Pyrrole-chalcone analogues as DNA binding agents

Nurin Syahmimi binti Azamudin[1], Siti Munirah Binti Mohd Faudzi[1, 2*,] Maryam Aisyah Abdullah[1], Haslina Ahmad[1], Ahmad Zaidi Ismail[1,4], M. Rashidi Abdull Manap[1,3] Tasnim Munshi[3], Ian J. Scowen[3]

[1]Department of Chemistry, Faculty of Science, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
[2]Laboratory of Natural Products, Institute of Bioscience, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
[3]School of Chemistry, University of Lincoln, Joseph Banks Laboratories, Green Lane, Lincoln, Lincolnshire, LN6 7DL, UK
[4]School of Chemical Sciences, 23 Symond St, 1010 Auckland CBD, New Zealand
Corresponding author*: sitimunirah@upm.edu.my

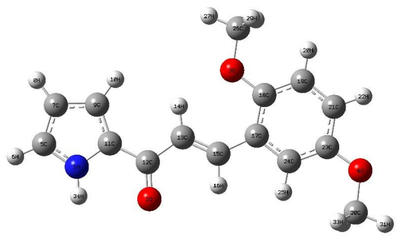
ABSTRACT

Cancer is a gene mutation in the cell that grows uncontrollably. Many drugs have been successfully developed to treat this disease but could not provide effective solutions for cancer treatment, in which the major problem of these drugs is their cytotoxicity. The usual cancer treatment tends to kills the cancerous cell along with healthy cell around it. An alpha,beta- (α,β-) unsaturated ketone at the core of the chalcone feature provides the basis for the wide range of its biological activities including anticancer effect and can be prepared *via* Claisen-Schmidt condensation reaction between acetophenone and benzaldehydes with base or acid as catalyst[1]. Pyrrole-chalcones of 3-(2,5-dimethoxy-phenyl)-1-(1*H*-pyrrole-3-yl)-propenone (compound **1**) and 1-(1*H*-pyrrol-2-yl)-3-*m*-tolylpropenone (compound **2**) were screened for anticancer properties through deoxyribonucleic acid (DNA) binding assay by Ultraviolet Visible (UV/VIS) absorption spectroscopy. The intrinsic binding constant (K_b) of complexes **1** and **2** with calf-thymus DNA (CT-DNA) are $1.08x10^3$ M^{-1} and $5.225x10^3$ M^{-1}, respectively. It was found that compound **1** has a higher binding affinity than compound **2** due to methoxyl ($-OCH_3$) group is a better electron donating group with an ability to form intramolecular hydrogen bonding with DNA in comparison to methyl ($-CH_3$) moiety. The UV-Visible titration studies suggest that chalcones bind to DNA via intercalation mechanism as it induces hyperchromic effect as shown in the λ_{max} [2]. Results obtained from this work would be very useful in understanding the mechanism of interaction of the Pyrrole-chalcone analogues binding to DNA and serve as preliminary information for the development as a new potential anticancer agents.

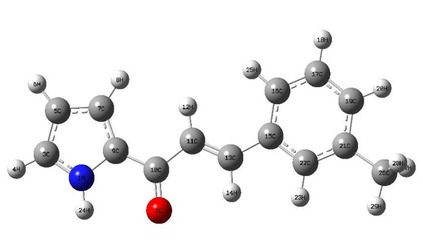
INTRODUCTION

During cancer process, the genomes of incipient cancer cells acquire mutant alleles of proto-oncogenes, tumor-suppressor genes, and other genes that control, directly or indirectly, cell proliferation[3]. The alternation of cellular DNA could actually stop the tumor spread. Chalcone derivatives structure has been known as an anticancer agent by binding with target site to stop the tumor cells from spreading. In addition to its anti-cancerous effect, chalcone derivatives have been targeted to inhibit DNA as the main target, as DNA does the replication and transcription in cancer cells. The interaction between DNA and several compounds that affect the replication process and inhibition of the cancer cells is the basic in designing anticancer drug[4]. Chalcones effectiveness as anticancer depends on the mode and affinity of their binding ability to the DNA strands[4]. The pyrrole show potent anticancer activity where the electron donating group is attached to pyrrole is believed to increased the anticancer activity[5]. Previous studies indicated that chalcone and pyrrole are an interesting substances that have wide usage and combinations of both scaffolds have attracted many biological interests. Hence, Pyrrole-chalcone analogues have been synthesized in order to find the DNA binding affinity towards DNA.

