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Original Article

Establishment of a 3D-structure Database for Chemical Compounds in Indonesian Sponges

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ABSTRACT

Objective: Nowadays, There hasn't any three-dimensional (3D) chemical structure database yet for biologically active compound in sponges from Indonesian origin. Therefore, this study aimed to create *in silico* a 3D-structure database of such compound and to evaluate the preferred software for this purpose. **Methods:** 2D- structure of selected compounds was established using MarvinSketch software. Conversion from 2D- into 3D-structures was evaluated by comparing MarvinSketch, OpenBabel and VegaZZ software packages. Visualization of the respective 3D-structures was perfomed by using PyMOL software. From 68 scientific articles, 212 chemical compounds were selected from 53 Indonesian sponge species. **Results:** The conversion of 2D-structures of the selected 212 chemical compound into 3D-structures lead to 7118 files, respectively consisting of 2508 files from the MarvinSketch, 1672 files from the OpenBabel and 1051 files from the VegaZZ software. The results based on the extention files were 1043 SDF, 1258 MOL and 2930 PDB format files of the three-dimensional structure. The valid and correct three-dimensional structure of chemical compound were 914 .sdf format files, 916 format .mol files and 72 .pdb format files. From the three-dimensional structures visualization, the database prefers established by using MarvinSketch with SDF or MOL format files since the results is consistent to literature and contain less number of errors.

Key words: 2D-and 3D-chemical structures, 3D-database of chemical structures, Evaluation of software packages, Indonesian sponges.

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INTRODUCTION

Ocean covered about 71% of the earth's surface and produced the largest source of bioactive compounds.[1] Indonesia, the world's largest archipelago comprising about 17,508 islands and had a coastline of 81,000 km, was known as the richest country in the world regarding marine organisms biodiversity.[2,3] Since the 1950's, research had shown marine organisms became the largest source of structural and active biological metabolites. Thus, it became the important field among the scientific community and have became an opportunity for drug discovery.[4]

Nowadays more than 14,000 new bioactive compounds had been identified from the ocean and approximately 300 patents had been issued for marine natural products.[2,5] Since 1990, research of marine bioactive compounds had been initiated by researchers in Indonesia.[6] In recent years, more than 100 marine bioactive compounds had been isolated from Indonesia marine organisms and reported in more than 70 publications. Marine organisms that became the largest research object in Indonesia were marine invertebrates, especially sponges and soft corals.[3] The publication of new bioactive compounds from Indonesia's sponges and soft corals in 2000-2009 increased by about 300% compared to 1900-1999.[4,7] Alkaloids, terpenoids, steroids and other types of new bioactive compounds were reported to be mostly derived from Indonesian sponges and soft corals.[7] Among other marine invertebrates, sponges were the largest source of active ingredients for pharmaceutical products.[2] The sponges were the feeder filter organisms where the various microorganisms could be through the pores of the body and the interaction between the host and the symbiotic microorganisms would produce various chemical compounds in the sponge.[7] Therefore, the sponges in Indonesia had a potential for new drug design development.

The study about bioactive compounds of marine organisms was not easy. It had a high risk of uncertain results. Also, the research needed long time to be done and the cost was not cheap. To overcome the initial obstacles in this study, *in silico* methods such as computer-aided drug design and software and molecular dynamics were used.[8,9] This method could reduce the number of samples required in the study and the pre-clinical stages of drug development, helped to handle the large data and improved the accuracy of the research results.[8,10] Recently, there are several databases used in the computer-aided drug design. PubChem was the common resource for information chemical compounds that consist of more than 60 million chemical compound structures, chemical properties, bioactivity and others.[8] Besides that, there was AntiMarin, containing about 50,000 chemical compounds and marine microorganisms from terrestrial and marine microorganisms. AntiMarin was the combination of AntiBase which was the database of microorganisms from terrestrial and marine and MarinLit was a literature database of marine natural products.[11] However, today database of a three-dimensional structure of chemical

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compounds from marine organisms in Indonesia is not available, especially sponges, whereas sponges had great potential for new drug development in Indonesia. Therefore, to support research in Indonesia, authors were interested in establishing the three-dimensional structure database of chemical compounds as a resource of the lead compounds required for the new drug development by *in silico*, especially from Indonesian sponges.

MATERIALS AND METHODS

Materials

Hardware

The hardware used was the computer HP Pavilion 14-D040TU with specifications Intel® Celeron N2810 2.00 GHz CPU and Random Access Memory (RAM) of 2GB DDR3 L. This computer ran Microsoft Windows 10 Pro 64-bit (United States) operating system and was connected to a connection local internet UI.

