Determination of Effective Functional Monomer and Solvent for R(+)-Cathinone Imprinted Polymer Using Density Functional Theory and Molecular Dynamics Simulation Approaches

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ABSTRACT

Determination of effective functional monomer and solvent for R(+)-cathinone imprinted polymer through modeling has been done using density functional theory (DFT) and molecular dynamics (MD) simulation approaches. The selection criteria of the best monomer and solvent are based on the classical potential energy (ΔE_{MM}) from molecular dynamics simulation and confirmed further by quantum potential energy (ΔE_{DFT}) from DFT calculation. The DFT calculation was performed in B3LYP exchange-correlation functional within the 6-31G(d) basis set of function including Polarizable Continuum Model (PCM) solvation effect. From this research, it is obtained that N,N'-methylene bis acrylamide and chloroform are respectively the best candidates for effective functional monomer and solvent, for the synthesis of R(+)-cathinone imprinted polymer.

Keywords: *R(+)-cathinone; molecular imprinted polymer; functional monomer; molecular dynamics; DFT calculation*

ABSTRAK

Pemilihan monomer fungsional dan pelarut yang efektif untuk rancangan polimer tercetak molekul R(+)-kathinon telah dilakukan dengan menggunakan pemodelan berbasis perhitungan teori kerapatan fungsi (Density Functional Theory, DFT) dan simulasi dinamika molekular (Molecular Dynamics, MD). Kriteria seleksi monomer fungsional dan pelarut terbaik adalah berdasarkan energi ikat (ΔE_{MM}) yang diperoleh dari simulasi MD dan dikonfirmasi dari energi ikat (ΔE_{DFT}) hasil perhitungan DFT. Perhitungan DFT dijalankan pada fungsi B3LYP exchange-correlation functional dengan himpunan basis 6-31G(d) yang melibatkan efek pelarutan Polarizable Continuum Model (PCM). Dari hasil penelitian diketahui bahwa N,N'-metilen bis akrilamida dan khloroform dapat dipilih sebagai kandidat terbaik sebagai monomer fungsional dan pelarut untuk keperluan sintesis polimer tercetak R(+)-kathinon.

Kata Kunci: *R(+)-kathinon; polimer tercetak molekul; monomer; simulasi dinamika molekular; perhitungan DFT*

INTRODUCTION

Cathinone, a narcotic compound of alkaloid monoamine group, was banned due to its dangerous effects except for medical treatment [1]. Various analytical methods such as HPLC and GC-MS has been developed to identify the presence of cathinone [2-3]. However, these methods, in general, require a long time of analysis, special operation skill, and immobile analysis. The need for faster, more accurate, and mobile analytical method leads to search of sensor-based chemical analysis.

Generally, sensor-based molecular analysis is done using Quartz Crystal Microbalance (QCM) and the selectivity of QCM sensor can be improved by adding a selective material known's as Molecular Imprinted Polymer (MIP) [4]. MIP is a polymer prepared by polymerization of template, functional monomer, crosslinker, initiator, and solvent with certain proportion and at the end of the process, template molecule should be released from the matrices to create template-like cavity [5]. To obtain the MIP with high selectivity to template molecules, the use of effective functional monomers and solvent are important things to be considered. Bakas et al. [6] reported that the use of inappropriate monomers and solvents gives rise to the decrease in the absorption capability (less imprinting factor).

In many cases, computer aided design before synthesizing a certain molecule is preferred than doing

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conventional trial and error methods. Nowadays, computationally design of MIP involves molecular mechanics (MM) and quantum mechanics (QM) approaches. For examples, some studies have reported the implementation of MM method to MIP design [7-8]. Basic concept of MM method in MIP design is important to consider all components of polymerization mixtures with less computational time. Unfortunately, this method can not explain electronic behavior of molecule and is relatively inaccurate. Another study of MIP design has reported the QM calculation [9-11]. Design of MIP using quantum calculation has been reported to give relatively accurate prediction based on interaction energy analysis. Nevertheless, this method needs a relatively long time of optimization process; therefore, it is not preferable for high system of calculations. Therefore, an effective and accurate computational method is highly recommended.