PYRROYLATED-CHALCONE ANALOGUES



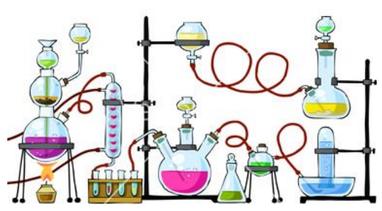
(1)



(2)

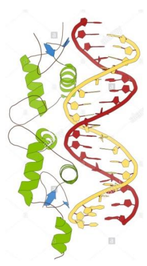
METHODOLOGY

SYNTHESIS → **CRYSTALLIZATION** → **CHARACTERIZATION**



CHARACTERIZATION → **STRUCTURAL STUDY**

CHARACTERIZATION → **DNA BINDING ASSAY**



- **DNA TITRATION**
- **VISCOSITY MEASUREMENT**

CONCLUSION

- Compound **1** and **2** are novel synthetic Pyrrole-chalcones that have been successfully synthesized and structurally characterized via IR, NMR and MS.
- A new single crystal of compound **1** was grown by slow evaporation of ethanol.
- The molecular structure, thermal properties and validation of the experimental vibrational spectra of the new single crystal of compound **1** were studied.
- The experimental and calculated vibrational spectra of the new single crystal of compound **1** were comparable.
- Substituent on the benzene ring of the synthesized compound affect the electronic properties of the whole molecules thus affected the DNA binding affinity of these molecules .
- Compound **1** showed higher binding affinity towards CT-DNA with greater DNA binding in comparison to compound **2** based on the intrinsic binding constant (Kb).
- Presence of methoxyl group in compound **1**, helps in improving the bioavailability of the compound. This is explained by the stabilization effect via resonance of the electron donating ability of the methoxyl moeity.
- Both compounds binded to the CT-DNA via intercalation mode.

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3. Yadav, VR. et al. (2011). "The role of chalcones in suppression of NF-κB-mediated inflammation and cancer." *Int. Immunopharmacol.*, 11(3):295-309.
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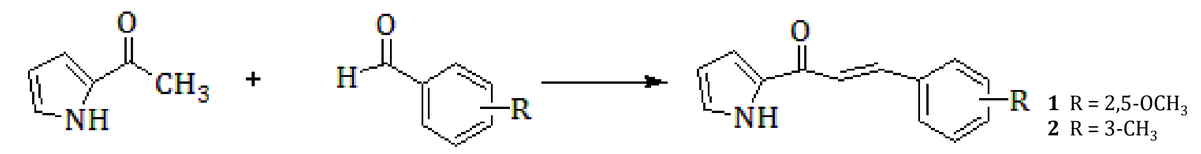
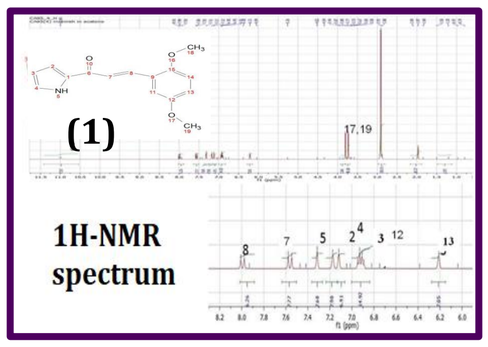
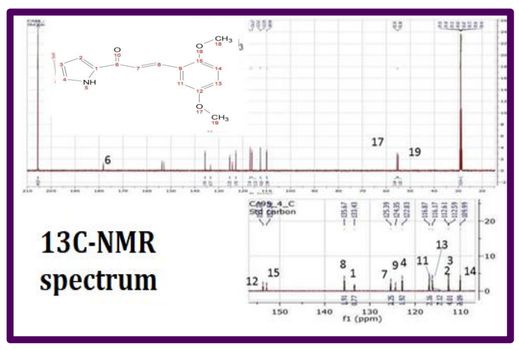
RESULTS AND DISCUSSION

