinal effects on human health. They display a wide range of biological and pharmaceutical properties such as antioxidant, antitumor, antibacterial, immune-stimulating, antiviral effects, prevention of bone lose (Elmastas et al., 2004; Erenler et al., 2017a; Erenler et al., 2017b; Erenler et al., 2017c; Erenler et al., 2016b; Erenler et al., 2016c; Erenler et al., 2016d; Iranshahi et al., 2015). They may have potential valuable effect against diseases such as cardiovascular disease, diabetes, and cancer. Lipophilic flavonoids absorb ultraviolet light that enable the protection of plants against UV radiation (Elmastaş et al., 2015; Li et al., 2016).
Quercetin, an aglycone lacks of an attached sugar. It is yellow needle crystal and insoluble in cold water. It dissolves poorly in hot water but quite soluble in alcohol. A quercetin glycoside is formed by replacement of OH with glycoside group (glucose, rhamnose, or rutinose). Hence, solubilility, absorption and activity can be changed by the attachment of corresponding groups to the quercetin. Quercetin derivatives such as quercetin glycosides are existent in plants extensively. They are found in various foods including berry, apple,

caper, onion, shallot, broccoli, tomato, tea, as well as seed, nut, bark, flower. An extensive biological and pharmacological properties of qurecetin was reported such as anti-inflammatory, gastrointestinal cytoprotective, antitumor, antioxidant, ant diabetic activities (Lin et al., 2019).

Due to the importance of active natural products in drug industry, synthetic chemists focus on synthesis of natural products and their derivatives. Some functional groups are attached to the natural compounds to increase the activities. The functional groups and position of molecules are important to enhance the activity. Therefore, theoretical studies gain a great interest for synthesis of target molecules before synthesis. In this work, theoretical calculations were executed for quercetin derivatives to display the active molecule as well as showing the activity-structure relation. Hence, the most active semi-natural products will be attracted by synthetic chemists to synthesis the target molecules without consuming time and spending redundant chemicals on inactive compounds.

2. Material and Methods

The chemical properties of qurcetin (**1**), 3-(aminomethyl)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one (**2**), 8-(aminomethyl)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one (**3**), 5,7-bis(aminomethyl)-2-(3,4-dihydroxyphenyl)-3-hydroxy-4H-chromen-4-one (**4**), 5,7-bis(aminomethyl)-2-(3,4-bis(aminomethyl)phenyl)-3-hydroxy-4H-chromen-4-one (**5**), (2-(3,4-bis(aminomethyl)phenyl)-4-(1,3-diisopropylhexahydropyrimidin-5-yl)-4H-chromene-3,5,7-triyl)trimethanamine (**6**), were evaluated as theoretical. The molecules were drawn by ChemDraw Ultra 11.0. Theoretical calculation was executed by B3lyp/6-31+g(d,p) method (Gökalp and Erenler, 2018).

3. Results and Discussion

The calculation of quercetin derivatives on B3lyp/6-31+g(d,p) revealed that compound **6** has the most energy with the highest HOMO-LUMA differences among the derivatives. So, the reaction can proceed from compound **1** to compound **6** spontaneously. The energy values of compounds were calculated as 6 > 3 > 5 > 4 > 2 > 1. High E_{HOMO} value indicates the electron releasing ability of a compound. (2-(3,4-bis(aminomethyl)phenyl)-4-(1,3-diisopropylhexahydropyrimidin-5-yl)-4H-chromene-3,5,7-triyl)trimethanamine (**6**) has the most E_{HOMO} value (-0.23394). Therefore, this product (**6**) has a potency to exhibit the most activity (Table 1). In addition, a compound bearing an amine group capable of revealing a large spectrum of activities. Ionization potential (I) is defined as the amount of energy required to remove an electron from a molecule (Geerlings et al., 2003). It is related to the energy of the E_{HOMO} through Eq. (1): $I = -E_{HOMO.}$ High HOMO-LUMO gap indicates the high excitation energy, a good stability, and high chemical hardness (Tanak, 2010). A high chemical reactivity can be associated with a small frontier orbital gap with high polarizability. Global hardness (η) can be rewritten using Koopman's theorem: $\eta = \varepsilon LUMO - \varepsilon HOMO$. In the reaction scheme (Figure 1), compound **3** had the lowest HOMO–LUMO gap and the polarity is also well in blood. Hence this compound has a tendency to react the other compounds i.e. radicals and has an ability to chelate the metal (Karan et al., 2018). The target molecule **6** has the most stable and the less polar molecule than the compound **3**. The stability is significant in drug discovery. Hence, compound **6** has potency to exhibit biological activity with high stability.

