Research Article

Effect of Alkylation of 4'-hydroxy of Kaempferol on its bioactivity: A Theoretical Approach

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ABSTRACT

In this paper, we study the effect of alkylation of 4-hydroxy group of kaempferol on its medicinal properties using Molinspiration software. We designed nine 4-alkoxy derivative kaempferol. All nine molecules obey Lipinski's rule for molecular properties which is essential for bioactivity. Bioactivity score of these compounds is obtained by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor. All alkoxy derivatives show moderate activity towards GPCR ligand, ion channel modulator, protease inhibitor and good activity towards nuclear receptor ligand, kinase inhibitor, and enzyme inhibitor.

Keywords: Bioactivity score, Kaempferol, Molecular properties, Lipinski'sule, Molinspiration.

INTRODUCTION

Flavonoids are a group of plant secondary metabolites characterized by a diphenylpropane structure. They are usually found in the plant kingdom. Flavonoids may play a role in the decreased risk of chronic diseases associated with a diet rich in plant-derived foods. Some epidemiological studies show that constructive relationship between the ingestion of foods containing flavonoids and a reduced risk of developing cancer and cardiovascular diseases [1]. The flavonoid kaempferol (3,5,7-trihydroxy-(2-4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a yellow compound with a low molecular weight found in plant-derived foods and in plants used in traditional medicine. Kaempferol is common in Pteridophyta, Pinophyta and Angiospermae, Dicotyledons and Monocotyledons of Angiosperms. Kaempferol shows various medicinal properties such as antioxidant, anti-inflammatory, anticancers, cardiovascular disease, neuron disorder and cholesterol [2]. Traditionally, kaempferol is used to treat hypertension, abdominal pains, headache, and rheumatism [3].

In this paper we study the effect of alkylation of 4-hydroxy group on bioactivity of kaempferol using molinspiration software.

MATERIALS AND METHOD

Structures of all the nine 4-alkoxy derivative of kaempferol were taken from the literature and their structures were drawn using online molinspiration software (www.molinspiration.com) for calculation of molecular properties (Log P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors). The bioactivity score and drug likeness properties of the all the ten compounds were compared.

Prediction of bio-activity

1. Molecular properties of nine alkoxy derivative of kaempferol were calculated using molinspiration and the values were given in Table 1.
2. Bio-activity scores of the nine alkoxy towards GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitors were given in Table 2.

Lipinski's Rule

Lipinski's rule of five commonly known as the Pfizer's rule of five or simply the Rule of five is a regulation of thumb to estimate drug likeness or to indentify a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in man. The principle was designed by Christopher A. Lipinski in 1997. The rule expresses molecular properties vital for a drug's pharmacokinetics in the human body, including their absorption, distribution,

metabolism and elimination (ADME) Components of the Lipinski's rule.

Lipinski's rule states

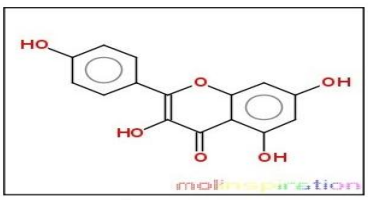
- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular weight less than 500
- An octanol-water partition coefficient log P not greater than 5
- No more than one number of violation

Molinspiration

Molinspiration, web based software was used to obtain parameter such as MiLogP, TPSA, drug likeness. MiLogP, is estimated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors. MiLog P parameter is applied to check good permeability across the cell membrane. TPSA is related to the hydrogen bonding potential of the compound. Computation of volume developed at Molinspiration is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good descriptor of absorption and bioavailability of drugs. Through drug likeness data's of a particle, it can be checked molecular properties and structure feature with regard to known drugs.

Bioactivity score

Bioactivity of the drug can be found out by estimating the activity score of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor. All the parameters were determined with the aid of software Molinspiration drug-likeness score online (www.molinspiration.com). Calculated drug likeness score of each compound and compared with the specific bodily process of each compound, and the results were compared with kaempferol. For organic molecules the probability is if the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive.



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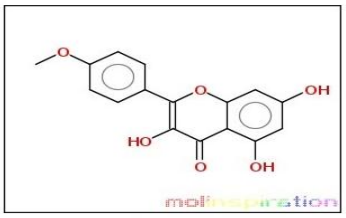

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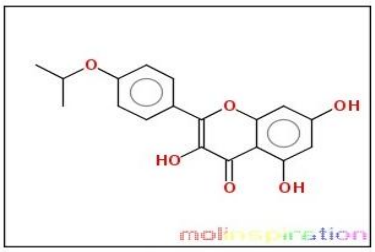

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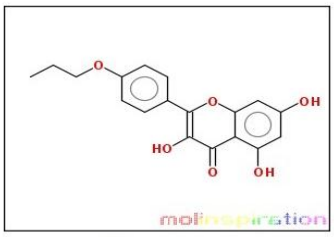

