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Preparation of Translated, Scaled, and Rotated ATS Drugs 3D Molecular Structure for the Validation of 3D Moment Invariants-based Molecular Descriptors

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Abstract. The campaign against drug abuse is fought by all countries, most notably on ATS drugs. The technical limitations of the current test kits to detect new brand of ATS drugs present a challenge to law enforcement authorities and forensic laboratories. Meanwhile, new molecular microscopy imaging devices which enabled the characterization of the physical 3D molecular structure have been recently introduced, and it can be used to remedy the limitations of existing drug test kits. Thus, a new type of 3D molecular structure representation, or molecular descriptors, technique should be developed to cater the 3D molecular structure acquired physically using these emerging molecular imaging devices. One of the applications of image processing methods to represent a 3D image is 3D moment invariants. However, since there are currently no repository or database available which provide the drugs imaging results obtained using these molecular imaging devices, this paper proposes to construct the simulated 3D drugs molecular structure to be used by these 3D moment invariants-based molecular descriptors techniques. These 3D molecular structures are also translated, scaled, and rotated to measure the invariance properties of the 3D moment invariants-based molecular descriptors. The drugs molecular structures are obtained from pihkal.info for the ATS drugs, while non-ATS drugs are obtained randomly from ChemSpider database.

Keywords: ATS drugs, drugs identification and analysis, molecular structure representation, dataset preparation, preprocessing

1 Introduction

Every country in this world is constantly interjected by the looming destruction potential of ATS drugs abuse, thus, United Nations feel obliged to combat these threats by establishing United Nations Office on Drugs and Crime (UNODC) in 1997. Seized drug analysis plays an important part in the forensic investigation of drug-related crimes. The presence or absence of controlled substance in the seized materials heavily affects the outcome of criminal justice system [1]. Law enforcement entities and their respective forensic laboratories generally employ a set of acceptable standard techniques outlined by UNODC to detect the presence of ATS in the samples of seized drug materials [2].

One of the main reasons the ATS drugs abuse, including manufacturing and distribution, is very difficult to combat, is that it is mostly synthetic in origin [2]. Therefore, provided with sufficient technical knowledge, a chemist can derive a novel and unregulated structure of ATS and manufacture it in the clandestine laboratories, using various simple and flexible approaches [3]. The precursors to manufacture these drugs are also publicly available and can be purchased over-the-counter or as prescription medicine, albeit being the controlled substances [4-6].

These innovative designs proven to be a challenge for law enforcement entities and introduce a new layer of difficulties in detecting and identifying using existing laboratory techniques, which sometimes lead to both false positive and negative results, and thus, incorrectly outline the outcome of criminal justice court [7-10]. Thus, there is a continuous demand for the improvement of current laboratory techniques to recognize common characteristics of the ATS drugs. Due to these limitations, it is preferable to perform the identification by relying on computational intelligence methods [11], and taking advantage of the shape of molecular structures.

Despite the apparent need of reliable methods to detect and identify ATS drugs in the field of forensic toxicology, the use of cheminformatics is only starting to be incorporated recently [12-18]. Cheminformatics researchers use molecular similarity to seek structurally similar compounds, since the drug design efforts are based on a principle which states that structurally similar compounds are more likely to exhibit comparable properties [19-23]. The success of molecular similarity depends on the molecular structures representation employed, also known as the molecular descriptors, which is discussed comprehensively in [24,25]. There are various categories of molecular descriptors, although the most commonly used molecular descriptors are 2D and 3D molecular descriptors.

Since a molecular structure representation involves the knowledge of the relative positions of the atoms in 3D space, 3D descriptors usually provide more information and discrimination power for similar molecular structures and molecule conformations than 2D descriptors [26]. Searching for relationships between molecular structures and complex properties can often be performed efficiently by using 3D descriptors, exploiting their large information content [27-29]. This paper believes that molecular similarity can also be used to detect the similarity between unknown compound and reference compounds, and consequently, can be used to detect new

brand of ATS drugs to the known samples of ATS drugs based on their molecular structure [12,13,16].

Recent advances in scientific domains have enabled the characterization of the physical molecular structure through molecular microscopy, such as by using transmission electron microscopy (TEM), scanning tunneling microscopy (STM), and more recently, non-contact atomic force microscope (nc-AFM) [30]. New discovery of tuning-fork-based nc-AFM provides a novel method capable of non-destructive sub-nanometer spatial resolution [31-35]. Single-molecule images obtained with this technique are reminiscent of wire-frame chemical structures and even allow differences in chemical bond-order to be identified [33]. The high-resolution images obtained using STM and nc-AFM reveals that the 3D model which is used for decades to depict molecular structure is virtually identical to the physical molecules, as shown in Figure 1.

Invariance with respect to labelling, numbering of the molecule atoms, and molecule translation and rotation is a required property of a molecular descriptor. Furthermore, it also must have a clear algorithmically quantifiable definition, and the values must be in an appropriate numerical range for the molecule set where it is applicable to [36,37]. Since a molecular descriptor is independent of the characteristics of the molecular representation, it is possible to consider the molecular shape as an image, and thus apply image processing to represent the shape of the molecular structure.

