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Molecular docking of active compounds from Kepok banana (Musa acuminata x balbisiana) peels extract on the NF-κβ pathway in acne vulgaris

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ABSTRACT

This study aimed to analyze the interaction between the active compound from Kepok banana peel extract (KBPE) and several transcription factors in the NF-κβ pathway. This is an in silico study. The active compound of KBPE was characterized by LC-HRMS. Molecular docking analysis using software OpenBabel, Hex 8.0, Chimera 1.6.2, Discovery Studio 4.1, LigPlot+ and LigandScout 3.1. The docking molecular targets include NF-κβ p65/DNA, NF- p50/p65/DNA, NF-κβ p52/RelB/DNA, and NF-κβ p50/RelA/DNA. At that target, the compounds that interacted the most were trigonelline, salsolinol, rutin, and rutin. It was concluded that the active compound of KBPE has an affinity for transcription factor molecules in the N-kB pathway. Therefore, KBPE can be an anti-inflammatory candidate in acne vulgaris.

Key words: bioinformatics; docking; inflammation; LC-HRMS; skin disease.

INTRODUCTION

Acne vulgaris is a skin condition that affects millions of people worldwide. This disease manifests itself on the face and upper trunk (chest and back) and primarily affects people aged 11 to 30 [1-3]. Acne has a psychosocial impact, despite the fact that it is not life threatening [1]. This disorder is classified as a complex chronic inflammatory disease with an unknown pathomechanism [2]. Acne vulgaris is caused by a variety of factors, including genetics, gender, diet, hormones, corticosteroids, and topical cosmetics. Epithelial cell proliferation, abnormal differentiation of hair follicles, abnormal sebum secretion, disruption of skin flora, and inflammation are among the molecular events involved [4].

Propionibacterium acnes overgrowth causes inflammation in acne vulgaris [5, 6]. These bacteria will produce chemotactic factors that will stimulate keratinocytes to secrete IL-6 and IL-8. Furthermore, these factors induce monocytic cells to produce IL-1, TNF-α, IL-8, and IL-12. The activation of toll-like receptor 2 is required for the production of these shared cytokines [7–8]. The activation of the NF-κβ pathway results in the production of these proinflammatory cytokines [9]. TNF-α levels increased in acne vulgaris patients, which was influenced by TNF-α polymorphisms [10].

Until recently, the standard treatment for acne vulgaris included benzoyl peroxide, retinoids, and topical antibiotics. Skin irritation is caused by benzoyl peroxide and retinoids, while antibiotics promote resistance [11, 12]. As a result, other therapeutic approaches, such as plant-derived materials, are required. Bananas are a source of food in tropical countries such as Indonesia [13]. The fruit is the only reason for using bananas as a functional ingredient. The fruit's skin can be used as a functional agent to promote health. For hepatoprotection, fresh banana peel outperforms dried banana peel [14]. Previous study has shown that banana peels have antihyperglycemic and antioxidant properties [15]. To the best of our knowledge, there was no study has been conducted on the use of Kepok banana peels extract (KBPE) as an anti-inflammatory agent for acne vulgaris.

The purpose of this study is to investigates the molecular docking bioinformatics of the active compound in KBPE on the NF-κβ pathway.

MATERIAL AND METHODS

Extraction

The Kepok banana (*Musa acuminata x balbisiana*) were obtained from a traditional market in Malang, East Java, Indonesia. The selected banana peel is made into powder at UPT Material Medica Batu City, East Java, Indonesia. The powder was then macerated for 14 hours in 0.01% v/v ethanol-HCl. The solvent in the extract was evaporated at a temperature of 45oC and low pressure with a rotary evaporator. The crude extract was centrifuged at 4500 rpm for 30 minutes then solvent extraction was performed using ethyl acetate. Freeze dry treatment of crude extract to produce yield. The resulting extract will be analyzed by LC-HRMS.

Analysis of LC-HRMS

The extracted sample was diluted according to the solvent (polar). Dilution was done by looking at the thickness of the sample (not too thick and not too runny) with a final volume of 1300 ul. The sample was vortexed for one minute and then spun down for 2 minutes. The supernatant was filtered using a 0.22 m syringe filter and put into a vial. The sample in the vial was put into the Autosampler and then injected into the LC-HRMS.

Analysis was carried out with HPLC (Thermo Scientific Dionex Ultimate 3000 RSLC Nano with microflow meter). The solution is 0.1% formic acid in water (A) or acetonitrile (B). The analysis used was the Hypersil GOLD AQ particle size of 50 x 1 mm x 1.9 u with a flow rate of 40 L/min. Processing time is 30 minutes with a temperature of 30oC in the oven column.