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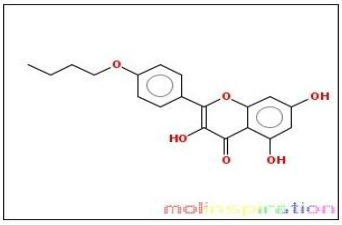

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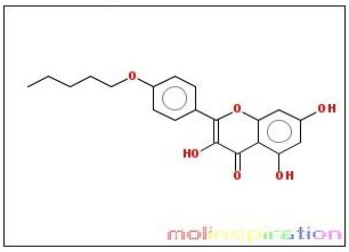

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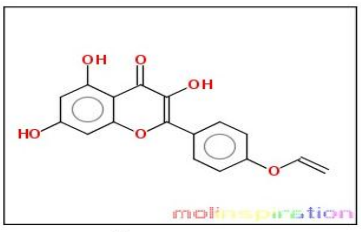

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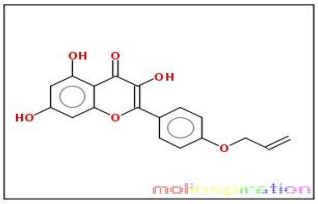

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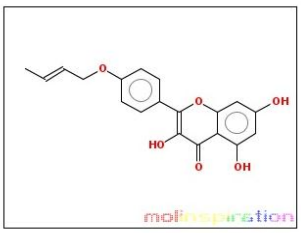

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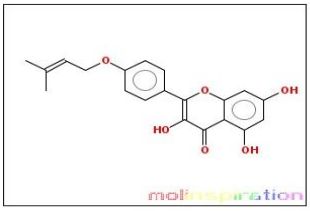

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Fig. 1: Structures of 4-alkoxy derivative of Kaempferol

Table 1: Calculation of Molecular Properties of 4-alkoxy derivatives of Kaempferol

Entry	Compound	miLOgP	TPSA	natoms	MW	nON	nOHNH	nviolations	nrotb	Volume
1	Kaempferol	2.17	111.12	21	286.24	6	4	0	1	232.07
2	4-Methoxy	2.71	100.13	22	300.27	6	3	0	2	249.59
3	4-Isoproxy	3.45	100.13	24	328.32	6	3	0	3	282.98
4	4-Propoxy	3.59	100.13	24	328.32	6	3	0	4	283.20
5	4-Butoxy	4.15	100.13	25	342.35	6	3	0	5	300
6	Pentyloxy	4.65	100.13	26	356.37	6	3	0	6	316.80
7	Vinyloxy	3.01	100.13	23	312.28	6	3	0	3	260.76
8	Allyloxy	3.35	100.13	24	326.30	6	3	0	4	277.57
9	4-But-2-enyloxy	3.60	100.13	25	340.33	6	3	0	4	293.81
10	3-Methylbut-2-enyloxy	4.38	100.13	26	354.36	6	3	0	4	310.37

Table 2: Bioactivity Score 4-alkoxy derivatives of Kaempferol

S. N.	Compound	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Kaempferol	-0.10	-0.21	0.21	0.32	-0.27	0.26
2	4-Methoxy	-0.12	-0.28	0.19	0.30	-0.28	0.20
3	4-Isoproxy	-0.06	-0.28	0.15	0.36	-0.22	0.19
4	4-Propoxy	-0.06	-0.25	0.15	0.41	-0.18	0.21
5	4-Butoxy	-0.01	-0.21	0.17	0.42	-0.13	0.24
6	Pentyloxy	0.01	-0.20	0.16	0.42	-0.10	0.24
7	Vinyloxy	-0.00	0.03	0.11	0.39	-0.19	0.16
8	Allyloxy	-0.21	-0.32	0.08	0.38	-0.28	0.11
9	4-But-2-enyloxy	-0.09	-0.18	0.11	0.51	-0.16	0.26
10	3-Methylbut-2-enyloxy	-0.09	-0.20	0.06	0.46	-0.24	0.26

Table 3: Green Test of 4-alkoxy derivative of Kaempferol

Sr. No.	Compound Name	ESR1 pkd prediction	ESR1 field prediction	Toxicity
1	Kaempeferol	6.12; Compound has predicted activity above 90 percent of approved drugs; above 12 percent of known binders	0.85; Compound has predicted activity above 83 percent of approved drugs; above 13 percent of known binders	
2	4-Methoxy	5.34; Compound has predicted activity above 67 percent of approved drugs; above 1 percent of known binders	0.27; Compound has predicted activity above 58 percent of approved drugs; above 2 percent of known binders	
3	4-isopropoxy	5.22; Compound has predicted activity above 61 percent of approved drugs; above 0 percent of known binders	0.2; Compound has predicted activity above 55 percent of approved drugs; above 2 percent of known binders	