Software

MarvinSketch 17.29.0 (ChemAxon), VegaZZ 3.1.1 (Università degli Studi di Milano, Italia), OpenBabel 2.4.0 (O'Boyle, Banck, James, Morley, Vandermeeersch, Hutchison, 2006) and PyMOL 2.0.4 (DeLano Scientific LLC, Italia).

List of chemical compounds from Indonesian sponges

The list of chemical compounds of Indonesian sponges were collected from books, journals or scientific publications and internet sites.

Two-dimensional structure of chemical compounds from Indonesian sponges

The two-dimensional reference structure of the sponge chemical compounds were downloaded from the PubChem Compound page with the site address http://www.ncbi.nlm.nih.gov/ and ChemSpider Search and Share Chemistry at http://www.chemspider.com/, then drew using the MarvinSketch software.

Three-dimensional structure of chemical compounds from Indonesian sponges

The three-dimensional structure of sponge chemical compounds were obtained by generating the structure using MarvinSketch, OpenBabel and VEGAZZ software.

METHODS

Data collection and selection of chemical compounds from Indonesian sponges

The information required for this database was the common name of the chemical compound, chemical compound structure, species, taxonomy, biological activity and reference. If the scientific publications obtained did not include the species and the location taking of the sponge, the articles could not be used. Then the species taxonomy of each chemical compound listed in this database list was carried out from the species to the subclass which referred to marinespecies.org.

Generating of a 2D-structure of chemical compounds from Indonesian sponges

The generating of two-dimensional structure files of sponge chemical compounds in this database was performed by MarvinSketch software and saved in several file extensions which were .mol, .sdf and .pdb. This file extensions variation aimed to find the file extension given the correct two-dimensional structure of chemical compounds compared with the references. Then the examination of the two-dimensional structures of sponge chemical compounds that had been recreated using MarvinSketch was performed by checking the IUPAC name or visualization of structures.

Generating of a 3D-structure of chemical compounds from Indonesian sponges

The generating of a three-dimensional structure of chemical compounds from Indonesian sponges was performed after all the chemical compounds in this database was created its two-dimensional structures in .mol, .sdf and .pdb file extensions. The three-dimensional structure generated by using MarvinSketch, OpenBabel and VegaZZ software. In the MarvinSketch, the three-dimensional structure was created by changing the conformations in the calculation menu to select the variation of the force field that provided the best visualization structure. Then the file was saved with .mol, .sdf and .pdb file extensions. In the Open Babel software, the two-dimensional structure file was converted to a three-dimensional structure with the output file extensions were .mol, .sdf and .pdb. While on the Vega ZZ software, the two-dimensional structure was added hydrogen to the molecule with the "Add Hydrogen" command then converted to a three-dimensional structure by the run script command. After the three-dimensional structure was established, the files were saved with the .mol, .sdf and .pdb file extensions.

Analysis and visualization of three-dimensional structures of chemical compounds from Indonesian sponges

The visualization structures were performed by using PyMOL software. Three-dimensional structure files that had been created using MarvinSketch, OpenBabel and VegaZZ with .mol, .sdf, or .pdb file extensions were opened one by one using PyMOL software for structural visualization. The purpose of this visualization was to check whether the three-dimensional structure had correct results and matches with the reference. This examination was checked if there was a broken or detached structure, a clipped chain, the loss of a double bond, an inverted stereochemical position at C chiral (R and S), also resonance in cyclic and aromatic. The visualization results of the three-dimensional structure of chemical compounds were recorded and summarized in the Microsoft Excel table.

RESULT AND DISCUSSION

Collection and selection of chemical compounds database from Indonesian sponges

Scientific articles of chemical compounds from Indonesian sponges used as the reference for this database were 68 articles from 1980 to 2018. From this article obtained a total of chemical compounds from Indonesian sponges were 212 from 53 species. The distribution of the chemical compounds in the different order of sponges shown in Figure 1.

Sponges were currently divided into four classes, 25 orders, 128 families and 680 genera.[3] Some the species or genera of sponges from the articles were invalid when inputted in marinespecies.org.[12] Therefore, the data of the species or genera in this database was the latest name on the page indicated by "accepted as". This case could happen because the scientific articles used in this database were old therefore the latest taxonomy did not used.