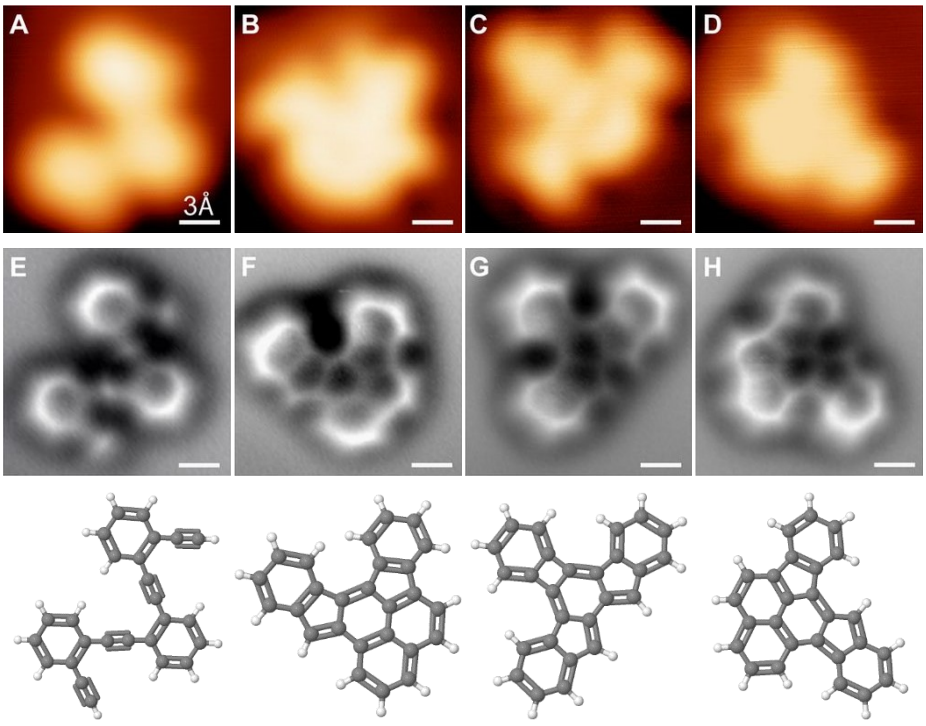


Fig. 1. Comparison of STM images, nc-AFM images, and 3D molecular structures model [30].

Representations of formal molecular shapes and surfaces provide more detailed and more chemically relevant information than simple molecular graphs and stereochemical bond structures and give a more faithful description of actual molecular recognition and interaction processes, which lead to the quantitative shape-activity relations (QShAR) domain [38]. Shape is an important visual feature and it is one of the basic features used to describe image content [39], and hence, searching for an image by using the shape features gives challenges for many researches, since extracting the features that represent and describe the shape is an arduous task [40], which also hold true in the QShAR domain [38].

In the QShAR domain itself, various molecular shape representation techniques have been proposed [41,38]. Meanwhile, in pattern recognition problem, there are many shape representations or description techniques have been explored to extract the features from the object. One of the most commonly used shape descriptors is Moment Invariants (MI), which can easily satisfy the invariance requirements. MI is a special case of Moments, which is a scalar quantities used to characterize a function and to capture its crucial features [42]. The first application of MI to represent molecular structure is 3D Zernike descriptors [43]. Although it was introduced to represent the molecular surface of protein structure, it provides an adequate motivation for further exploration of engaging MI as a numerical representation of molecule in the computer system, whether it is for molecular structure or for molecular surface.

There are several advantages of 3D MI-based molecular shape representation compared to conventional representations. First, 3D MI-based molecular descriptors allow for fast retrieval and comparison of molecular structures. Second, due to its rotation and translation invariance properties, molecular structures need not be aligned for comparison. Lastly, the resolution of the description of molecular structures can be easily and naturally adjusted by changing the order of shape descriptors [43,44].

Prior of the construction of these 3D MI-based molecular descriptors, it is necessary to prepare a standardized image format as an input for these techniques, which will be discussed in this paper. Thus, the remainder of the paper is organized as follows. The ensuing section will provide an overview of ATS drug identification and analysis domain. In Section 3, the proposed dataset preparation method is presented, while the conclusion and future works are discussed in Section 4.

2 ATS Drug Identification and Analysis

ATS are a group of substances, mostly synthetic in origin, that are structurally derived from β-phenethylamine, as shown in Figure 2, portraying its essential features: aromatic phenyl ring, carbonyl side-chain and amino moiety [2]. Structural modifications of β-PEA create multiple synthetic derivatives known as ring substitute analogues. The substitution positions on the carbonyl side-chain (R1-R4) and aromatic phenyl ring (R5-R9) are shown in Figure 3.

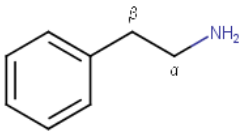


Fig. 2. 2D molecular structure of *β*-phenethylamine [2].

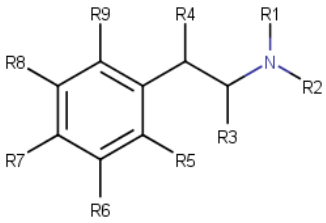


Fig. 3. Basic 2D molecular structure of ATS [2].