Dong et al. [12] have successfully designed acetochlorine imprinted polymer using molecular dynamics simulation approach followed by DFT calculation and showed suitability of the results with those of experimental result. The application of this method is claimed to be very efficient for screening effective functional monomer and solvent. Therefore, by considering of this result of Dong's works, here we applied the same method to study effective functional monomer and solvent for R(+)-cathinone imprinted polymer.

EXPERIMENTAL SECTION

Materials

This research has evaluated R(+)-cathinone, nineteen functional monomers, chloroform, and acetonitrile solvent. The structure of functional monomer used in this study has previously been used by Karim and co-workers [13] as depicted in Table 1. Equilibrated chloroform and acetonitrile solvent was provided by GROMACS.

Instrumentation

This calculation was conducted using a computer with specification: Intel® Core™ i5-3470 CPU @ 3.20 GHz and Linux Ubuntu 13.04 as the operating system. All of the QM calculations processes, geometry optimization and electronic structure analysis were performed using Gaussian 09 and GaussView 5.0 software package. As MD simulation tools, GROMACS 4.5.6 [14] software package was used in this research. Then, simulation result and graphical representation was visualized using VMD [15] and XMGRACE respectively.

Table 1. List of functional monomers used in modelling

No	Name
1	2-Vinylpyridine
2	4-Vinylpyridin
3	Acrolein
4	Acrylamide
5	Acrylic acid
6	Acrylamido-2-methyl propane sulfonic acid
7	Allylamine
8	Methacrylic acid
9	Ethylene glycol dimethacrylate
10	Hydroxy ethyl methacrylate
11	m-Divinylbenzene
12	p-Divinylbenzene
13	Styrene
14	Urocanic acid
15	N,N'-methylene bis acrylamide
16	N,N-diethyl amino ethyl methacrylate
17	Urocanic ethyl ester
18	Itaconic acid
19	Vinylimidazole

Computational Methods

MD simulation setup

First screening process of functional monomer was carried out using MD simulation prior to QM calculation. Each topology contained GROMOS53A6 force field [16] and the coordinate of monomer was obtained by insertion of monomer structure into online PRODRG software (http://davapc1.bioch.dundee.ac.uk/prodrg) [17]. The template/monomer complex with ratio 1:1 was conditioned in a 5 nm x 5 nm x 5nm of cubic cell and immersed in porogenic solvent. Before real simulation, the systems were first classically minimized in energy by 1000 steps of steepest descent and then were equilibrated in NVT and NPT ensemble condition. Finally, the equilibrated complex was simulated for 2 ns (1 million steps) in explicit solvent using leapfrog algorithm with applied LINCS constrain parameter.

To accommodate t/m interactions, 1 nm cutoff distance applied in non-bonded interaction and Particle Mesh Ewald (PME) summation applied in long range interactions. Then, the coordinate and energy were sampled every 1000 step. The interaction energy of t-m complex obtained from simulation study was calculated based on the following equation:

$$\Delta E_{MM} = E_{complex} - E_{template} - nE_{monomer} \quad (1)$$

ΔE_{MM} is interaction energy of complex t-m whereas $E_{complex}$, $E_{template}$, $nE_{monomer}$ is total energy of complex, energy of template, and energy of a number of monomer involved in the interaction. Based on classical potential energy (ΔE_{MM}) as molecular dynamics result, there were chosen top five effective functional monomer with highest value of ΔE_{MM} for the next treatment by QM calculation. All of the simulation process and analysis was done using GROMACS 4.5.6 software package and visualized using VMD.