Taxonomic changes could occur for several reasons. Firstly, there were no universal criteria for assigning sequences on taxons such as species or subspecies, or setting boundaries between taxons such as between species or genus causing the subjectivity of sequences and boundaries between taxons. Second, the development of science, especially the phylogenetic relationships that could cause the transfer of species between genera (at least still under the nomenclature Linneus system). Third, the development of knowledge about the gene that could lead to

the separation of taxon eventhough the previous taxonomy had been done objectively. Fourth, there is an error in the previous nomenclature, such as priority or homonymy.[13]

Figure 1 showed that the chemical compounds of Indonesian sponges were most widely isolated from the order of Haplosclerida and Dictyoceratida (55 and 50 compounds) followed by order of Agelasida and Poecilosclerida (22 and 19 compounds). It could happen because the order had a large number and diversity of species. Thus, the chances of chemical abundance isolated from the sponge order were also greater.

Generating of a two-dimensional structure of chemical compounds from Indonesian sponges

The rearrangement of the two-dimensional structure of the sponge chemical compound with the .pdb file extension gave the result of different chemical compound structure compared to the reference when the structure was checked. This difference caused the naming error of the structure. This change includes the loss of all double bonds in the structure and the not detected of the stereochemical direction of the functional group. Therefore, two-dimensional structures of chemical compounds were not generated in the .pdb file extension. An example of a two-dimensional structure change in the .pdb file extension compared to the .mol file extension was shown in Figure 2.

There was the difference in the numbering of two-dimensional structures of chemical compounds that had been recreated compared to the reference articles. This differences could occur due to the different priorities in naming. The MarvinSketch in this study used the 2014 IUPAC rules for structure nomenclatures. Furthermore, there was a complex chemical compound such as Callyaerin A-F which were difficult to redraw therefore the generation of this chemical compounds were performed by the "import name" procedure of the IUPAC name of the two-dimensional reference structure of the MarvinSketch. The structure of Callyaerin A chemical compound were shown in Figure 3. The total two-dimensional structure of chemical compounds from Indonesian sponges in this database were 212 .mol and 212 .sdf file extensions.

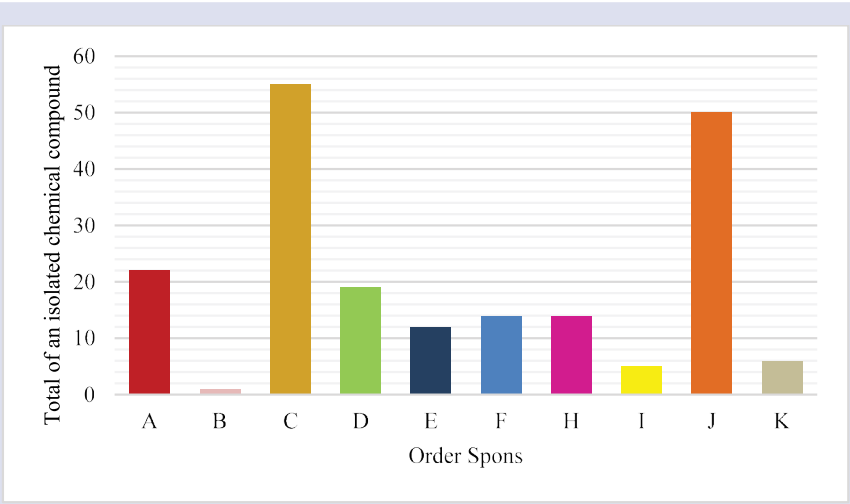

Figure 1: Distribution of chemical compounds in different order of Indonesian sponges.