Chemical modification at the positions R1 to R9 results in a practically unlimited number of pharmacologically active compounds, some of which are more potent stimulants than others. Although there are several possibilities for carbonyl side-chain modification, substitution on the aromatic phenyl ring contributes the most to substantial qualitative differences in pharmacological effects [2].

Based on its structural characteristics, there are three major sub-groups of ATS, which essentially correspond to the following substitution patterns on the aromatic ring: no substitution, methylenedioxy-substitution, and other substitution patterns, usually including one or more alkyloxy group. The substitution patterns are depicted in Figure 4, and some of the notorious examples of ATS drugs are shown in Figure 5.

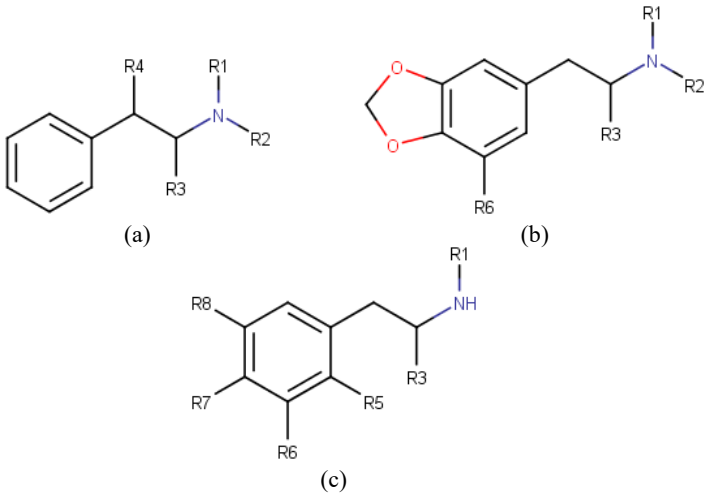


Fig. 4. Sub-groups of ATS per substitution patterns: (a) no substitution, (b) methylenedioxy-substitution, and (c) other substitution patterns [2].

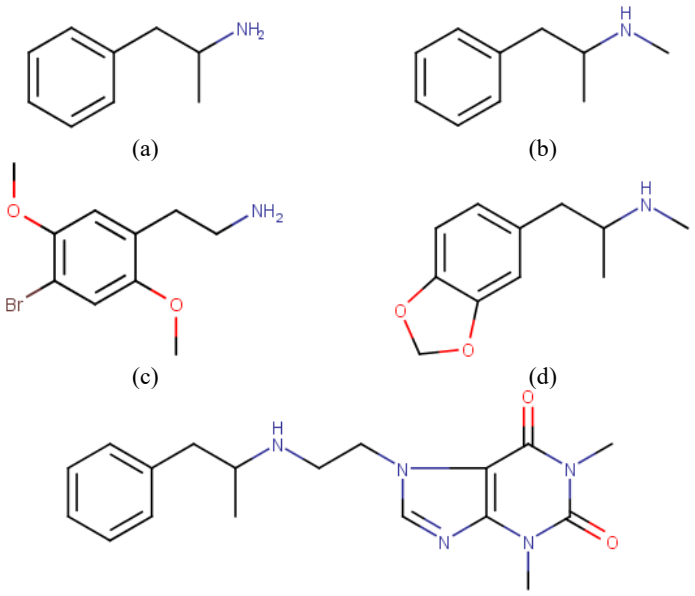


Fig. 5. Samples of ATS drug molecular structure: (a) amphetamine, (b) methamphetamine, (c) 2C-B, (d) MDMA, and (e) fenethylline [2].

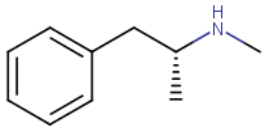


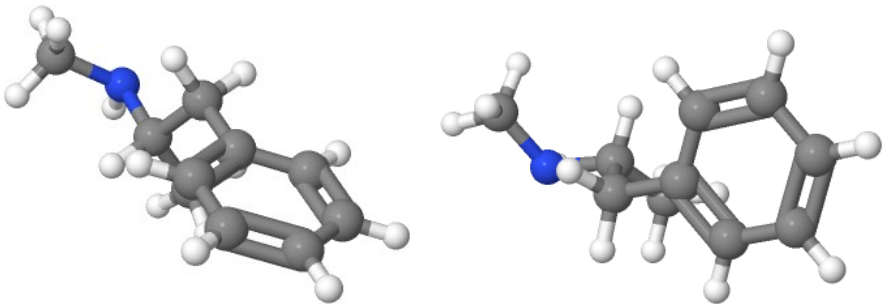
Fig. 6. 2D molecular structures of *l*-methamphetamine [45].

To facilitate faster, more accurate and more specific methods for varying ATS drugs identification and analysis, Laboratory and Scientific Section of UNODC has established recommended methods of testing for national drug testing laboratories. However, different results are possibly obtained from different testing laboratory because of their non-conformance to these standards. Nevertheless, most of these laboratories agree to use gas chromatography/mass spectrometry (GC/MS) as the most common method to identify a chemical substance [2,46,47]. The flaws of GC/MS which are surfacing while trying to identify several ATS drugs are recently discovered in a study, most notably in identifying methamphetamine [48].