Searching for amino acids in the NF-κβ pathway

The amino acid composition of the protein making up the NF-κβ pathway was obtained from the National Center for Biotechnology Information (NCBI), United States National Library of Medicine (NLM), National Institute of Health (NIH) (http://www.ncbi.nlm.nih). .gov). The 3D structure of the protein that makes up the NF- pathway is obtained in the form of a *.sdf file format, which will then be converted into a *.pdb file using OpenBabel software [16].

Searching for the structure of the active compound of kepok banana peel extract

The 3D structure of the active compound components of the Kepok (*Musa acuminata x balbisiana*) banana peel extract was obtained from the PubChem Open Chemistry Database. The structure is in the form of a *.sdf file format, which will then be converted into a *.pdb file using OpenBabel software [17].

Protein 3D structure modeling

The 3D structure of the target proteins was predicted using the SWISS-MODEL webserver using the homology modeling method. The 3D structure of the protein was then validated using Ramachandran plot analysis [16,18].

Docking and visualization between protein-ligand

Docking simulations between kepok banana peel extract and target proteins were carried out using HEX 8.0 software [19]. The docking protocol consists of three visualization stages, namely minimization of rigid-body energy, semi-flexible repair and finishing refinement in an explicit solvent. The docking results are then visualized with Chimera 1.6.2 and Discovery Studio 4.1 software.

Analysis of the binding interaction between protein and ligand

The results of the docking analysis will then be visualized using Discovery Studio 4.1, LigPlot+ and LigandScout 3.1 software [20, 21]. Analysis of the interaction between proteins and ligands was carried out to find out the number and types of bonds formed, such as hydrogen bonds, hydrophobic bonds, and van der Waals bonds.

RESULTS

The active compound content of KBPE as determined by LC-HRMS is shown in Table 1 and Figure 1. Trigonelline, isovanillic acid, vanillin, ferulic acid, 3-methoxyfavone, rutin, and salsolinol are among the active ingredients.

Figure 2 and Table 2 show the docking of the NF-κβ p65/DNA complex with various active compounds from KBPE. Vanillin, ferulic acid, 3-methoxyfavone, rutin, and salsolinol are examples of compounds that do not interact with the NF-κβ p65/DNA complex. Trigonelline (binding energy is -38.02 kJ/mol) and isovanillic acid (binding energy is -27.81 kJ/mol) are two compounds that interact with the NF-κβ p65/DNA complex. The interactions for trigonelline are arranged by van der Walls bonds at ILE134, GLN135, and THR136. Van der Walls bonds in ILE134 and GLN135, as well as carbon-hydrogen bonds in GLN135, govern isovanillic acid interactions.

The docking of various KBPE compounds and the NF-κβ p50/p65/DNA heterodimer complex is shown in Figure 3 and Table 2. Trigonelline has a bonding energy of –189.09 kJ/mol, vanillin has a bonding energy of –187.31 kJ/mol, isovanillic acid has a binding energy of –203.20 kJ/mol, and salsolinol has a binding energy of –214.38 kJ/mol. Pi-Alkyl interactions on MET32, electrostatic interactions on ARG35 and ARG 33, and Pi-hydrogen donor bonds on DA13 are among the other bonds. Van der Walls bonds form at GLY31, ASN186, ARG35, and SER35 in vanillin. Carbon hydrogen bonds are also formed in ALA43. The Pi-Alkyl interaction on ARG33 and MET32 is another bond. Van der Walls bonds form in GLY36L, HIS364, ILE439, PHE353, LEU437, GLY365, and SER363 for isovanillic acid. Furthermore, carbon hydrogen bonds are formed with GLY438 and PRO362. ARG354 forms conventional hydrogen bonds, while VAL412 and ARG356 form Pi-Alkyl interactions.

The docking properties of the NF-κβ p52/RelB/DNA complex and various active compounds of KBPE are shown in Figure 4 and Table 2. Vanillin (binding energy -184.62 kJ/mol), trigonelline (binding energy -188.57 kJ/mol), ferulic acid (binding energy -199.15 kJ/mol), isovanillic acid (binding energy -257.20 kJ/mol), rutin (binding energy -355.52 kJ/mol), and salsolinol (binding energy -197.67 kJ/mol) were found to interact with the p52/RelB/DNA complex.

