The influence of metal on the performance of 2,4,5-triphenylimidazole as an inhibitor of dengue virus replication

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The influence of metal on the performance of 2,4,5-triphenylimidazole as an inhibitor of dengue virus replication

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Abstract. Dengue is a contagious disease caused by dengue virus and transmitted to humans by the bite of infected *Aedes aegypti* mosquito. Imidazole and its derivatives are proven have ability impairing dengue virus. One of potential imodazole's derivatives is 2,4,5-triphenylimidazole (TPI). The presence of metal to the 2,4,5-triphenylimidazole (TPI) structure through a complex compound formation highly contributes to their ability as an inhibtor dengue virus replication. Iron, cobalt and zinc were used as an ion center in the complex compound. Complex Zn-TPI and Fe-TPI showed low cytotoxic effect at all the evaluated concentrations (viability > 50%). Complex Co-TPI showed reduction of DENV-3 growth, at the lowest concentration (6.25 μg/ml) exhibited the antiviral activity (DENV-3 reduction 43%). For Fe-TPI and Zn-TPI, the reduction values of DENV-3 were 56% and 54.9% respectively.

Keywords: metal, 2,4,5-triphenylimidazole, influence, complex-compound, inhibitor, virus-replication

INTRODUCTION

Dengue is one of the most important public health problems affecting the global community. This disease commonly occurs in the tropic and sub-tropics area, and Indonesia becomes one of the countries that has the largest dengue-endemic region (E Setiati *et al.,* 2006; Fahri *et al.*, 2013; Kotaki *et al.*, 2014). Until now, there is no vaccine or anti-viral for humans that could overcome this disease. Imidazole and their derivatives are proven has potency against dengue virus infection in cell lines (Sucipto *et al.*, 2018; Sucipto *et al.*, 2017). On the other hand, the presence of metal on the structure of organic ligand is proven could improve their biological activity (Geersing *et al.,* 2018) The complex compound is formed as a result of metal and organic compound reaction. It can be used as an anti-inflammatory, antimicrobial, antifungal, antibacterial, and antivirus (Agotegaray *et al.*, 2012; Arjmand, Mohani, & Ahmad, 2005; Ranford, Sadler, & Tocher, 1993). The metal complexes with deprotonated imidazole as ligand hold promise as an approach to enhance the biological activity. Previous reports have described the use of cobalt(II)-morin and zinc(II)-morin based systems for anti-DENV (dengue serotype) type 2 applications. The value of inhibition activity of zinc(II)-morin was 2.00 μg/ml and cobalt(II)-morin was 3.08 μg/ml (Sucipto *et al.*, 2017; Sucipto *et al.*, 2019).

Thus, this research investigated the influence of metals on the imidazole derivative (2,4,5-triphenylimidazole) in their anti-dengue activity. Studies on the compound of imidazole-4,5- showed higher antiviral potency against yellow fever virus (YFV) than dengue virus (DENV).

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This bioactivity may be within the imidazole series of a 'para-'attachment of a heterocycle to its 'C' (Saudi *et al*., 2014).This research only focuses on Iron(II), Cobalt(II) and Zinc(II) as metal resources because three of them exhibit biological activity for humans and include as an essential mineral that needed by the humans body. The interaction of metals and 2,4,5-triphenylimidazole as a ligand was investigated through to the complex compound formation and characterized by spectrophotometer UV-Vis, spectrophotometer FTIR, and electron microscope. An inhibitor virus assay will be investigated through the ELISA (Enzyme-Linked Immunosorbent Assay) method using dengue virus type 3.

MATERIALS AND METHODS

Materials

Materials used were pure analysis (pa) degree. They were 2,4,5-triphenylimidazole (TPI), zinc chloride ($ZnCl_2$), cobalt (II) chloride di hydrate ($CoCl_2.2H_2O$), iron (III) chloride hexahydrate ($FeCl_3.6H_2O$), N, N-dimethyl formamide (DMF), methanol, ethanol 95%, distilled water, Vero cells derived from the kidney of an African green monkey from ATCC, Dimethyl Sulfoxide (DMSO) (Merck 99,98%), Minimum Essential Medium Eagle (MEM) Media (Sigma-Aldrich), Fetal Bovine Serum (Biowest), L-glutamine, $NaHCO_3$, Trypsin-EDTA, Dengue virus type 3 (DENV-3) Surabaya Isolate with GenBank accession number KF709426, Cell Proliferation Reagent WST-1 (Roche Applied Science), counting cells and DENV antibody (4G2) for Enzyme-Linked Immunosorbent Assay (ELISA).