QM calculation setup

Selected functional monomers obtained from MD simulation result were confirmed again by quantum potential energy (ΔE_{DFT}) as DFT result. The density functional calculation was carried out in B3LYP exchange-correlation functional and basis set of 6-31G(d). Solvent effect was also applied in calculation system using Polarizable Continuum Solvation Model (PCM) [18]. Output of DFT calculation such as interaction strength, partial atomic charges and interaction distances were analyzed to explain monomer interaction effectiveness towards template of R(+)-cathinone.

RESULT AND DISCUSSION

Analysis of MD Simulation Result

The classical potential energy resulted by MD simulation was evaluated and used as a basic data in the selection of top five functional monomers that formed fairly strong interaction to R(+)-cathinone. The use of various solvent in this study was aimed to systematically investigate the solvent effect on the effectiveness of template-monomer interaction. Fig. 1a shows ΔE_{MM} of template/monomer complex in chloroform medium. Five functional monomers with the highest ΔE_{MM} are acrylamido-2-methylpropane sulfonic acid (-83.10 kJ/mol), N,N'-methylene bis acrylamide (-60.90 kJ/mol), itaconic acid (-53.80 kJ/mol), acrolein (-52.90 kJ/mol), and acrylic acid (-52.20 kJ/mol) whereas the five functional monomers with the smallest ΔE_{MM} are p-divinyl benzene (-2.20 kJ/mol), styrene (-6.50 kJ/mol), 2-vinyl pyridine (-6.50 kJ/mol), m-divinyl benzene (-6.70 kJ/mol), and N,N'-diethyl amino methyl methacrylate (-8.90 kJ/mol).

These ΔE_{MM} values could be explained based on the type of the complex interactions occurring between the template and the functional monomer. Generally complex interaction that occurs through the formation of hydrogen bonds leads to high value of ΔE_{MM} whereas a relatively small ΔE_{MM} is dominated by phi-phi interactions. Based on experimental data, the strength of hydrogen bond interaction is 60-120 kJ/mol and phi-phi interaction is 0-50 kJ/mol [19]. The complex interactions between R(+)-cathinone and functional monomers are through (a) hydrogen bonding and (b) phi-phi interactions in chloroform.

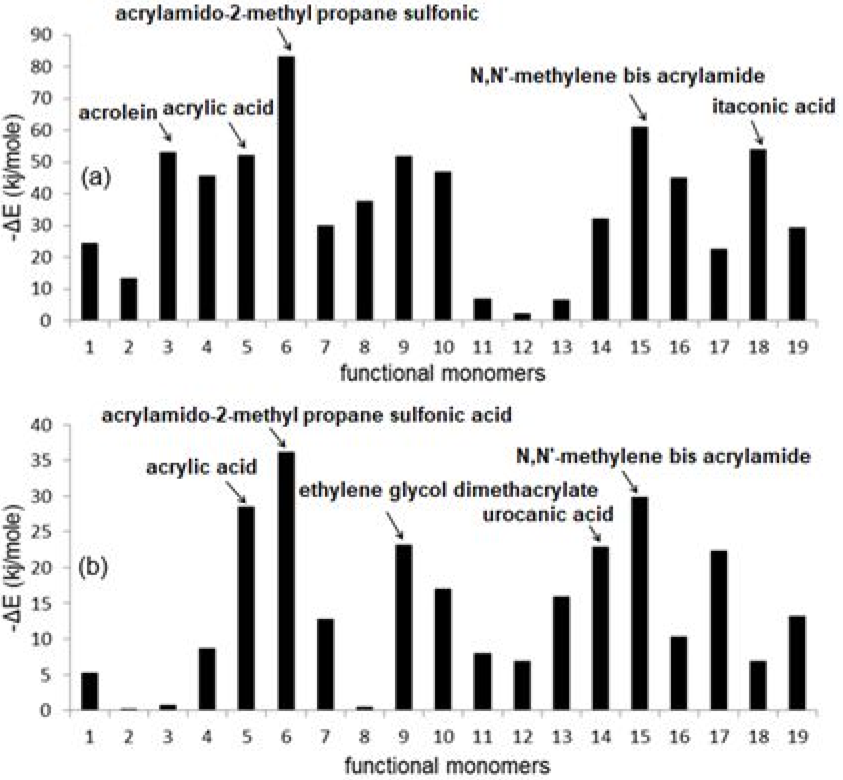

Fig 1. ΔE_{MM} of R(+)-cathinone with functional monomers in (a) chloroform and (b) acetonitrile