Figure 5 and Table 2 show the docking of NF-κβ p50/RelA/DNA with various active compounds from KBPE. Several compounds, including trigonelline, 3-methoxyfavone, and salsolinol, have no interaction with RelA. The interaction energy of vanillin is -16.92 kJ/mol. Van der Walls binds to Leu154, Asp153, Tyr152, Arg94, and His86 to form these interactions. The interaction is also mediated by hydrogen bonding with Lys123. Tyr152 and Asp153 form covalent bonds as well. Asp151 is involved in carbon-hydrogen bonding. The interaction energy of ferulic acid is -22.71 kJ/mol. Covalent bonds (Phe434) and van Der Walls bonds form these interactions (Phe 434, Pro380, Leu437, Gly366, Gly365). The interaction energy of isovanillic acid is -16.22 kJ/mol. Van der Walls bonds (Lys123, Leu154, Tyr152, Asp153), covalent bonds (Lys123, Tyr152, Tyr352, Tyr152, Asp153), and conventional hydrogen bonds form these interactions (Arg84). The bond energy of rutin is -44.12 kJ/mol. Van der Walls bonds, conventional hydrogen bonds, carbon hydrogen bonds, and covalent bonds all contribute to these interactions.

DISCUSSION

We simulated the interaction of the NF-κβ p65/DNA complex with the active compound of KBPE. Only trigonelline (bonding energy -38.02 kJ/mol) and isovanillic acid (binding energy -27.81 kJ/mol) interacted with the p65/DNA complex. In terms of negative bond energy, trigonelline interacts with the p65/DNA complex more easily than isovanillic acid. Trigonelline is a short alkaloid compound [22]. Several studies have demonstrated trigonelline's anti-inflammatory capacity by lowering inflammatory cytokines [23]. Trigonelline was found to interact with the NF-κβ p65/DNA complex in this study. This elucidates the mechanism by which trigonelline inhibits NF-κβ activation. Previous study has demonstrated the effect of isovanillic acid on the reduction of TNF-α in monocyte cells induced by lipopolysaccharide [24]. Several other compounds did not interact with the NF-κβ p65/DNA complex, indicating that vanillin, ferulic acid, 3-methoxyfavone, rutin, and salsolinol are involved in the NF-κβ pathway via different mechanisms.

We also simulated the interaction of the NF-κβ p50/p65/DNA heterodimer complex with the active compound in NF-κβ. Trigonelline (binding energy of –189.09 kJ/mol), vanillin (bonding energy of –187.31 kJ/mol), isovanillic acid (binding energy of –203.20 kJ/mol), and salsolinol (binding energy of –214.38 kJ/mol) are among the interacting compounds. Salsolinol is the compound with the lowest bonding energy and thus the easiest to form interactions with. Salsolinol is classified as a tetrahydroisoquinoline alkaloid. The presence of salsolinol in this extract confirms previous findings in bananas [25, 26].

Vanillin (bond energy -184.62 kJ/mol), trigonelline (bond energy -188.57 kJ/mol), ferulic acid (bond energy -199.15 kJ/mol), isovanillic acid (bond energy -257.20 kJ/mol), and rutin (bond energy -355.52 kJ/mol) were found to interact with the NF-κβ p52/RelB/DNA complex. Rutin is the most easily interacting compound. Rutin (binding energy of -44.12 kJ/mol) was the most easily interacting compound with complex of NF-κβ p50/RelA/DNA. Strong bonds, namely covalent bonds in several amino acids, are formed. This study extends previous findings that rutin is a downregulator of NF-κβ [27, 28].

It was concluded that various compounds found in KBPE had different affinities for molecules involved in the NF-κβ pathway. Thus, the KBPE can be a candidate as an anti-inflammatory in acne vulgaris.