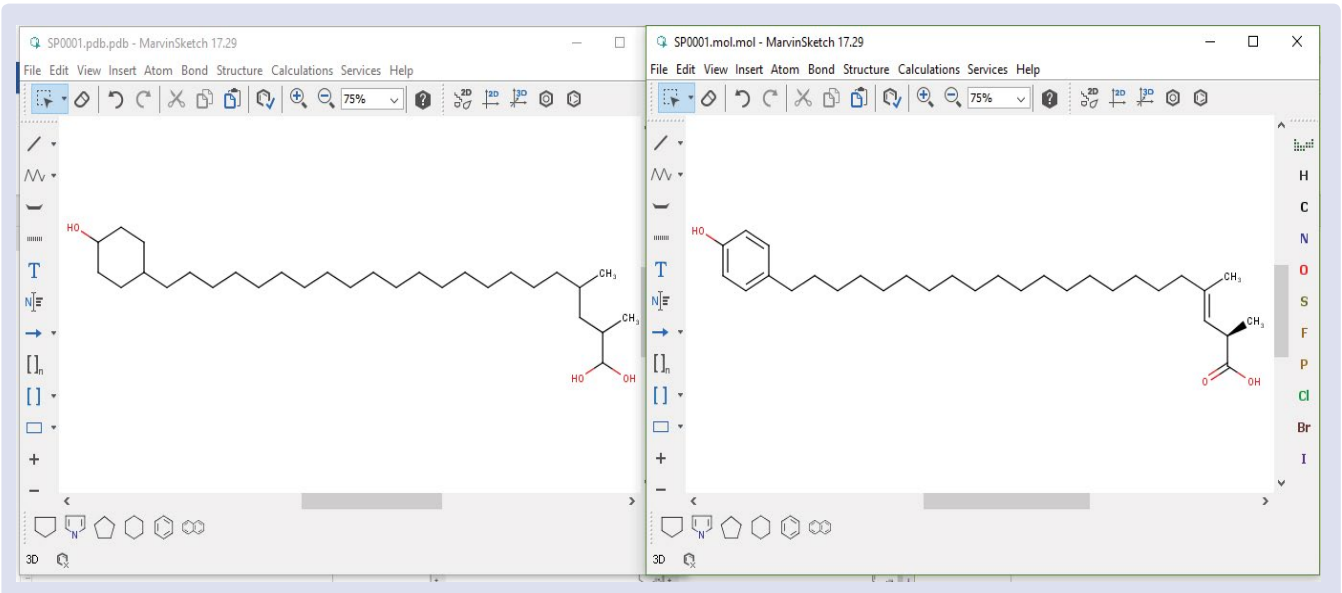

Figure 2: The differences of the two-dimensional structure of Elenic acid (SP0001) *.pdb file extension (left) compared the *.mol file extension (right).

Generating of a three-dimensional structure of chemical compounds from Indonesian sponges

These three-dimensional structures became an important step because the three-dimensional structure played an essential role in the study of virtual screening and molecular docking. These studies were based on a match between the conformation of a three-dimensional structure of the chemical compound or ligand with the receptor structure or protein macromolecule. This three-dimensional structure was expected to provide the more accurate prediction regarding the interaction of the receptors with the real conditions.

The generation of a three-dimensional structure of the chemical compound with MarvinSketch used the Force Field variation of Dreiding and MMFF94 to check which force fields that provided the correct three-dimensional visualization of the structure. The computational duration in the conversion of a three-dimensional structure depends on the size and complexity of the molecule. The conversion duration of the larger and more complex chemical compounds tended to be longer. There was the two-dimensional structure of chemical compounds that could not be converted using MarvinSketch such as 12, 34-oxamanzamine E (SP0023) and Petroquinone A (SP0176) indicated by the program warning boxes due to the conformation invalid for the structure. Figure 4 showed the warning dialog box of the MarvinSketch software. Therefore, the two compounds were only made in a two-dimensional structure using MarvinSketch. Furthermore, there was one chemical compound in salt form, Dibromophakellin HCl (SP0191), of which structure could not be generated.