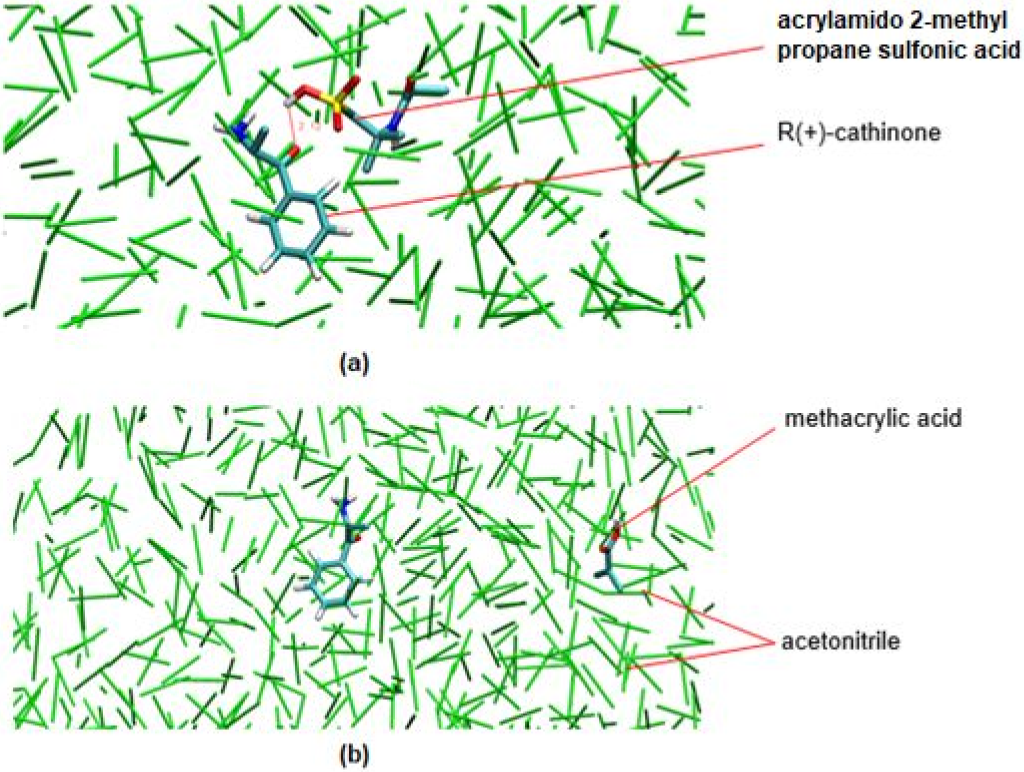

Fig 2. Complex interaction of R(+)-cathinone with (a) acrylamido-2-methyl propane sulfonic acid and (b) methacrylic acid in acetonitrile

Unlike in chloroform medium, five functional monomers with the highest ΔE_{MM} in acetonitrile medium (Fig. 1b) are acrylamido-2-methyl propane sulfonic acid (-36.10 kJ/mol), acrylic acid (-28.40 kJ/mol), ethylene glycol dimethacrylate (-23.20 kJ/mol), urocanic acid (-22.80 kJ/mol), and N,N'-methylene bis acrylamide (-29.80 kJ/mol) whereas the five functional monomer with the smallest ΔE_{MM} are p-divinyl benzene (-6.80 kJ/mol), 2-vinyl pyridine (-5.20 kJ/mol), acrolein (-0.70 kJ/mol), methacrylic acid (-0.50 kJ/mol), and 4-vinyl pyridine (-0.10 kJ/mol). The ΔE_{MM} value of t-m complexes in acetonitrile are shown in Fig. 1b.