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FIGURE

Figure 1. Active compounds from Kepok banana peel extract identified by LC-HRMS

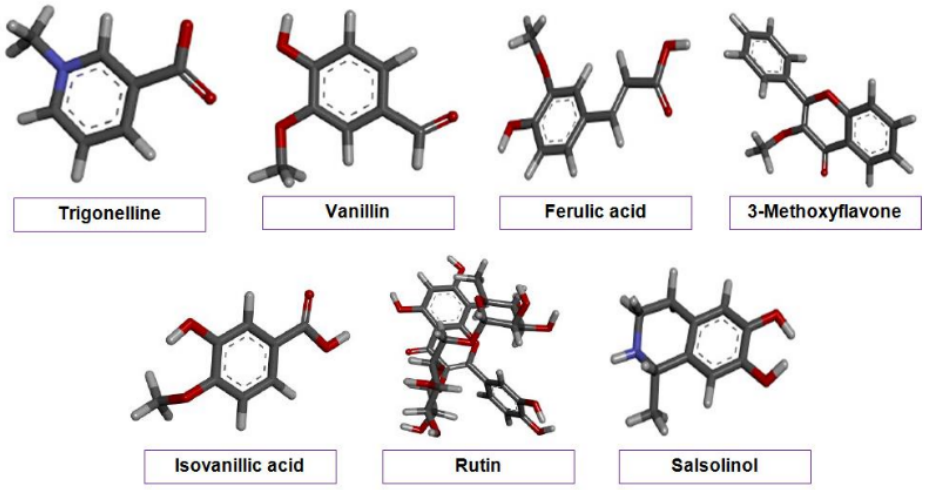


Figure 2. Molecular docking of NF-κβ p65/DNA complex with trigonelline (A) and isovanillic acid (B).

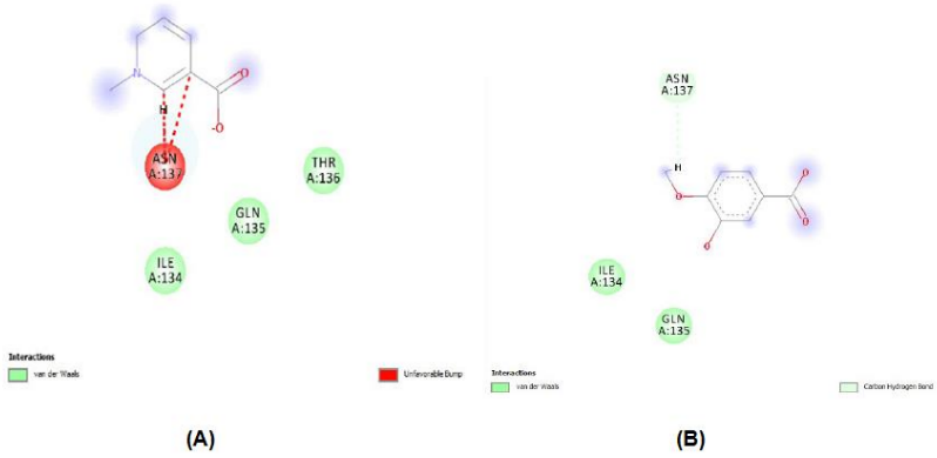


Figure 3. Molecular docking of the NF-κβ p50/p65/DNA heterodimer complex with trigonelline (A), vanillin (B), isovanillic acid (C), and salsolinol (D).

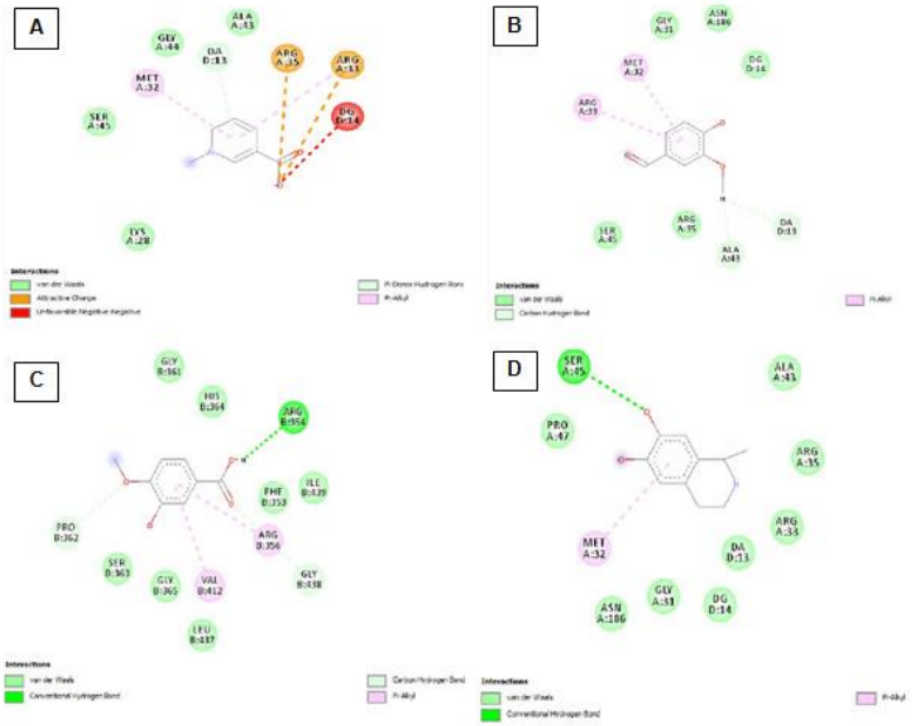


Figure 4. Molecular docking of NF-κβ p52/RelB/DNA complex with vanillin (A), trigonelline (B), ferulic acid (C), isovanillic acid (D), and rutin (E).