Synthesis and characterization of complex compounds from metal and 2,4,5-triphenylimidazole as a ligand

All of the complex compounds were synthesized with the ratio mole metal to ligand = 1:1 (Martak *et al.,* 2016; Sucipto & Martak, 2016). The metal was dissolved by ethanol and reacted to the ligand (in ethanol) and then put in a 25 ml flask and then refluxed for 4 hours at 76°C. After that, the mixture was left until the sediment formed. Next, the sediment was separated from the filtrate then washed with 5 ml of ethanol then dried in a desiccator (Martak *et al*., 2016). All of solids were characterized by Olympus light microscope, spectrophotometer UV-VIS and spectrophotometer FTIR.

Vero cells preparation

Vero cell lines (African green monkey kidney) was used in this study, maintained and propagated in Minimum Essential Eagle Medium containing 10% fetal bovine serum. Cultured Vero cell lines were incubated at 37°C, respectively in 5% CO_2. Confluent monolayer of Vero cells were detached with trypsin-EDTA and incubate cells at 37°C for 5 minutes. Then Minimum Essential Eagle Medium containing 10% fetal bovine serum was added by pipetting gently to break up any clumps of cells and counted using a Hemocytometer. Next, cells in 96-well plate with 1×10^6 cells/10 ml were added and incubated in 37 °C incubator with 5 CO_2 cells were monitored daily until cells reached a >90 % confluent monolayer (Ammerman *et al.,* 2008; Plotkin *et al.,* 2018).

Antiviral activities assay

First, Vero cells were added with 2 ml trypsin-EDTA then incubated with 5% CO_2 at 37 °C for 5 minutes. Then, it was added with 8 ml of the new MEM 10% FBS and was vortexed until it was homogenous. After that, 10 µl was pipetted and added with tryptophan blue strain. Then, the living cell was counted by a Hemocytometer counting chamber. This process required Vero cells ($1x10^6$ cells/10ml) in a 96-well plate (Ammerman *et al*., 2008).

Second, preparation of a complex compound (each complex compound) was weighed 0.0006 gram, dissolved with 4 µl DMF and added by 996 µl of MEM 10% FBS. Then, it was vortexed until homogeneous. After being homogeneous, 150 µl of the complex compound was added in every well in U bottom plate and then added by 50 µl MEM 10% FBS to it. The first well line 50 µl was pipetted which was then filled in the second well line and so on. This process gets complex compound with various concentrations (serial dilution).

To the flat bottom plate, was added by a mixture of 50 µl of Vero cells, 25 µl of a complex compound, and 25 µl of the DENV-3 (2×10^4 FFU/well). 100 µl medium control and 100 µl of

cell control were added. Subsequently, the plates were incubated with 5% CO_2 at 37°C for 24 hours. Finally, the plate was verified using DENV antibody (4G2) for quantitative ELISA using Microplate Reader with a wavelength of 415 nm (Sucipto *et al.*, 2018).

Cytotoxicity assay

First, Vero cells were added with 2 ml trypsin-EDTA then incubated with 5% CO_2 at 37°C for 5 minutes. Then, 8 ml new MEM 10% FBS was added and was vortexed until homogenous. After that, 10 µl was pipetted and added by tryptophan blue strain. Then, the living cell was counted with a Hemocytometer counting chamber. This process required Vero cells ($1x10^6$ cells/10ml) in a 96-well plate. Monitor cells until cells reach a >90 % confluent monolayer (Ammerman *et al.*, 2008). Second, preparation of a complex compound (each complex compound) was weighed 0.0006 gram, dissolved with 4 µl DMF and added by 996 µl of MEM 10% FBS. Then, it was vortexed until it is homogeneous. Next, 150 µl of the complex compound was added in every well in U bottom plate and then 50 µl MEM 10% FBS was added. The first well line 50 µl was pipetted which was then filled in the second well line and so on. This process got the complex compound with various concentrations (serial dilution).

After that, a 50 µl serial dilution was added to the Vero cells that had been prepared on the first day. Then, added 50 new MEM that containing 10% FBS. Then incubated 24 hours at 37 °C. After that second day, the supernatant was removed which was then washed twice with PBS. Then 100 µl of the new MEM 10% FBS was added and added 10 µl of WST-1 reagent into Vero cells. Then the mixture was vortexed until homogeneous which is then incubated 30-60 minutes. After that, it is analyzed with a microplate reader with a wavelength of 450 nm and a reference wavelength of 650 nm (Sucipto *et al.*, 2018).