Methamphetamine itself has two stereo-isomers, which are *l*-methamphetamine and *d*-methamphetamine. The 2D molecular structure of *d*-methamphetamine is shown in Figure 5(b), while 2D molecular structure of *l*-methamphetamine is depicted in Figure 6. Isomers are defined by [49] as one of several species (or molecular entities) that have the same atomic composition but different line or stereo-chemical formulae and hence different physical and/or chemical properties. GC/MS is also increasingly incapable to determine that several molecular structures are ATS drugs.

While *l*-methamphetamine has very little pharmacodynamics effect, *d*-methamphetamine on the other hand is a controlled substance that has high potential for abuse and addiction [45].

Based on the molecular structures shown in Figures 5(b) and 6, there are very minor differences between *d*-methamphetamine and *l*-methamphetamine. The differences on the atom orientation only become apparent if the structure is represented using 3D model of molecular structure. Therefore, this paper believes that the shape of 3D molecular structure can be used to identify the molecular compounds, especially ATS drugs, due to the presence of aromatic phenyl ring and carbonyl side chains which gives its unique characteristics in all ATS analogues [2,50,51], which theoretically can be obtained using recent molecular microscopy imaging devices, such as nc-AFM. The example of 3D molecular structure for *d*-methamphetamine and *l*-methamphetamine are depicted in Figure 7.



(a) (b)

Fig. 7. 3D molecular structures of (a) *d*-methamphetamine and (b) *l*-methamphetamine

Although nc-AFM can show the 3D conformation of a molecular compound, it is still in early development stage and requires further improvements before it has real life applications, especially in forensic domain [30-33,52]. Furthermore, since nc-AFM is only surface probe, probing must be conducted several times so that molecules can be captured from multiple angles, and processed afterward using 3D object reconstruction algorithm before it can be recognized in a computer system [53,54].

However, since there is currently no repository or database available which provide the imaging results of nc-AFM and the existing model of 3D molecular structure is similar to 3D conformation of molecular compounds [30], this paper alternatively generates the same output file format produced by 3D object reconstruction algorithm, which is binary volume pixel (voxel) grid [55,56] to simulate the drugs molecular structure construction process obtained using nc-AFM. The detailed procedure on how this paper generates these files will be discussed in Section 3.

3 Proposed Dataset Preparation Method

This section describes the process of data collection and transformation of 3D molecular structure of ATS drugs into 3D computational data representations, which has

been briefly outlined in [57]. As discussed earlier, 2D images taken from multiple angle from multiple probing can be reconstructed into binary voxel grid, such as by using 3D Recurrent Reconstruction Neural Network (3D-R2N2) [55]. However, since the probing images of ATS molecular structure are not available, this paper proposes the conversion of 2D molecular structure model into binary voxel grid to train the 3D MI-based molecular descriptors should the probing images become available in the future.

The ATS dataset used in this paper comes from pihkal.info [58], which contains 3780 molecular structures for potentially and typically abused ATS drugs. On the other hand, same number of non-ATS molecular structures are obtained from ChemSpider [59]. These structures are drawn in 2D molecular structure format using MarvinSketch 16.11.28 [60]. The molecular structure depicted in Figure 8 and the subsequent figures throughout this paper is an example of ATS molecular structure, ecstasy (3,4-methylenedioxy methamphetamine, MDMA).

After the 2D molecular structure is drawn, the structure is transformed to 3D molecular structure, also by using MarvinSketch. However, before the conversion takes place, the explicit hydrogens must be added to the structure by using 'Structure' > 'Add' > 'Explicit Hydrogens' command. It is then converted by using 'Structure' > 'Clean in 3D' command, and the output is as depicted in Figure 9. The structure is then saved as Molecular Design Limited (MDL) Structure Data File (SDF) format.