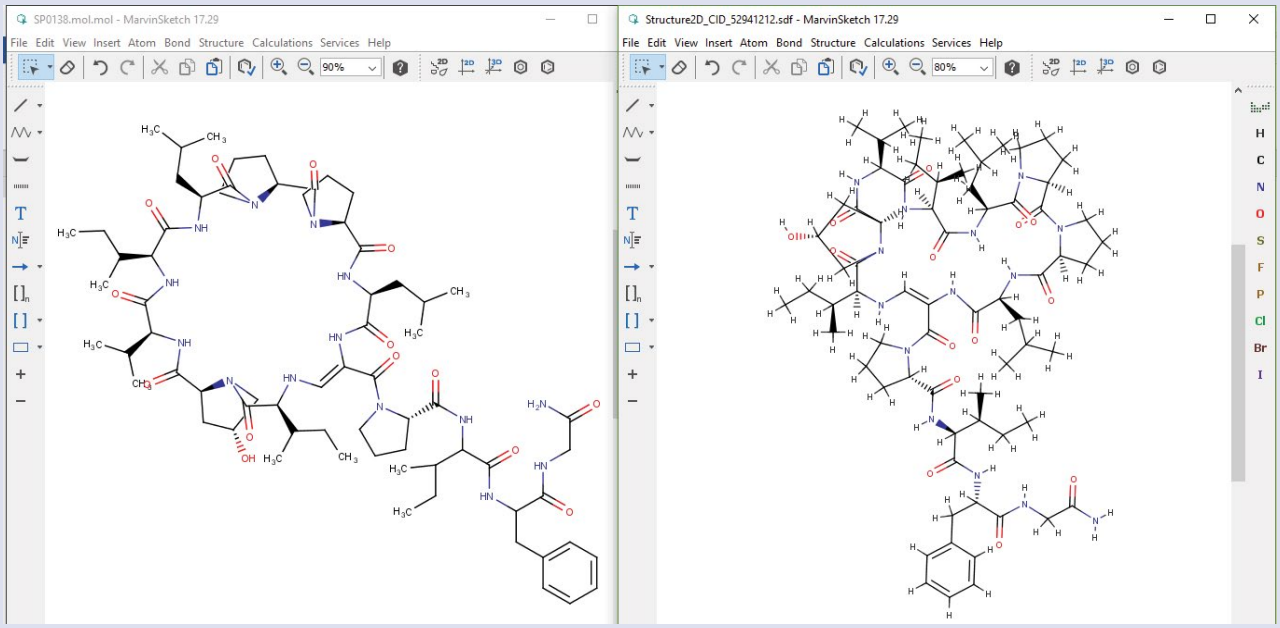

Figure 3: The two-dimensional structure of the Callyaerin A (SP0138) after redrawing (left) and the structure from PubChem (right).

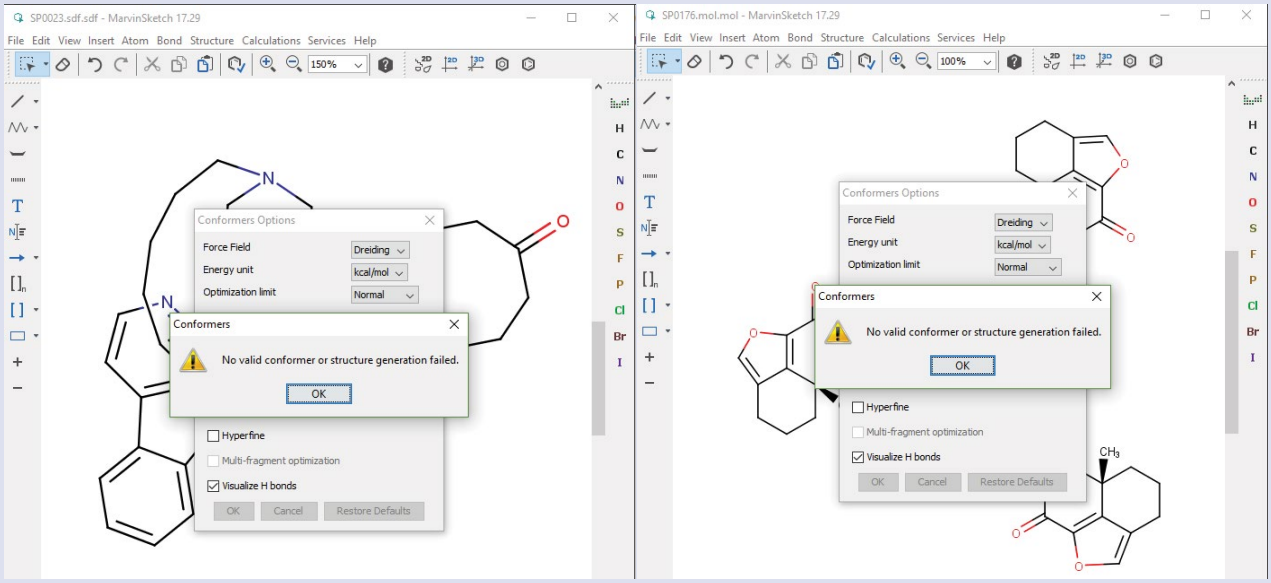

Figure 4: The two-dimensional structure of a chemical compound that could not be converted into the three-dimensional structure: 12, 34-oxamanzamine E (left) and Petroquinone A (right).

The total three-dimensional structure files of each chemical compound created using MarvinSketch were 12 files consisting of 4 .mol, 4 .sdf and 4 .pdb files extension. Therefore, the total of a three-dimensional structure files for 209 chemical compounds from sponges made using MarvinSketch were 2508 files which 836 files were .mol, 836 files were .sdf and 836 files were .pdb.