Statistical analysis

Microsoft Excel 2010 for Windows was used to determine the cytotoxicity concentration 50 (CC_{50}), inhibitory concentration (IC_{50}) values of the complex compounds, *t* test and standard deviation. A *p* value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Synthesis of complex compounds

In this research, complex compounds were synthesized using the reflux method by reacting 2,4,5-triphenylimidazole (TPI) as a ligand and Fe, Co and Zn as a central atom. The complexes were synthesized using ratio mole metal to ligand 1:1. The obtained crystals were then put in the freeze dryer to make the complete dryness of crystal. The crystals that formed was characterized by light microscope (Figure 1). Complex Co-TPI and Zn-TPI showed a perfect needle crystal. However, Fe-TPI showed a broken needle crystal. The broken crystal is caused by high heating temperature when crystallization step.

Characterization of complex compounds

Complex compounds that have been successfully synthesized then characterized to determine their nature and characteristic. The characterization was conducted by UV-Vis spectrophotometer and FTIR spectrophotometer.

Characterization using UV-Vis spectrophotometer was used to determine the maximum wavelength and UV-Vis spectra pattern in a compound. The crystalline of the complex compound was dissolved with DMF, then the absorbance was measured (Figure 2 and Table 1). Figure 2 and Table 1 show that there is a shift in the maximum wavelength of the complexes and the ligand. This peak shifted due to the density of asymmetric electric charges in the imidazole ring was altered after coordinated with metal ions. It will drive a shift over a wide absorption range because the metal ion has many electrons on the d orbital. Consequently, the π- π * transition takes place easier. All complex compounds show the maximum wavelength in the UV region (under 400 nm). This wavelength shows the metal-ligand charge transfer phenomenon which only has by complex compound (Deng *et al.*, 2012).

(a) Fe-TPI (b) Co-TPI (c) Zn-TPI

Figure 1. Crystal of TPI- complex compounds. (a) for Fe-TPI complex (b) for Co-TPI (c) for Zn-TPI. Each solid has been characterized by light microscopes with 40x magnification.

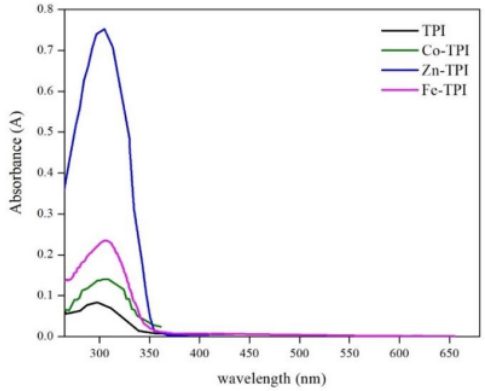

Figure 2. The electronic spectra of complex compounds on DMF solvent. All solutions were charcterized by spectrophotometer UV-VIS in the region 200-650 nm.

Table 1. The maximum wavelength of complex compounds Fe-TPI, Co-TPI, Zn-TPI, and the ligand TPI. All compounds were soluted in DMF solvent.

Compound	Maximum wavelenth (nm)
TPI	304
Fe-TPI	308.5
Co-TPI	309
Zn-TPI	306

Characterization using FTIR spectrophotometer was used to determine the functional groups formed in the complex compound and to determine the bonds formed between metals and ligands. The result of the FTIR spectra shows that there are differences in the FTIR spectra of TPI ligands and the complex compounds (Figure 3 and Table 2).

If we compare the spectra of the ligand and the complexes, we can see that there is some shifted of the wavenumber on characteristic functional group. In other words, the metal is proven bonded to the ligand structure. From this characterization we also could conclude that all metals from complex compounds have bonded to the –N- functional group from ligand. (Figure 4).

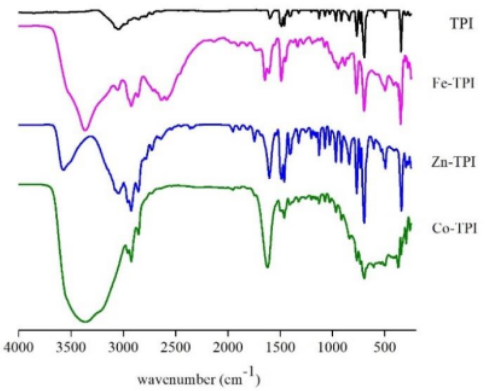

Figure 3. The FTIR spectra of complex compounds Fe-TPI, Co-TPI, Zn-TPI, and the ligand TPI. All compounds were characterized by FTIR the wavenumber range 3500-250 cm^{-1}.