Tablo1. E, HOMO, LUMO, Δ (HOMO-LUMO) and Dipol Moment values of moleculas using rb3lyp/6-31+g(d,p) (Dielectric constant in blood*,EPS=58)

Compounds	E	HOMO	LUMO	GAP	Dipol moment
	Hartree	eV	eV	eV	Debye
1	-1104.2681215	-0.22352	-0.07973	0.14379	9.5412
2	-1123.7193398	-0.23024	-0.07625	0.15399	6.9797
3	-1198.9387161	-0.22273	-0.07921	0.14352	10.3907
4	-1143.1432550	-0.22260	-0.07574	0.14686	4.9247
5	-1182.0325967	-0.22683	-0.07581	0.15102	8.3796
6	-1630.0591179	-0.21311	-0.04365	0.16946	5.9618

1 Hartree: 627.509 kcal mol^{-1},
*https://www.microwaves101.com/encyclopedias/miscellaneous-dielectric-constants

The compound **6** can be synthesized as a target molecule to yield the most bioactive and stable compound. The stabilities of compounds were calculated as 6>2>5>4>1>3 order. In addition, the polarity orders were calculated as 3>1>5>2>6>4. The compound **3** has the highest polarity, so it dissolves in blood more than the others. The energy level of the compound **6** is the highest so it can be said to be more advantageous than others in terms of the desired reaction.

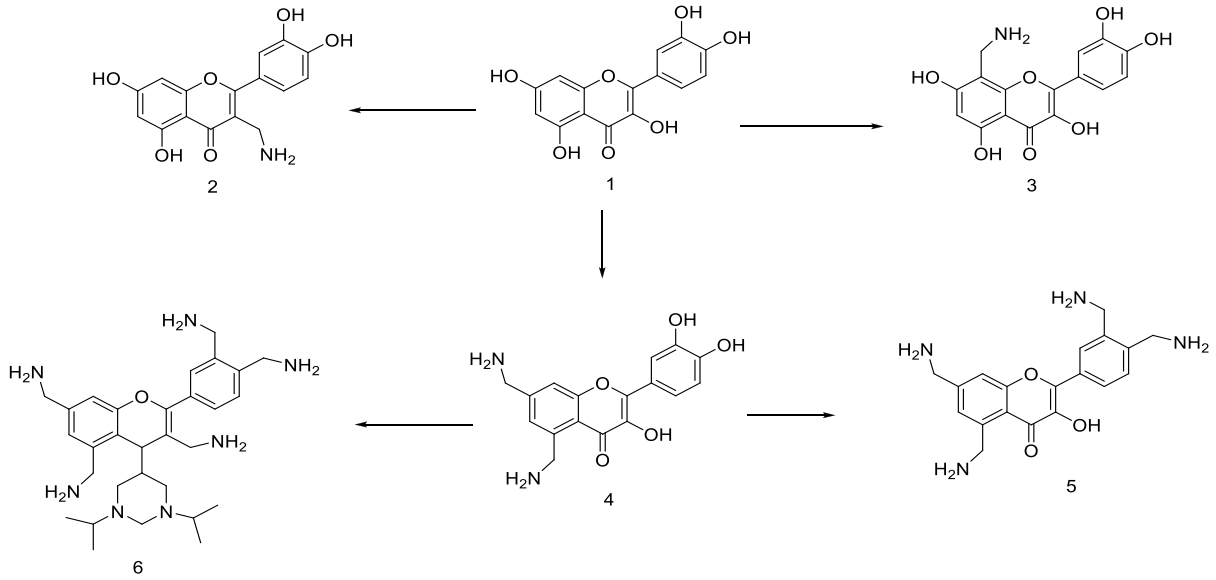

Figure 1. Theoretical calculation of quercetin derivatives.

4. Conclusion

In this study, compound **3** and compound **6** were found to have a potency to reveal the biological activity. These compounds should be synthesized and biological activities should be executed. Due to the significance of stability for pharmaceutical effects, compound **6**

should be a target molecule to be synthesized. In addition, compound **3** has the most polar, so it can dissolve in blood easily.

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