The three-dimensional structure conversion file from the two-dimensional structure using OpenBabel showed there was different structure compared to reference chemical structure for all file extension types. It was because OpenBabel was less sensitive in processing carbon bonds. Hence, when the two-dimensional structure of the compound was converted into the three-dimensional structure, there was no difference in carbon position, resulting in the changing of the structure. Therefore, the procedure for generating the three-dimensional structure using OpenBabel could be changed to improve the visualization of the three-dimensional structure. This procedure was only to convert three-dimensional structure file extensions that had been created using MarvinSketch to the .pdb file extension instead of converting the two-dimensional structure into the three-dimensional structure. The total files generated from those conversion for each chemical compound were 8 .pdb files extension. And the total three-dimensional structure files for 209 chemical compounds were 1672 .pdb files extension.

The generating of a three-dimensional structure using VegaZZ only had two files extension which was .mol and. pdb whereas the .sdf file extension was only available for the initial file extension of a two-dimensional structure with the .sdf file extension. Therefore, not all file extension of a three-dimensional structure could be saved in the .sdf file extension. There were some three-dimensional structures became curved and presented an indistinguishable of carbon when the structure of long chain carbon was converted. Thus, it needed to add hydrogen to the molecule to overcome it manually. The total three-dimensional structure files for each compound made using the VegaZZ were 1051 files whereas 422 files are .mol, 422 files were .pdb and 207 files were .sdf. The recapitulation of three-dimensional structure files created using the three software shown in Table 1.

Analysis and visualization of a three-dimensional structures of chemical compounds from Indonesian sponges

The three software used to generate this three-dimensional structure of sponge chemical compound gave the different visualization results of their structure.

MarvinSketch

The three-dimensional structure of .mol and .sdf file extension generated using MarvinSketch had a similar visualization. There was the difference in the conformational energy of the structure generated using Force Field Dreiding compared to MMFF94. However, there was no difference when perfomed visualization of the three-dimensional structure of compounds using PyMOL. Meanwhile, the visualization results of a three-dimensional structure with the .pdb file extension showed damage on the structure, such as the resonance in aromatic and cyclic that had two double bond or more and the loss of double bond on carbon chain. It happened because the .pdb file extension could not describe the type of bond, but only the atoms and coordinates. The .pdb file extension estimated the bonding type from the bond length therefore when the two-dimensional structure was converted to three-dimensional, all bond lengths would be the same and when the files were reopened all bonds became single bonds. The summary of errors that occurred in the three-dimensional structure generated using MarvinSketch shown in Tables 2 and 3.

VegaZZ

The three-dimensional structure of the chemical compound generated by VegaZZ with .mol and .sdf file extensions gave inappropriate visualization to the two-dimensional or three-dimensional structure reference. The damages of the structure such as resonance in the cyclic compound having a double bond >1 and aromatics, for example, Naamine G (SP0019) having aromatic and cyclic 5 with two double bonds in the structure. The damages on .pdb file extension such as loss of all the double bonds on the structure usually happened in the MarvinSketch .pdb file extension. The summary of errors occurring in the three-dimensional structure generated using VEGA ZZ shown in Tables 3 and 4.

OpenBabel

The three-dimensional structure .pdb file extension converted by OpenBabel had improper structure visualizations compared to the reference chemical compounds. The damages that occurred was the resonance on cyclic with double bonds more than one and aromatic as well as the loss the double bonds on the carbon chain although using repair procedures. The summary of errors that occurred in the three-dimensional structure .pdb file extension converted using OpenBabel shown in Table 5.

Chemical compounds that did not have double bonds on cyclic and carbon chains gave the proper visualization results with the reference chemical compounds when its three-dimensional structure was converted to .pdb file extension using OpenBabel. Figure 5 showed an example of a three-dimensional structure converted to .pdb file extension using OpenBabel that had the correct structure visualization results. The comparison of three-dimensional structure visualization results of the three software used in this study shown in Table 6.

Table 1: Recapitulation of total three-dimensional structure files created using MarvinSketch, OpebBabel and VegaZZ software.

File extension	MarvinSketch* (2 file extension types: MOL &SDF)		OpenBabel* (8 file extension types)	VegaZZ** (2 file extension types)	Total
	Dreiding	MMFF94			
MOL	418	418	-	422	1258
SDF	418	418	-	207	1043
PDB	418	418	1672	422	2930
Total	2508		1672	1051	7118

*There were 209 of 212 compounds that could be converted to a three-dimensional structure.
**There were 211 of 212 compounds that could be converted to a three-dimensional structure.