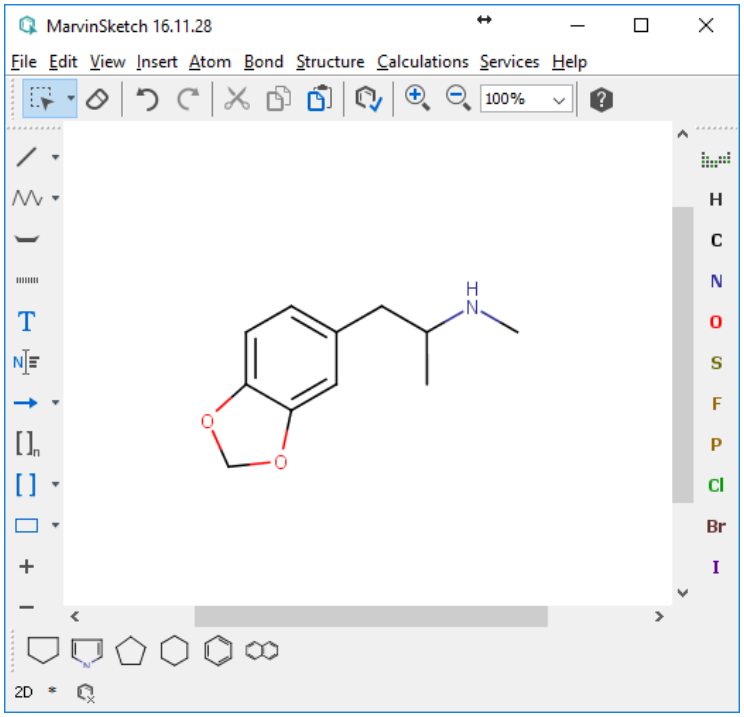


Fig. 8. MarvinSketch used to draw 2D molecular structure

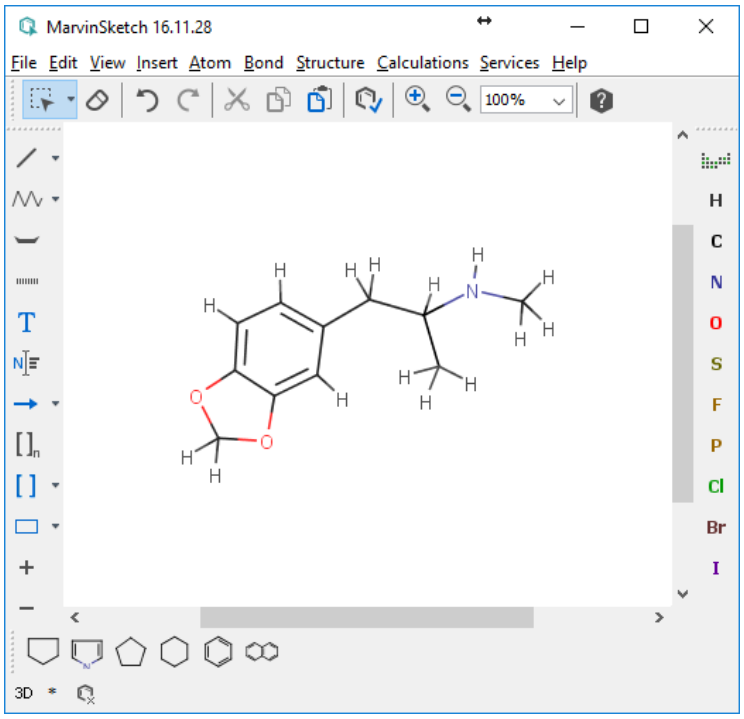


Fig. 9. MarvinSketch used for 3D conversion

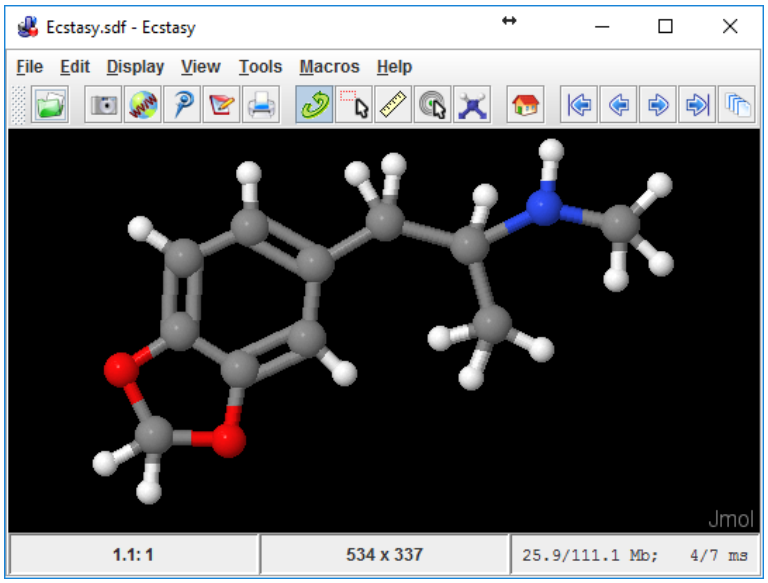


Fig. 10. Jmol used for verifying conversion process and converting to VRML file

Since the objective of this paper is to prepare the dataset for the validation of the 3D MI-based molecular descriptors, the translation, scale, and rotation transformations must also be applied to the drugs molecular structure to simulate the acquisition process using nc-AFM, where the atom location, resolution and camera distance, and angles of rotation for the same molecular structure may differ between each acquisition. To validate the rotation invariance property of the 3D MI-based molecular descriptors, the MDL SDF format are incrementally rotated for 90 degrees in x-, y-, and z-axis.

Although there are 64 possible orientations if a 3D object is rotated 90 degrees incrementally in x-, y-, and z-axis, there are only 24 distinct orientation exist, and thus, for each molecular structure, there will be 24 files for each distinct orientation. The conversion from 2D to 3D molecular structure and the ensuing rotation transformation of these structures are considered successful if the molecular structure can be opened and viewed by using Jmol 14.6.4 [61], as shown in Figures 10 and 11.

Furthermore, this paper also proposes to construct standardized input format for 3D MI-based molecular descriptors, and thus, the MDL SDF format must be converted to appropriate input file format for the 3D MI-based molecular descriptors, which is binary voxel (BINVOX) grid data. Therefore, the MDL SDF format must be then converted to Virtual Reality Markup Language (VRML) image format. This conversion is required because VRML format is the input type required for generating the BINVOX grid data.