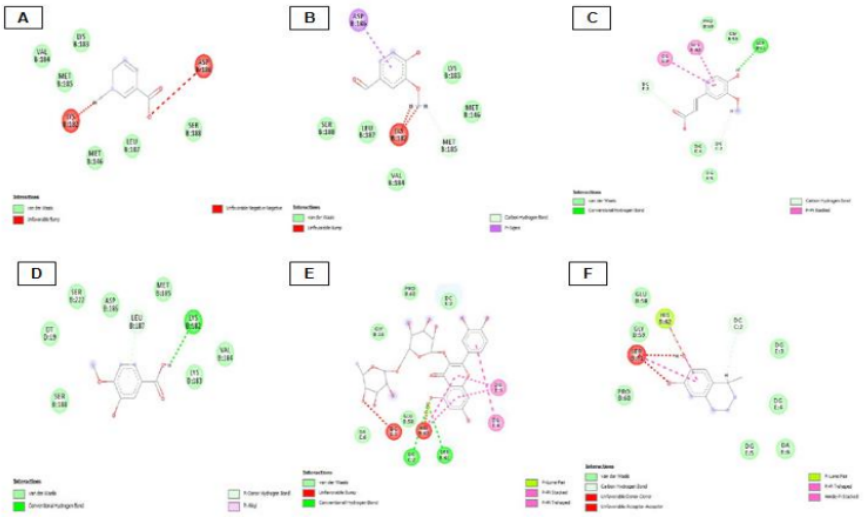
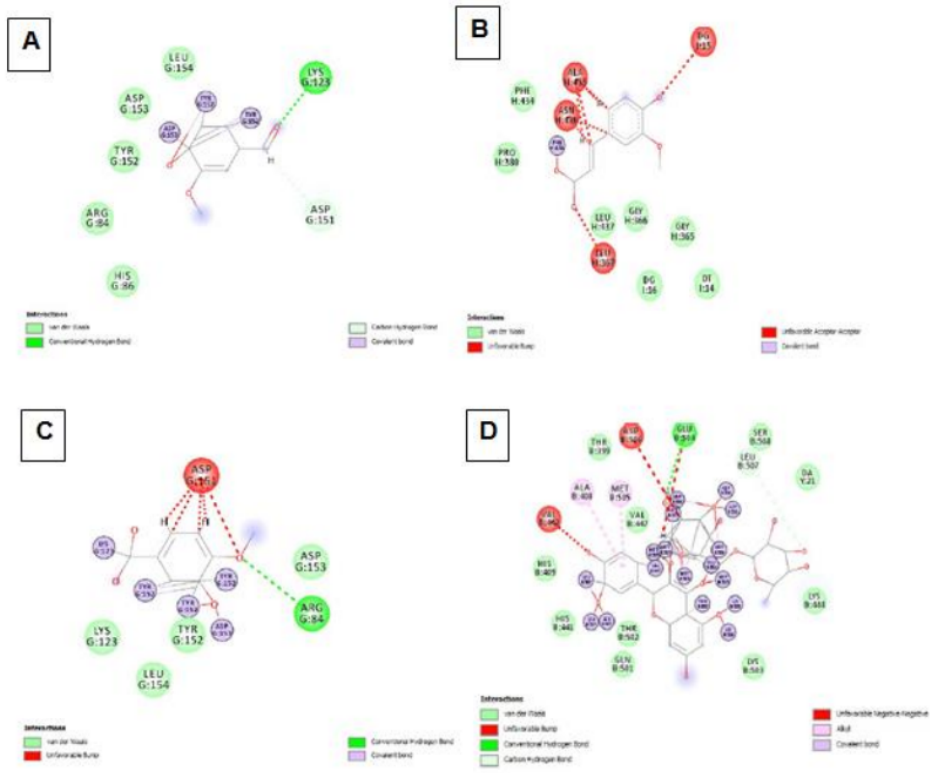


Figure 5. Molecular docking of NF-κβ p50/RelA/DNA complex with vanillin (A), ferrulin (B), isovanillic acid (C), and rutin (D).