Table 2. The FTIR spectra data of complex compounds Fe-TPI, Co-TPI, Zn-TPI. The spectra of complex compounds were compared with the ligand spectrum TPI.

Functional Group	Wavenumber (cm^{-1})			
	TPI	Fe-TPI	Co-TPI	Zn-TPI
Metal-N	-	370.33	368.4	298.96
O-H	3591.45	3365.78	3379.28	3650
N-H	3100.34	3124.21	3367.71	3113.13
C-H	2924.47	2856.58	2924.09	2988.08
C=C	1601.65	1489.05	1504.48	1602.85
C-N	1129.09	1604.77	1627.92	1128.36

Reference: (Badertscher *et al.,* 2009).

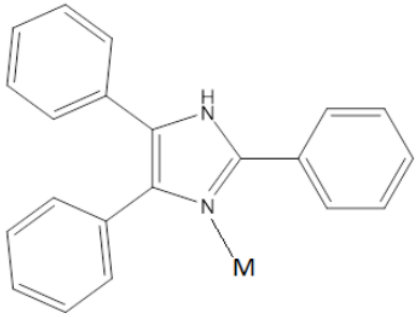

Figure 4. The bonding prediction of metal ion (M) with a functional group of TPI ligand. M is metal ion Fe, Co, and Zn that act as central ion of complex compound.

Anti-dengue activity of complex compounds. The purpose of this study is to find antiviral to DENV-2 using Vero cells line (IC_{50}). Vero cells could be infected by DENV as well as hepatocyte cells because the characteristic of the cell is similar to hepatocyte which is a host of dengue virus to replicate itself. The CC_{50} presented cytotoxicity level of complex compounds against the host, and the host used in the study was Vero cells.

Based on Table 3, all complexes have IC_{50} lower than their CC_{50} except Co-TPI. It means that almost all complexes are able to kill the pathogen before destroying the host cell. This condition is beneficial because the complex compound only kill the virus-cell without make suffering the host.

As shown in Figure 5, we can see that TPI and Cu-TPI are classified as highly toxic compared by Fe-TPI and Zn-TPI which classified as a medium toxic. The inhibition at IC_{50} was not significantly higher (p<0.005) compared to that of the metal-free imidazole (IC_{50} = 0.38 µg/ml). But, the metal-free imidazole is more toxic for Vero cells (CC_{50} = 2.91 µg/ml). The level of toxicity of an extract is classified based on the IC_{50} value, which is a very high category (highly toxic) if it is able to kill 50% of larvae at a concentration of 1-10 µg/ml, a medium category (medium toxic) at a concentration of 10-100 µg/ml and a low category (low toxic) at a concentration of 100-1000 µg/ml (Thiel *et al.,* 1982) . For this purpose, we tested each compound at various concentration and observed that both Zn-TPI and Fe-TPI low exhibit any cytotoxic effect at all the evaluated concentrations (viability > 50%). Compound Co-TPI showed reduction of DENV-3 growth, at the lowest concentration (6.25 µg/ml) exhibited the antiviral activity (DENV-3 reduction 43%). It showed reduction of DENV-3 56% and 54.9%.

In this study, medium control and cell control were treated without DENV-3. The data distribution of mean of response from each concentration was normal, with p-value more than 0.05. The response is a total energy from cell mitochondrial in each concentration of complexes. The value of response from medium control was <0.001 and value of cell control was >2.63, with analogy viability cells medium control is 0% and control cells is 100%. The data in this study was analyzed by using t-test on Microsoft Excel 2010 and inhibition of compound to DENV-3 replication was significant (p value <0.05). The Figure 6 indicates the mean of response with its standard deviation.

The C terminal in the imidazole structure plays important role to improve cellular uptake and nuclear localization of complex compound. Besides, phenyl-imidazole has a great potential as drug candidate to treatment of a variety of viral diseases, phenyl rings in imidazole presence of electron withdrawing groups improved the biological activity (Sharma *et al.*, 2009).

Table 3. The anti-dengue activity of complex compounds in terms of cytotoxicity concentration.

