UNIVERSITI TEKNOLOGI MARA

DESIGN AND SYNTHESES OF *ORTHO*-, *META*- AND *PARA*-XYLYLGUANIDINIUM-Zn^{2+}-CYCLEN COMPLEXES AND THEIR INTERACTIONS WITH DNA

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Thesis submitted in fulfillment
of the requirements for the degree of
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CONFIRMATION BY PANEL OF EXAMINERS

I certify that a Panel of Examiners has met on 7th February 2018 to conduct the final examination of Nor Amin Bin Hassan on his **Master of Science** thesis entitled "Design and syntheses of *ortho*-, *meta*- and *para*-xylylguanidinium-Zn^{2+}-cyclen complexes and their interactions with DNA" in accordance with Universiti Teknologi MARA Act 1976 (Act 173). The Panel of Examiners recommends that the student be awarded the relevant degree. The panel of Examiners were as follows:

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This topic has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Three new zinc ions (Zn^{2+}) complexes, $\mathbf{C^1}$, $\mathbf{C^2}$ and $\mathbf{C^3}$, were designed and synthesized by coordination of Zn^{2+} into the integrated 1,4,7,10-tetraazacyclododecane (cyclen) and *ortho*-, *meta*- and *para*-bromoxylylguanidinium pendants group. A retrosynthetic analysis was carried out to identify and solve problems with regard the selection of organic reactions. The syntheses were performed in five steps including of (i) Gabriel and Ing-Manske primary amine synthesis, (ii) S_N2 substitution reaction, (iii) guanylation of primary amine, (iv) deprotection of Boc group, and (v) coordination of Zn^{2+} complex. All the Zn^{2+} complexes structures were characterized by ^{1}H- and ^{13}C-NMR spectroscopy, infrared spectroscopy and mass spectrometry. The aim of synthesizing these Zn^{2+} complexes was to confirm the anticipated interactions of Zn^{2+} complexes towards natural DNA as well as to explore the phosphatase activity of such complexes. Hence, ethidium bromide (EB) fluorescence assay and circular dichroism (CD) spectroscopy were used to ascertain the interaction between Zn^{2+} complexes towards natural DNA *i.e.* calf thymus (ctDNA). The former assay demonstrated a displacement of EB from its complexes with ctDNA, thus confirming the affinity of these Zn^{2+} complexes towards DNA. CD spectroscopic results also revealed that $\mathbf{C^1}$ has disturbed both base stacking and right handed helicity properties of ctDNA, but retained the B-form of its structure. By contrast, $\mathbf{C^2}$ and $\mathbf{C^3}$ transformed the conformation of ctDNA from B-form into Z-form. This was further supported by thermal denaturation studies showing ΔT_m values of $\mathbf{C^1}$, $\mathbf{C^2}$, and $\mathbf{C^3}$ to be +2, +4 and +5, respectively. The catalytic properties of these complexes for phosphate hydrolysis was evaluated using phosphodiesters bis(*p*-nitrophenyl)phosphate (BNPP) as a model and monitoring by UV spectrometry. The BNPP hydrolysis results (*ca.* 17% after 8 days incubation) suggested that $\mathbf{C^1}$, $\mathbf{C^2}$, and $\mathbf{C^3}$ were endowed with still modest yet significant catalytic properties.

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