The high value of ΔE_{MM} in acetonitrile generally has the same reason as ΔE_{MM} in chloroform. However, acrolein and methacrylic acid has relatively small ΔE_{MM} in acetonitrile whereby it is different in chloroform medium. This behavior can be explained by solvents effect on template-monomer interaction. Acetonitrile which contains a nitrogen atom in cyanide group interferes template-monomer interaction by hydrogen bonding formation to template and monomer, therefore, the interaction of template-solvent or monomer/solvent is greater than template-monomer interaction [20]. Fig. 2 visualizes the complex interaction of R(+)-cathinone with acrylamido-2-methylpropane sulfonic acid (Fig. 2a) and R(+)-cathinone with methacrylic acid (Fig. 2b). It can be observed that acrylamido-2-methyl propane sulfonic acid interact closely with R(+)-cathinone during simulation time whereas R(+)-cathinone and methacrylic acid move away from each other which is caused by stronger interaction between acetonitrile and methacrylic acid. Thus, on the basis of the ΔE_{MM} data, the best five functional monomers have been selected for the next analysis using DFT calculations.

Analysis of DFT Calculation Result

The computational method used in this study is analogous to that used by Dong and co-workers [12]. They have selected an effective functional monomers and solvent for synthesis of MIP selective acetochlor by using this approach. However, this method should be first validated by applying it to the experimental data. Validation process was carried out by comparing 3 set of data obtained from NMR calculation using different methods and H-NMR experimental data of acrolein. Experimental H-NMR was obtained from spectral database website (www.sdbs.db.aist.go.jp) with SDBS No. 4448HSP-43-221. Theoretical calculation of H-NMR chemical shift was analyzed using GIAO methods (Gauge Including Atomic Orbitals). Chemical shift value is shown in Table 2 and acrolein structure is represented in Fig. 3.

According to acrolein structure in Fig. 3, it is understood that H atoms of acrolein are not identical to each other so that they will give different value of chemical shift (δ_{shift}). However, calculation result using MP2 methods in Table 2 shows a degenerate peak for H(2) and H(3) atoms, hence this methods is not reliable. HF method also gives relatively high deviation, therefore this method results in inaccurate calculation. Compared with three others, the B3LYP/6-31G(d)-integrated PCM solvation method is most appropriate to be used in this study because it gives a minimum error compared to experimental data. Thus, the last method was selected for the next calculations.

DFT calculation generate ΔE_{DFT} as shown in Fig. 4. The ΔE_{DFT} values give an information about template/monomer interaction strength. Generally, ΔE_{DFT} could represents the number of hydrogen bond formed, partial atomic charge contributed to the interaction as well as interaction distance. From Fig. 4, it can be observed that interaction of R(+)-cathinone with functional monomer (1) and (8) have small value of ΔE_{DFT}. This small value of ΔE_{DFT} is due to limited facilities that support template-monomer interaction, e.g. only by one hydrogen bond whereas the other complexes have two hydrogen bonds. Unlike monomer (1) and (8), monomer (4) N,N'-methylene bis acrylamide has the highest ΔE_{DFT} values. This can be explained from the fact that hydrogen bond between R(+)-cathinone and N,N'-methylene bis acrylamide occurred at a distance of 1.662 Å through the N (amine) atom of template and the H (amine) atom of monomer and the other at a distance of 1.987 Å through the H (amine) atoms of template and O (carbonyl) atom of monomer. According to Garcia [21], the moderate hydrogen bond has interaction energy around 4–15 kcal/mol with H···B length of1.5–2.2 Å and bond angle of 130°–180°, hence, interaction of R(+)-cathinone/N,N'-methylene bis acrylamide is considered to be relatively strong. In addition, the atomic partial charges contributed to hydrogen bond of