Compound	Cytotoxicity Concentration (CC_{50}) (µg/ml)	Inhibition Concentration (IC_{50}) (µg/ml)	Selectivity Index (SI)
TPI*	36.75	1.46	25.17
Fe-TPI	1231.71	98.66	12.48
Co-TPI	509.14	-56.29	-9.04
Cu-TPI	44.17	2.30	19.20 [(Sucipto *et al.*, 2018)]

*Unpublished Data

(CC50), Inhibition Concentration (IC50), and Selectivity Index (SI). The anti-dengue activity of complex compounds was also compared with the ligand TPI.

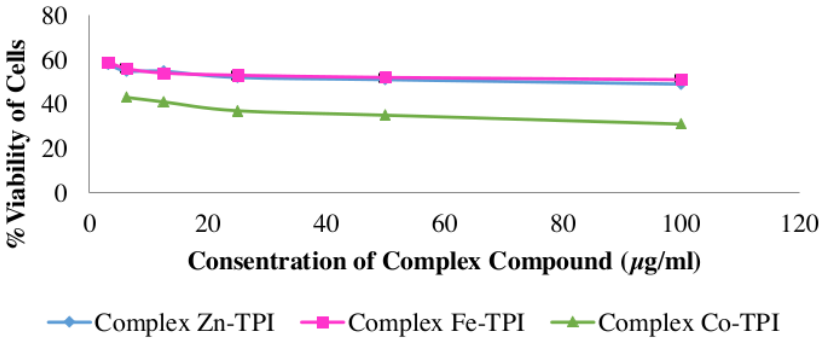

Figure 5. The inhibition DENV-3 curve of complex compounds Fe-TPI, Co-TPI, and Zn-TPI. The inhibition activity was gained by analyzing the inhibition of Vero cells that treated with the complex compounds.

In the present study, the death cell rates were not determined for the Vero cells that were treated for 24 h by the complex compound with different concentrations. The results revealed that it was found that these complex compound stimulate almost same with Vero cells compared to control (data not shown), for example in the 200 µg/ml concentration of complex compounds not showed the cell death with shown viability of cells >100% (Figure 7). This result demonstrates that three complex compounds did not cause the death cell or toxic effects on Vero cells. If the concentration of the compound is high, it will be toxic and could inhibit cell growth. A strong oxidative compound can cause cell death in more than one way: passive cell death, such as necrosis caused by the disruption of osmotic balance and apoptosis, such as active cell death caused by caspases. Based on previous research, active cell death is characterized by cytoplasmic vacuolation, largely in the endoplasmic reticulum and by the absence of caspases (cysteine proteases) (Sucipto & Martak, 2016).

Compare with a previous study, for example Cu-TPI (Sucipto & Martak, 2016), the result of cytotoxicity and antiviral activity of DENV-3 for three complex compounds in this study showed low cytotoxicity to Vero cells and high activity. Activity against human immunodeficiency virus type 1 (HIV-1) strain IIIB and HIV-2 strain ROD in MT-4 cells (IC_{50}) by Zn(II) with 3,14-dimethyl-2,6,13,17-tetraazatricyclo(16.4.0.0^{7,12})docosane) diacetate ligand were 3.50 ± 0.33 µM and >110.67 µM (Biot *et al.,* 2012).