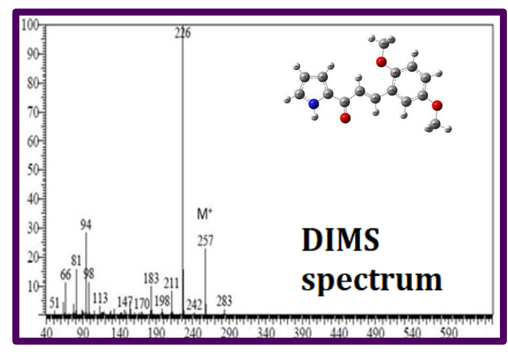
GENERAL REACTION SCHEME FOR THE SYNTHESIS :

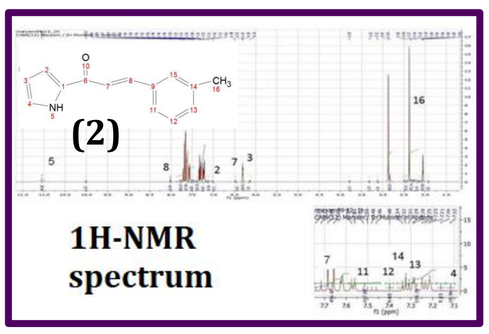


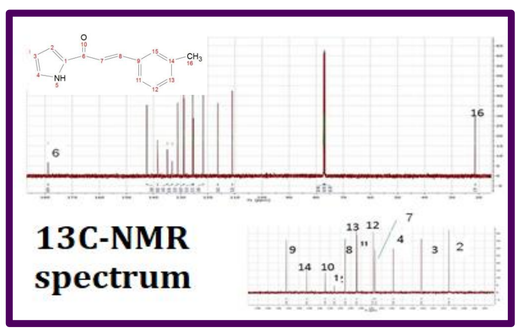
SPECTROSCOPY AND MASS SPECTROMETRY CHARACTERIZATIONS:

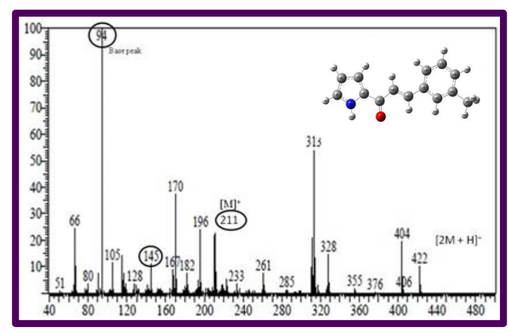






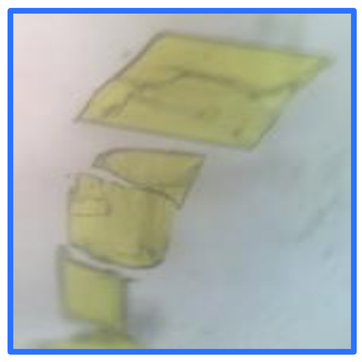






CRYSTALLIZATION OF 1

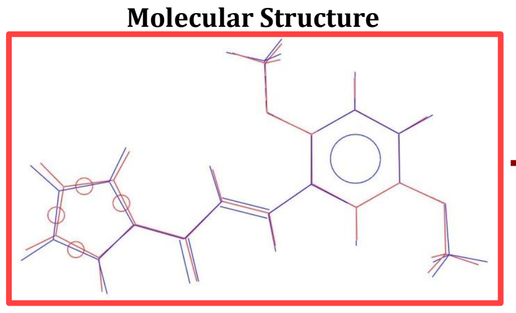
Grown crystal of (1)



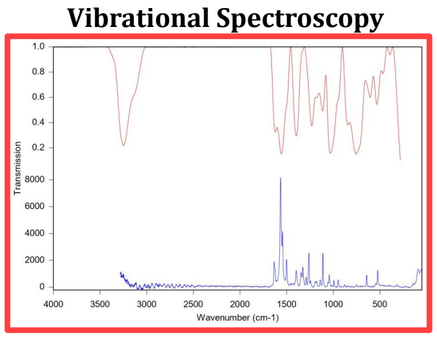
A single crystal of compound **1** was obtained and successfully characterized both theoretically and experimentally, using quantum chemical calculation, solid-state Raman and IR spectroscopy and sc X-ray diffraction.