Table 2: Recapitulation of three-dimensional structure visualization of MarvinSketch which initial file extension of two-dimensional structure was MOL.

Force Field	File extension	Error types	Numbers*	Total error*
Dreiding	Mol	The position difference of the functional group compared to the reference structure of PubChem but appropiated to the article	7	7
	Sdf	The position difference of the functional group compared to the reference structure of PubChem but appropiated to the article	7	7
	Pdb	Resonance in aromatic	9	202
		Resonance on ring with double bond more than 1	14	
		Resonance on aromatics and rings with double bonds more than 1	51	
		Resonance on ring and/or aromatics and lost double bonding	51	
		Resonance in ring and/or aromatics and lost double bond in COOH	3	
		Resonance on ring and/or aromatics and lost double bond in SO	5	
		Lost the double bond on the ring and/or carbon chain	69	
MMFF94	Mol	The position difference of the functional group compared to the reference structure of PubChem but appropiated to the article	7	7
	Sdf	The position difference of the functional group compared to the reference structure of PubChem but appropiated to the article	7	7
	Pdb	Resonance in aromatic	9	202
		Resonance on ring with double bond more than 1	14	
		Resonance on aromatics and rings with double bonds more than 1	51	
		Resonance on ring and/or aromatics and lost double bonding	51	
		Resonance in ring and/or aromatics and lost double bond in COOH	3	
		Resonance on ring and/or aromatics and lost double bond in SO	5	
		Lost the double bond on the ring and/or carbon chain	69	

*This results were to .mol file extension whereas the .sdf file extension of a two-dimensional structures had the similar results

Table 3: Recapitulation of three-dimensional structure visualization of VegaZZ which initial file extension of two-dimensional structure was MOL.

File extension	Error types	Numbers	Total error
Mol	Resonance in aromatic	22	155
	Resonance on ring with double bond more than 1	33	
	Resonance on aromatics and rings with double bonds more than 1	59	
	Resonance in ring and/or aromatics and lost double bond in CO	2	
	Resonance in ring and/or aromatics and stereochemical changes (reversed)	12	
	Stereochemical changes (reversed)	27	
Pdb	Lost all the double bond	210	211
	Stereochemical of H changed	1	

Table 4: Recapitulation of three-dimensional structure visualization of VegaZZ which initial file extension of two-dimensional structure was SDF.

File extension	Error types	Numbers	Total error
Mol	Resonance in aromatic	22	155
	Resonance on ring with double bond more than 1	33	
	Resonance on aromatics and rings with double bonds more than 1	59	
	Resonance in ring and/or aromatics and lost double bond in CO	2	
	Resonance in ring and/or aromatics and stereochemical changes (reversed)	12	
	Stereochemical changes (reversed)	27	
Sdf	Resonance in aromatic	22	152*
	Resonance on ring with double bond more than 1	31	
	Resonance on aromatics and rings with double bonds more than 1	58	
	Resonance in ring and/or aromatics and lost double bond in CO	2	
	Resonance in ring and/or aromatics and stereochemical changes (reversed)	12	
	Stereochemical changes (reversed)	27	
Pdb	Lost all the double bond	210	211
	Stereochemical of H changed	1	

*There were 4 chemical compounds that did not have .sdf file extension from total chemical compound.

Table 5: Recapitulation of three-dimensional structure converted using OpenBabel visualizations.

File extension	Error types	Numbers	Total error
pdb	Resonance in aromatic	9	203
	Resonance on ring with double bond more than 1	16	
	Resonance on aromatics and rings with double bonds more than 1	51	
	Resonance on ring and/or aromatics and lost double bonding	45	
	Resonance in ring and/or aromatics and lost double bond in COOH	2	
	Resonance on ring and/or aromatics and lost double bond in SO	5	
	Lost the double bond on the ring and/or carbon chain	68	
	All damages	7	

Table 6: Comparison of appropriate three-dimensional structure visualization results.

File extension	MarvinSketch* (2 file extension types: MOL &SDF)		OpenBabel* (8 file extension types)	VegaZZ** (2 file extension types)	Total
	Dreiding	MMFF94			
MOL	402	402	-	112	916
SDF	402	402	-	110	914
PDB	12	12	48	0	72
Total	1632		48	222	**1902**

* There were 209 of 212 compounds that could be converted to a three-dimensional structure.
** There were 211 of 212 compounds that could be converted to a three-dimensional structure.