TABLES

Table 1. Active compounds from Kepok banana peel extract identified by LC-HRMS

Active compunds	Group	Molecular Weight	Retention time
Trigonelline	Alkaloid	137.04747	2.023
Vanillin	Phenolic acid	152.04723	8.003
Ferulic acid	Phenolic acid	194.05777	8.625
3-methoxyflavone	Flavone	274.06264	12.89
Isovanillic acid	Phenolic acid	168.04209	7.386
Rutin	Flavonoid	610.15331	8.189
Salsolinol	Alkaloid	179.09441	2.741

Table 2. Interaction between active compounds from Kepok banana peel extract with protein in NF-κβ pathway

Ligand	Protein as target	Binding energy
Trigonelline	Homodimer complex of NF-κβ p65/DNA (PDB ID: 2RAM)	-38.02 kJ/mol
Vanillin	Homodimer complex of NF-κβ p65/DNA (PDB ID: 2RAM)	0 kJ/mol
Ferulic acid	Homodimer complex of NF-κβ p65/DNA (PDB ID: 2RAM)	0 kJ/mol

3-methoxyflavone	Homodimer complex of NF-κβ p65/DNA (PDB ID: 2RAM)	0 kJ/mol
Isovanillic acid	Homodimer complex of NF-κβ p65/DNA (PDB ID: 2RAM)	-27.81 kJ/mol
Rutin	Homodimer complex of NF-κβ p65/DNA (PDB ID: 2RAM)	0 kJ/mol
Salsolinol	Homodimer complex of NF-κβ p65/DNA (PDB ID: 2RAM)	0 kJ/mol
Trigonelline	Heterodimer complex of NF-κβ p50/p65/DNA (PDB ID: 1VKX)	-189.09 kJ/mol
Vanillin	Heterodimer complex of NF-κβ p50/p65/DNA (PDB ID: 1VKX)	-187.31 kJ/mol
Ferulic acid	Heterodimer complex of NF-κβ p50/p65/DNA (PDB ID: 1VKX)	0 kJ/mol
3-methoxyflavone	Heterodimer complex of NF-κβ p50/p65/DNA (PDB ID: 1VKX)	0 kJ/mol
Isovanillic acid	Heterodimer complex of NF-κβ p50/p65/DNA (PDB ID: 1VKX)	-203.20 kJ/mol
Rutin	Heterodimer complex of NF-κβ p50/p65/DNA (PDB ID: 1VKX)	0 kJ/mol
Salsolinol	Heterodimer complex of NF-κβ p50/p65/DNA (PDB ID: 1VKX)	-214.38 kJ/mol
Trigonelline	Complex of NF-κβ p52/RelB/DNA (PDB ID: 3DO7)	-188.57 kJ/mol
Vanillin	Complex of NF-κβ p52/RelB/DNA (PDB ID: 3DO7)	-184.62 kJ/mol
Ferulic acid	Complex of NF-κβ p52/RelB/DNA (PDB ID: 3DO7)	-199.15 kJ/mol
3-methoxyflavone	Complex of NF-κβ p52/RelB/DNA (PDB ID: 3DO7)	0 kJ/mol
Isovanillic acid	Complex of NF-κβ p52/RelB/DNA (PDB ID: 3DO7)	-257.20 kJ/mol
Rutin	Complex of NF-κβ p52/RelB/DNA (PDB ID: 3DO7)	-355.52 kJ/mol
Salsolinol	Complex of NF-κβ p52/RelB/DNA (PDB ID: 3DO7)	-197.67 kJ/mol
Trigonelline	Complex of NF-κβ p50/RelA/DNA (PDB ID: 3GUT)	0 kJ/mol
Vanillin	Complex of NF-κβ p50/RelA/DNA (PDB ID: 3GUT)	-16.92 kJ/mol
Ferulic acid	Complex of NF-κβ p50/RelA/DNA (PDB ID: 3GUT)	-22.71 kJ/mol
3-methoxyflavone	Complex of NF-κβ p50/RelA/DNA (PDB ID: 3GUT)	0 kJ/mol
Isovanillic acid	Complex of NF-κβ p50/RelA/DNA (PDB ID: 3GUT)	-16.22 kJ/mol
Rutin	Complex of NF-κβ p50/RelA/DNA (PDB ID: 3GUT)	-44.12 kJ/mol
Salsolinol	Complex of NF-κβ p50/RelA/DNA (PDB ID: 3GUT)	0 kJ/mol

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