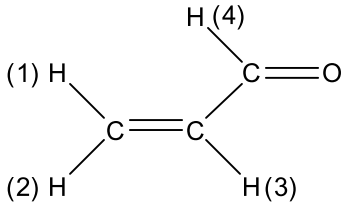

Fig 3. Acrolein structure with numbering on each hydrogen atom

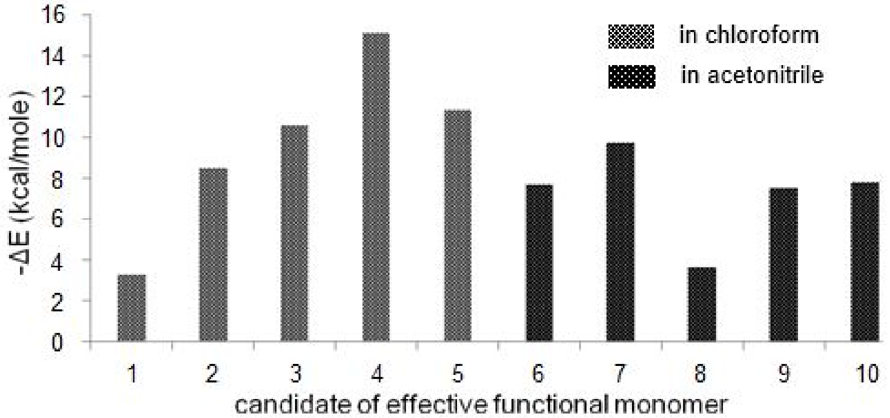

Fig 4. Theoretical ΔE_{DFT} of the interaction of R(+)-cathinone with (1) acrolein, (2) acrylic acid, (3) acrylamido-2-methylpropane sulfonic acid, (4) N,N'-methylene bis acrylamide, (5) itaconic acid, (6) acrylic acid, (7) acrylamido-2-methylpropane sulfonic acid, (8) ethylene glycol dimethacrylate, (9) urocanic acid, (10) N,N'-methylene bis acrylamide

Table 2. Chemical shift data of ^{1}H-NMR (ppm) obtained from experiments and calculation

Atoms	Experimental	Calculation			
		B3LYP	HF	HF/MP2	MP2
7H	9.586	9.349(2.472)	8.456(11.788)	8.883(7.334)	9.250(3.505)
2H	6.522	6.331(2.929)	5.756(11.745)	5.579(14.459)*	6.172(5.366)**
5H	6.370	6.045(5.102)	5.631(11.601)	5.579(12.417)*	6.172(3.108)**
3H	6.350	6.040(4.882)	5.452(14.142)	5.649(11.039)	5.966(6.047)

Note:
a. All the theoretical calculation performed in 6-31G(d) level with PCM solvation effect
b. * and ** are degenerate peak
c. Data in brackets shown % deviation of each computational method versus those of experiment

Table 3. Interaction distance and partial atomic charge of t/m interaction

Solvent	Monomer	Atomic net charge (coulomb)		Distance (Å)	Type
		R(+)-cathinone	monomer		
Chloroform	Acrolein	H (0.338)	O (-0.437)	2.172	M
	Acrylic acid	H (0.346)	O (-0.518)	2.134	M
		O (-0.516)	H (0.459)	1.754	
	Acrylamido-2-methyl propane sulfonic acid	H (0.548)	O (-0.563)	1.654	M
		O (-0.525)	H (0.494)	2.130	
	N,N'-methylene bis acrylamide	N (-0.775)	H (0.402)	1.662	M
		H (0.562)	O (-0.566)	1.987	
	Itaconic acid	H (0.345)	O (-0.509)	2.152	M
		O (-0.516)	H (0.462)	1.746	
Acetonitrile	Acrylic acid	H (0.341)	O (-0.519)	2.143	M
		O (-0.522)	H (0.458)	1.748	
	Acrylamido-2-methyl propane sulfonic acid	H (0.495)	O (-0.533)	1.644	M
		O (-0.566)	H (0.344)	2.174	
	Ethylene glycol dimethacrylate	H (0.337)	O (-0.518)	2.298	W
	Urocanic acid	H (0.342)	O (-0.541)	2.123	M
		O (-0.521)	H (0.455)	1.767	
	N,N'-methylene bis acrylamide	N (-0.776)	H (0.408)	1.939	M
		H (0.354)	O (-0.576)	2.234	