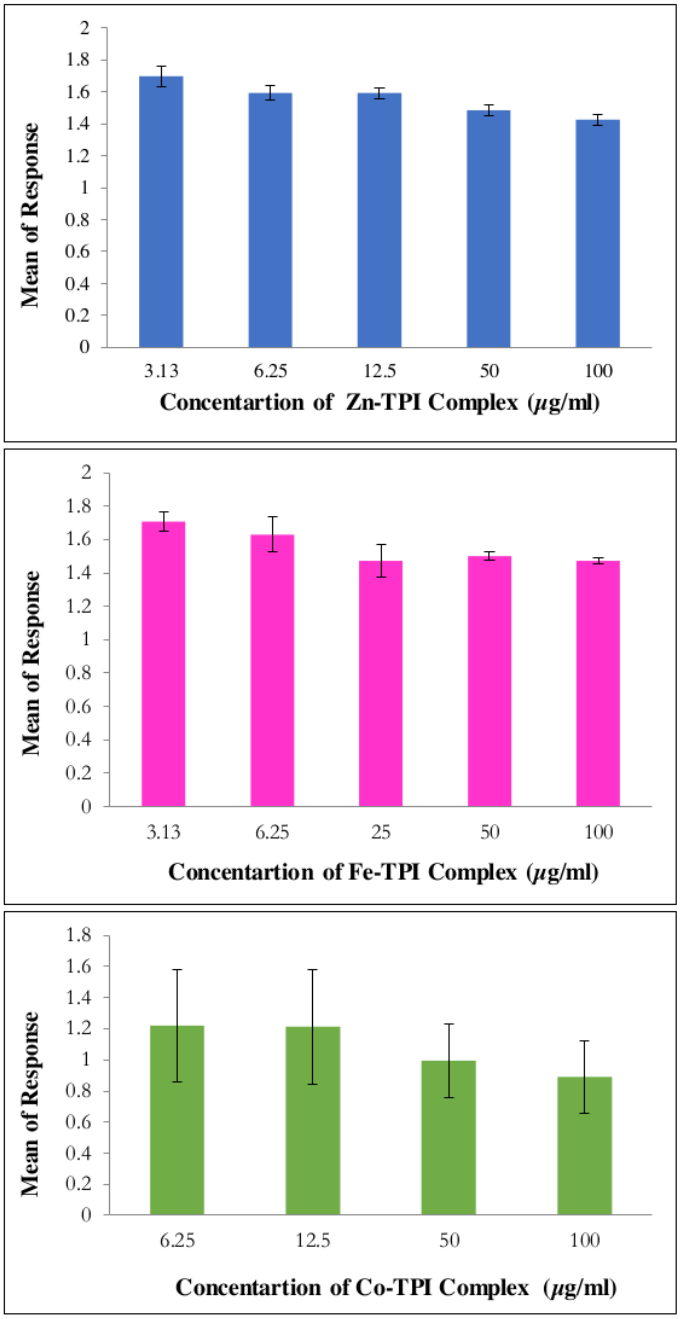

Figure 6. Standard deviation curve on the antiviral assay of complex compounds Fe-TPI, Co-TPI, and Zn-TPI. For Fe-TPI and Zn TPI complex was analyzed in 5 concentrations. However, for the Co-TPI complex, in 4 concentrations.

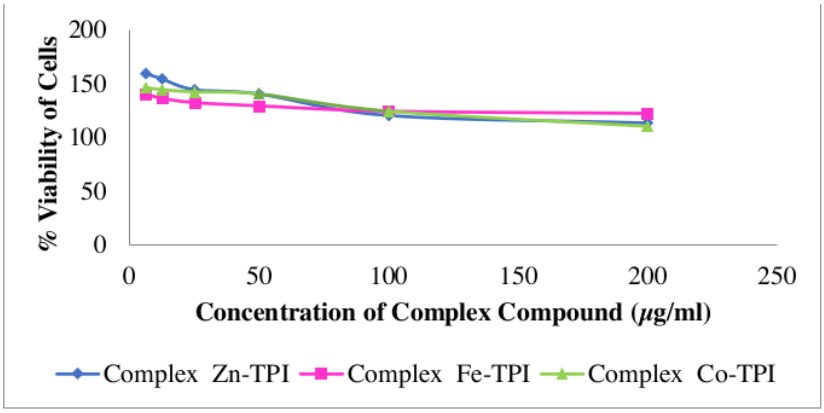

Figure 7. The cytotoxicity curve of complex compounds Fe-TPI, Co-TPI, and Zn-TPI. The cytotoxicity curve was gained by analyzing the cytotoxicity of Vero cells that treated with the complex compounds.

According to SI value, almost complex generate value more than 3. This denotes that almost complex compounds has a high selectivity. A compound is said to have high selectivity if the SI value is ≥ 3 and is said to be less selective if it has SI value <3 (Prayong *et al.,* 2008). Selectivity means that only viral cells are attacked while normal cells are not attacked (Alali *et al.,* 1999). For Co-TPI, the result shows negative on the CC_{50}, IC_{50} and Selective Index (SI). This result revealed that this complex is highly toxic so the result will always be negative

CONCLUSION

This research successfully investigated the influence of metal presence on the anti-dengue activity of derivative imidazole. The interaction of metal and 2,4,5-triphenylimidazole was revealed through the complex compound formation. All of the obtained complex compounds showed a bathochromic shift of wavelength and indicate a metal-ligand bonding through – N- group from the ligand. Complex Fe-TPI and Zn-TPI showed potency as an inhibitor of dengue viruses. However, Co-TPI complex was not found to be potent as an anti-dengue candidate.

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