To convert MDF SDF format to VRML file format, Jmol is also used. VRML file is then voxelized into BINVOX grid file using binvox 3D mesh voxelizer 1.22 [62] with randomly selected resolution between $384 \times 384 \times 384$ to $512 \times 512 \times 512$ grid dimension, as shown in Figure 12, to validate the scale invariance property of the 3D MI-based molecular descriptors. The result of the voxelization process is depicted in Figure 13 by using viewvox 3D voxel model viewer 0.44 [63], and the voxelization result of each scaled and rotated version of the drugs molecular structure is shown in Figure 14.

The procedure to convert the 3D molecular structure to binary voxel grid is adopting the procedure outlined by [44] and hybridizing it with the procedure outlined by [64], despite different tools are employed in this study. To produce 3D Zernike descriptors, [44] calculates the triangle mesh of Connolly surface from Protein Data Bank (PDB) file, which is a 3D molecular structure format similar to MDL SDF, using MSROLL program in Molecular Surface Package 3.9.3 [65], and then the triangle mesh is placed in a 3D voxel grid. However, the tools used to convert the triangle mesh into 3D voxel grid is not specifically mentioned.

Thus, this study alternatively followed the procedure outlined by [64] to convert VRML file to 3D voxel grid. Although the VRML used in their study comes from Princeton Shape Benchmark, but the tools to convert the VRML to 3D voxel grid is clearly mentioned, which is the binvox 3D mesh voxelizer (older version than the version used in this study). It should be noted that even though [44] and [64] used 3D voxel grid for different purposes, both studies produced 3D voxel grid with $200 \times 200 \times 200$ grid dimension. However, this study instead produced 3D voxel grid with at least $384 \times 384 \times 384$ grid dimension for finer detail and resolution.