Note:
M = moderate
W = weak

this complex is higher than those of the others. For example, the hydrogen bonds for complex of R(+)-cathinone/itaconic acid was facilitated by interaction of H(+0.345)···O(-0.509) and O(-0.516)···H(+0.462), while the hydrogen bond for complex of R(+)-cathinone/N,N'-methylene bis acrylamide was facilitated by interaction of N(-0.775)···H(+0.402) and H(+0.562)···O(-0.566). The complete data of partial atomic charge contributed to hydrogen bonds and interaction distances are shown in Table 3. Based on this ΔE_{DFT} parameters, it is obvious that N,N'-methylene bis acrylamide and chloroform are the most effective functional monomer and solvent for the design of MIP-selective R(+)-cathinone. This prediction of effective functional monomer and solvent through modeling and simulation is recommended to be used in the synthesis of MIP-selective R(+)-cathinone.

CONCLUSION

Molecular dynamics and DFT methods of calculation have been carried out to determine an effective functional monomer and solvent for the design of MIP selective R(+)-cathinone. From this research, it has been shown that the most effective interaction of template/monomer occurs only in chloroform medium; therefore chloroform is preferable medium solvent of reaction compared to acetonitrile. Furthermore, it also has been demonstrated that monomer N,N'-methylene bis acrylamide gives a relatively strong interaction with R(+)-cathinone, thus it is expected that preparation of MIP using this monomer will give good performance of adsorption towards template molecule, R(+)-cathinone.

REFERENCES

[1] Jones, S., Fileccia, E.L., Murphy, M., Fowler, M.J., King, M.V., Shortall, S.E., Wigmore, P.M., Green, A.R., Fone, K.C., and Ebling, F.J., 2014, Cathinone increases body temperature, enhances locomotor activity, and induces striatal c-fos expression in the Siberian hamster, *Neurosci. Lett.*, 559, 34–38.

[2] Correll, D., 2013, *Development of a Rapid SPME/GC-MS Method for the Detection and Quantification of Synthetic Cathinones in Oral Fluid*, Theses, Trinity College, Hartford.

[3] Santali, E.Y., Cadogan, A.K., Daeid, N.N., Savage, K.A., and Sutcliffe, O.B., 2011, Synthesis, full chemical characterisation and development of validated methods for the quantification of (±)-4′-methylmethcathinone (mephedrone): A new “legal high”, *J. Pharm. Biomed. Anal.*, 56 (2), 246–255.

[4] Sellergren, B., and Allender, C., 2005, Molecularly imprinted polymers: A bridge to advanced drug delivery, *Adv. Drug Delivery Rev.*, 57 (12), 1733–1741.

[5] Danielsson, B., 2008, Artificial receptors, *Adv. Biochem. Eng. Biotechnol.*, 109, 97–122.

[6] Bakas, I., Oujji, N.B., Moczko, E., Istamboulie, G., Piletsky, S., Piletska, E., Ait-Addi, E., Ait-Ichou, I., Noguer, T., and Rouillon, R., 2013, Computational

and experimental investigation of molecular imprinted polymers for selective extraction of dimethoate and its metabolite omethoate from olive oil, *J. Chromatogr. A*, 1274, 13–18.