4	4-Propoxy	6.11; Compound has predicted activity above 90 percent of approved drugs; above 11 percent of known binders	0.27; Compound has predicted activity above 58 percent of approved drugs; above 2 percent of known binders	
5	4-Butoxy	6.03; Compound has predicted activity above 88 percent of approved drugs; above 9 percent of known binders	0.27; Compound has predicted activity above 58 percent of approved drugs; above 2 percent of known binders	
6	Pentyloxy	6.23; Compound has predicted activity above 92 percent of approved drugs; above 15 percent of known binders	0.29; Compound has predicted activity above 59 percent of approved drugs; above 2 percent of known binders	
7	Vinyloxy	5.72;Compound has predicted activity above 82 percent of approved drugs; above 3 percent of known binders	0.32; Compound has predicted activity above 62 percent of approved drugs; above 2 percent of known binders	
8	Allyloxy	6.11; Compound has predicted activity above 90 percent of approved drugs; above 11 percent of known binders	0.25; Compound has predicted activity above 57 percent of approved drugs; above 2 percent of known binders	Toxicity: Contain chemical substructures that may be associated with genotoxic carcinogenicity
9	4-But-2-enyloxy	6.03; Compound has predicted activity above 88 percent of approved drugs; above 9 percent of known binders	0.3; Compound has predicted activity above 60 percent of approved drugs; above 2 percent of known binders	Toxicity: Contain chemical substructures that may be associated with genotoxic carcinogenicity
10	3-Methylbut-2-enyloxy	5.76; Compound has predicted activity above 83 percent of approved drugs; above 4 percent of known binders	0.28; Compound has predicted activity above 58 percent of approved drugs; above 2 percent of known binders	Contain chemical substructures that may be associated with genotoxic carcinogenicity

RESULTS AND DISCUSSION

a. Molecular property of the Chalcones

The nine 4-alkoxy derivate of kaempferol obeyed the Lipinski's rule of five and showed good drug likeness scores. MiLog P values of these alkoxy derivatives were found to be >5 (2.17-4.65) indicated their good permeability across the cell membrane. All the derivatives were found to have TPSA will be below 160Å^2 (100.13), molecular weight < 500, No. of hydrogen bond donors ≤ 5, No. of hydrogen acceptor ≤ 10, n-violations 0, number of rotatable flexible bonds >5.

b. Bioactivity scores of the Chalcones

The bioactivity scores of the fourteen compounds have shown the following observations.

1. GPCR Ligand: Among the nine 4-alkxoy derivative of kaempferol, pentyloxy derivative were found to be highly active (≥ 0) towards GPCR ligands and other eight derivative is moderately active (≤ 0).
2. Ion channel modulator: Among the nine 4-alkoxy derivative of kaempferol, vinyloxy derivative were found to be highly active (≥0). The remaining eight derivatives were to be moderately active.
3. Kinase inhibitor: All alkoxy derivatives were found to be highly active (≥ 0) towards Kinase inhibitor.
4. Nuclear receptor ligand: All alkoxy derivatives were found to be highly active (≥ 0) towards Nuclear receptor ligand.
5. Protease inhibitor: All alkoxy derivatives were found to be moderately active (≤ 0) towards Protease inhibitor.
6. Enzyme inhibitor: All alkoxy derivatives were found to be highly active (≥0).

Green Test

We calculate the toxicity of all alkoxy derivative of kaempferol using Molsoft L. L. C. Green Test prediction [7]. Using this software we test chemical interferes with biological pathway. The pathways described in this software are Estrogen Receptor 1(ESR 1) is ESR1 is a ligand-activated transcription factor. Many chemicals in food and the environment can mimic estrogen and bind to ESR1 thereby disrupting the endocrine system. Xenoestrogen chemicals can adversely affect human health and cause sexual development and reproductive diseases as well as osteoporosis.

pKd is –log(Kd[M])

APF score is the Field match score normalized to the normal distribution with the mean of 0 and standard deviation of 1. Actives correspond to the positive values.

The results of Green Test are given in Table 3. The compound no. 1 to 7 are safe to human beings as well as environment. The compound no. 8 to 10 shows genotoxicity.

CONCLUSION

In conclusion, all alkoxy derivatives show highly active to moderate bioactivity score. All alkoxy derivatives obey Lipinski's rule for Drug Likeness activity of the molecules. 4-Pentyloxy show high activity towards GPCR ligand, vinyloxy show high activity towards ion channel modulator, 4-butoxy show high activity towards kinase inhibitor, 4-but-2-enyloxy high activity towards nuclear receptor activity. Prenyloxy and buteneoxy shows high enzyme inhibitor activity. All alkoxy derivatives are moderately active towards protease inhibitor. As the carbon chain increases the Drug Likeness also increases upto five carbon, branching decreases Drug Likeness score, double bond also increases Drug Likeness score.

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