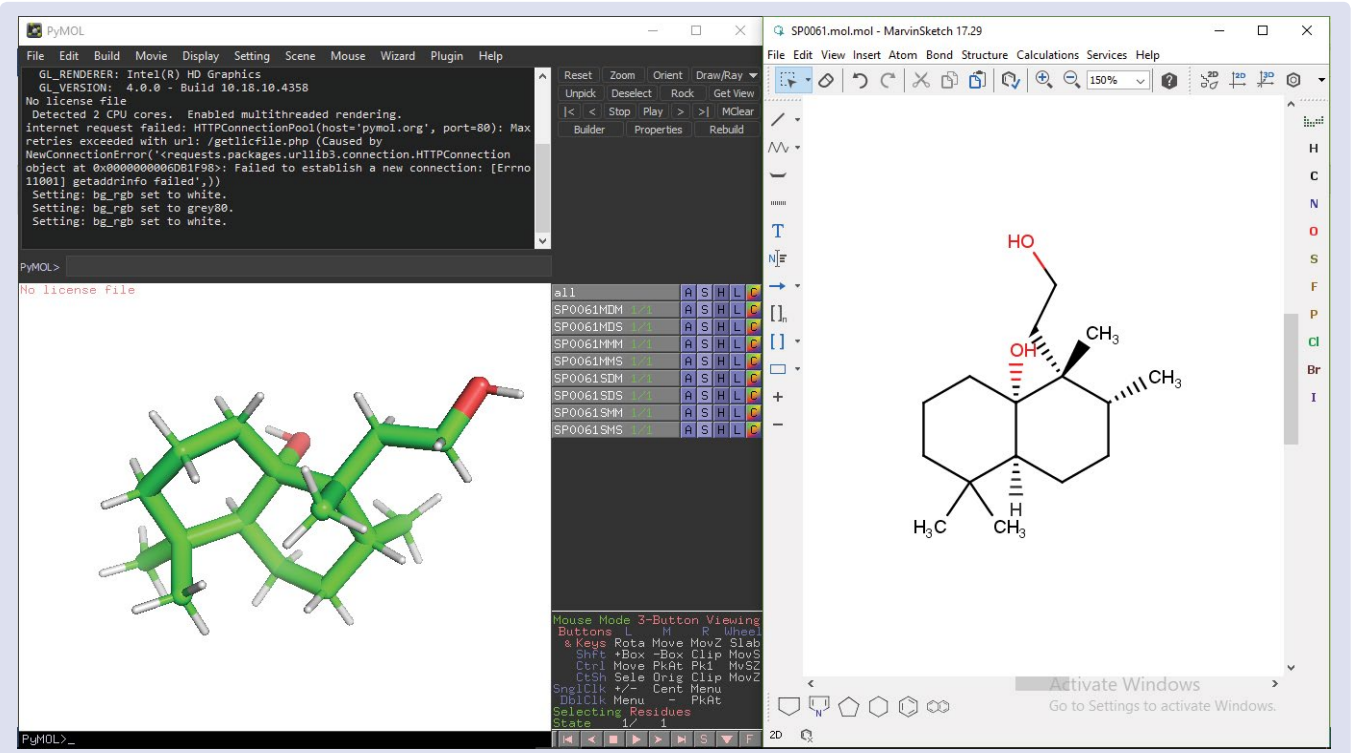

Figure 5: Structure of Euplectellidiol (SP0061): A three-dimensional structure converted using OpenBabel (left) and a two-dimensional structure (right).

CONCLUSIONS

The database consists of 53 species of sponges, 212 chemical compounds and generated the correct three-dimensional structure (914 .sdf, 916 .mol and 72 .pdb file extensions) which relevant to the references. The database also contained the ID name compound, chemical compound names, SMILES, biological activity, the taxonomy of species, structure visualization results and the two-dimensional structure of sponge chemical compounds. The preferred software used this generation of three-dimensional structure database was the MarvinSketch with the .sdf and .mol file extension because their three-dimensional structure visualization results did not have damage and suitable with the references.

The database that had been made should supplement with other information such as the description of the sponge, images or photos of the sponge, the uses, the habitat and other information related to the sponge. Additionally, the database of a three-dimensional structure of chemical compounds from the other phylum of marine organisms needs to be upgraded as well. Therefore, it could serve as the reference for further research. Furthermore, the needs to establish a website is necessary to enter the database that could be accessed by

others. Upcoming research should conduct for other file extension and software, so that it can compare the visualization of the three-dimensional structure of the chemical compounds.

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CONFLICTS OF INTEREST

The Authors declare that there is no conflicts of interest.

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