STRUCTURAL STUDY OF 1

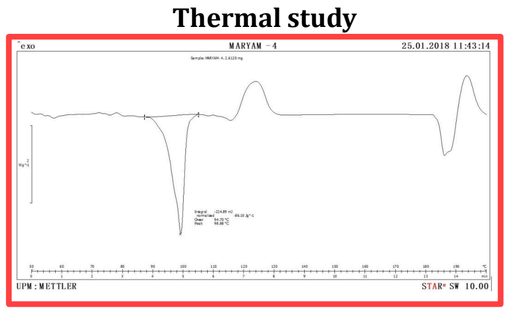
Molecular Structure



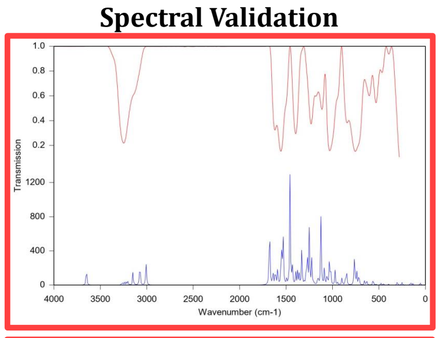
Vibrational Spectroscopy

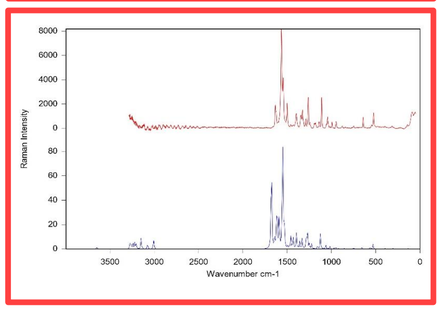


Thermal study



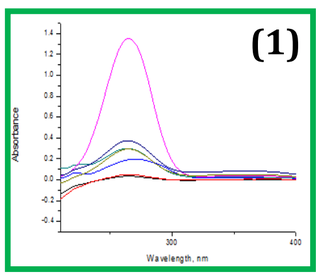
Spectral Validation

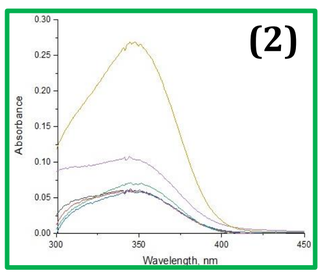




DNA BINDING ASSAY

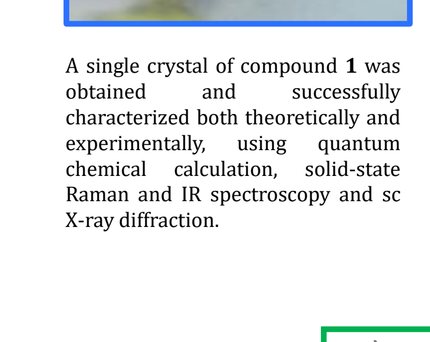
UV/VIS SPECTRA





Auxochrome molecule in compound **1** increase the electron density in the π-system. As they lower the excitation π∗-level, a longer wavelength is needed for the excitation along π→π∗, hence the λmax value is shifted to a longer wavelength (bathochromic effect)[6].

DNA TITRATION



VISCOSITY MEASUREMENT

DNA titration and viscosity showed that both compound **1** and **2** binds with DNA via intercalation. UV–Vis absorption of compound **1** and **2** upon addition of CT-DNA change upon increment of DNA concentration. The intrinsic binding constant (Kb) of the complexes **1** and **2** are $1.08x10^3$ M^{-1} and $5.225x10^3$ M^{-1}, respectively. with the CT-DNA.

ACKNOWLEDGEMENT

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