[7] Nicholls, I.A., Karlsson, B.C.G., Olsson, G.D., and Rosengren, A.M., 2013, Computational strategies for the design and study of molecularly imprinted materials, *Ind. Eng. Chem. Res.*, 52 (39), 13900–13909.

[8] Wei, S., Jakusch, M., and Mizaikoff, B., 2007, Investigating the mechanisms of 17β-estradiol imprinting by computational prediction and spectroscopic analysis, *Anal. Bioanal. Chem.*, 389 (2), 423–431.

[9] Gholivand, M.B., Torkashvand, M., and Malekzadeh, G., 2012, Fabrication of an electrochemical sensor based on computationally designed molecularly imprinted polymers for determination of cyanazine in food samples, *Anal. Chim. Acta*, 713, 36–44.

[10] Saputra, A., Wijaya, K., Ahmad, M.N., and Tahir, I., 2013, Penggunaan metode semiempirik AM1 untuk pemilihan monomer fungsional efektif pada prasintesis polimer tercetak diazinon, *Valensi*, 3 (1), 1–9.

[11] Del Sole, R., Lazzoi, M.R., Arnone, M., Della Sala, F., Cannoletta, D., and Vasapollo, G., 2009, Experimental and computational studies on non-covalent imprinted microspheres as recognition system for nicotinamide molecules, *Molecules*, 14 (7), 2632–2649.

[12] Dong, C., Li, X., Guo, Z., and Qi, J., 2009, Development of a model for the rational design of molecular imprinted polymer: Computational approach for combined molecular dynamics/quantum mechanics calculations, *Anal. Chim. Acta*, 647 (1), 117–124.

[13] Albrecht, M., 2007, Supramolecular chemistry-general principles and selected examples from anion recognition and metallosupramolecular chemistry, *Naturwissenschaften*, 94 (12), 951–966.

[14] Manali, K., Monojit, D., and Sukla, V.J., 2012, Solvent effect on extraction of Gallic acid from Amalaki churna (*Emblica officinalis* Gaertn.) to reduce matrix effect using HPTLC and UV-spectroscopy with 12 different nature solvents, *IRJP*, 3 (6), 155–158.

[15] García, E.S., 2006, *Computational Study of Weakly Interacting Complexes*, Dissertation, Fakultät für Chemie Ruhr-Universität Bochum, Bochum.

[16] Karim, K., Breton, F., Rouillon, R., Piletska, E.V., Guereiro, A., Chianella, I., and Piletsky, S.A., 2005, How to find effective functional monomers for effective molecularly imprinted polymers?, *Adv. Drug Delivery Rev.*, 57 (12), 1795–1808.

[17] van der Spoel, D., Lindahl, E., Hess, B., van Buuren, A.R., Apol, E., Meulenhoff, P.J., Tieleman, D.P., Sijbers, A.L.T.M., Feenstra, K.A., van Drunen, R., and Berendsen, H.J.C., 2010, *Gromacs User Manual version 4.5.6.*, www.gromacs.org.

[18] Humphrey, W., Dalke, A., and Schulten, K., 1996, VMD: Visual molecular dynamics, *J. Mol. Graphics*, 14 (1), 33–38.

[19] Oostenbrink, C., Villa, A., Mark, A.E., and van Gunsteren, W.F., 2004, A biomolecular force field based on the free enthalpy of hydration and solvation: The GROMOS force-field parameter sets 53A5 and 53A6, *J. Comput. Chem.*, 25 (13), 1656–1676.

[20] Schüttelkopf, A.W., and van Aalten, D.M., 2004, PRODRG: A tool for high-throughput crystallography of protein-ligand complexes, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 60 (Pt 8), 1355–1363.

[21] Tomasi, J., Mennucci, B., and Cammi, R., 2005, Quantum mechanical continuum solvation models, *Chem. Rev.*, 105 (8), 2999–3093.