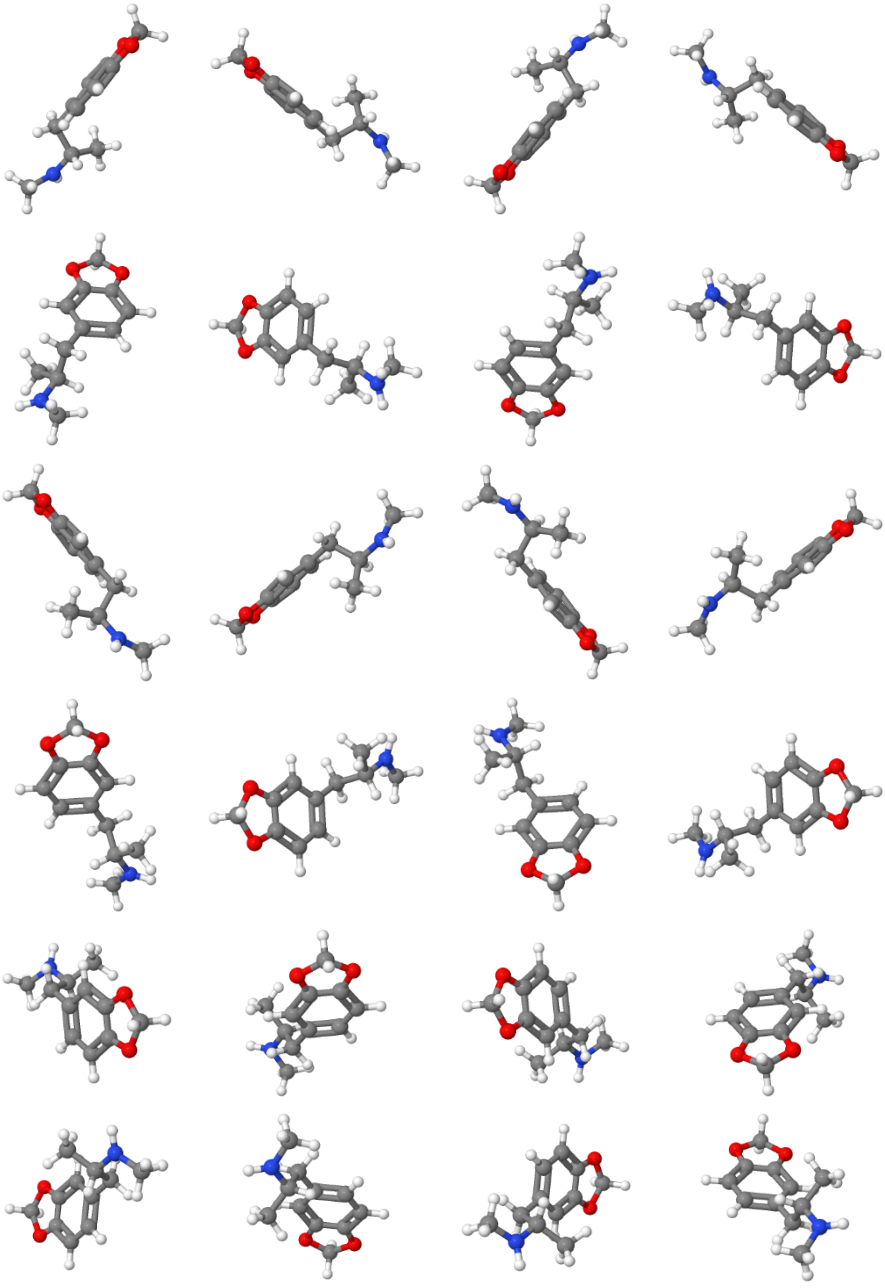


Fig. 11. Rotation transformation results

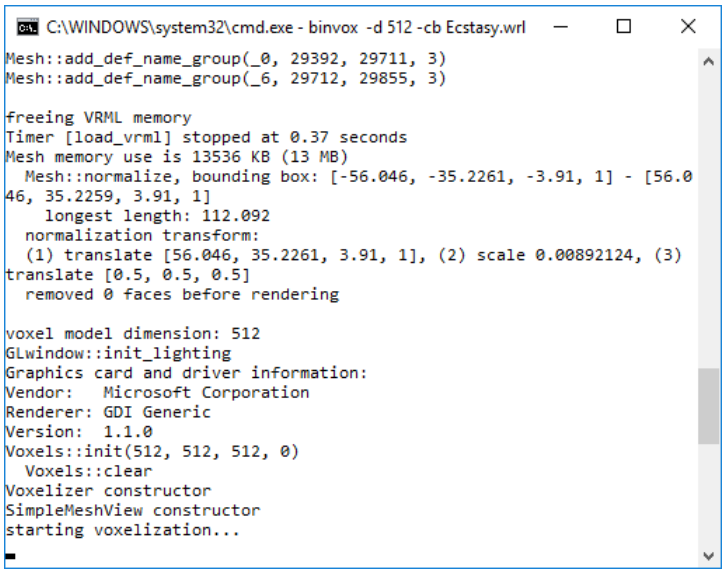


Fig. 12. binvox used to convert VRML to BINVOX format

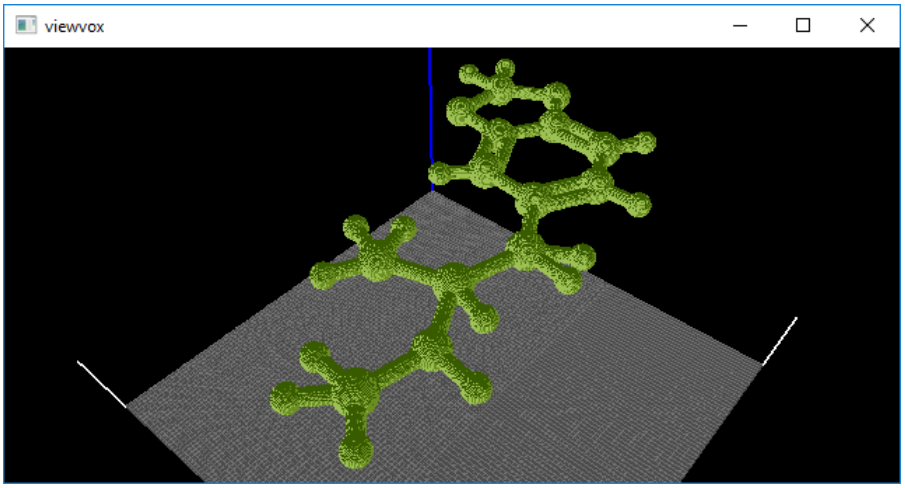


Fig. 13. Output of the voxelization process visualized using viewvox

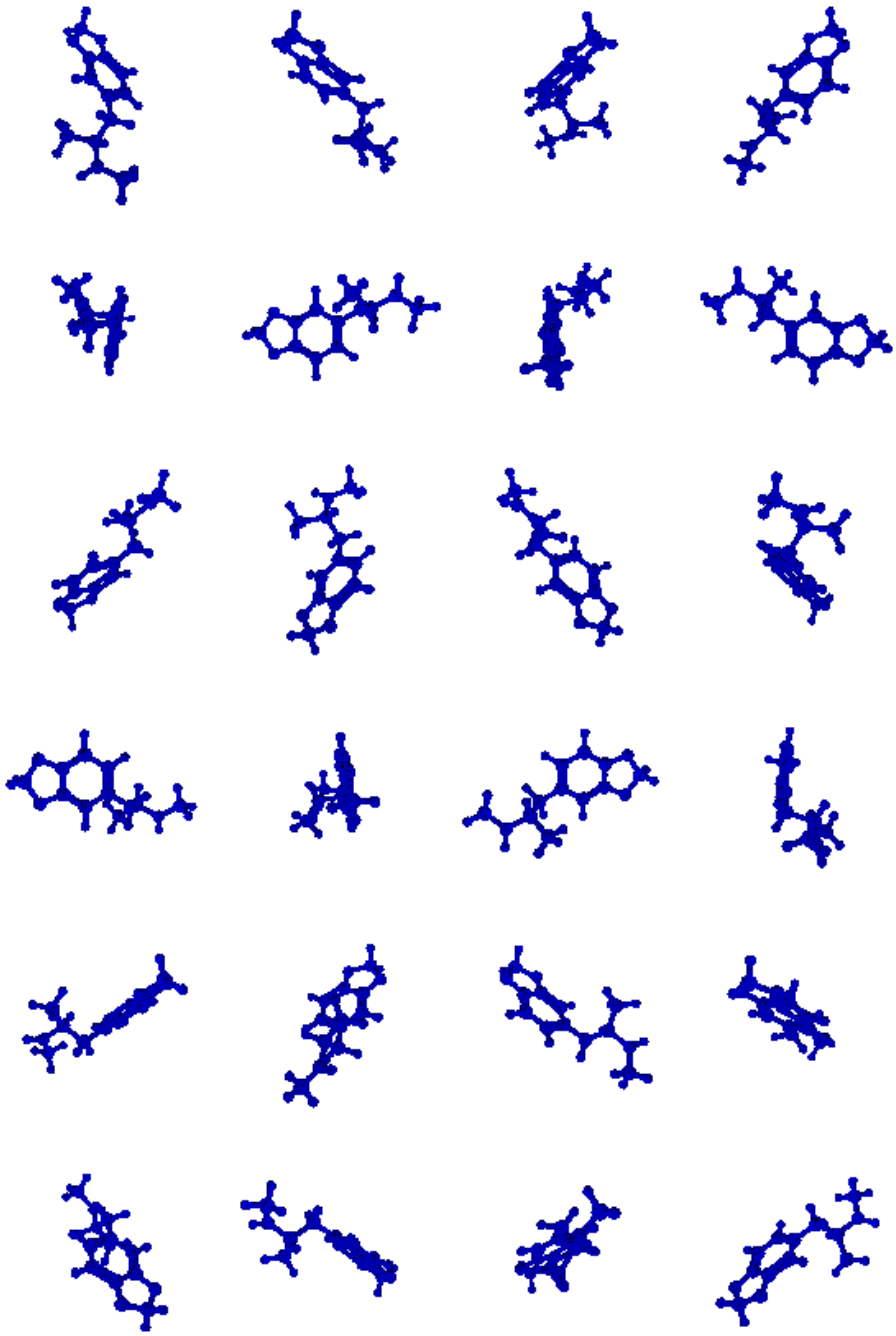


Fig. 14. Voxelization results of the scaled and rotated molecular structures

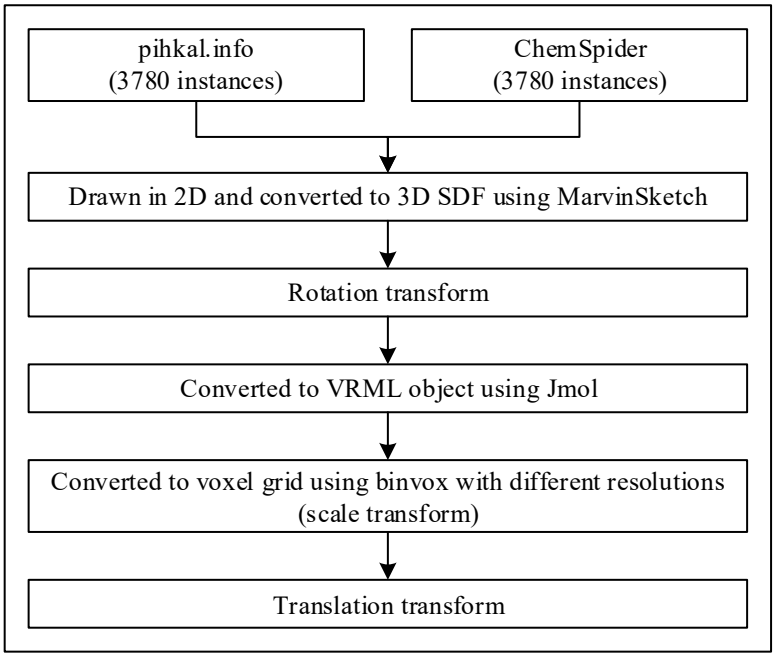


Fig. 15. Summary of dataset preparation process

To further validate the translation invariance property of moment invariants techniques, the BINVOX voxel grid files are also randomly translated by shifting its voxels in one or more directions of x-, y-, and z-axis, ensuring that the 3D image will not be cropped after being translated. The resulting BINVOX grid files are then used as the input for the 3D MI-based molecular descriptors. The summary of the dataset preparation procedure is depicted in Figure 15.

Another point should be noted is that this study focuses on the preparation of input format for 3D MI-based molecular descriptors derived from 3D volumetric moments. As for the techniques derived from 3D surface moments, meshconv 3D model converter 1.26 [66] can be used instead of binvox 3D mesh voxelizer to generate triangular mesh from VRML files as its input format. Additionally, there are also several notable studies which can benefit from the dataset produced in this study, such as studies conducted by [67-73].

4 Conclusions and Future Works

This paper proposed a method to construct an input format to be employed for 3D MI-based molecular descriptors, as an alternative input format for the time being, while the recent molecular microscopy imaging devices are being perfected and implemented as a forensic laboratory equipment for the ATS drug identification and analysis. Hence, future works employing the output of this paper as an input for 3D MI-based

molecular descriptors should be commissioned, especially on the development of these techniques.

Acknowledgement

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