GREEN APPROACH TO SYNTHESIS OF OXINDOLE DERIVATIVES AND INVESTIGATION OF THEIR ANTIMICROBIAL AND ANTIOXIDANT ACTIVITIES

By

HAPUHINNE PALLAYAGE SHYAMALI KUMARI WIJEKOON

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Thesis submitted to the University of Sri Jayewardenepura for the award of the Degree of Master of Philosophy

DECLARATION BY THE CANDIDATE

The work described in this thesis was carried out by me under the supervision of Dr. Upul Kumarasinghe (Principal Investigator), Prof. P M Jayaweera, Dr. Lalinda Palliyaguru (Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura) Prof. Chinthika Gunasekara, Prof. Neluka Fernando (Department of Microbiology, Faculty of Medical Sciences, University of Sri Jayewardenepura) and a report on this has not been submitted in whole or in part to any university or any other institution for another Degree/Diploma.

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CERTIFICATION OF SUPERVISORS

We certify that the candidate has incorporated all corrections, additions and amendments recommended by the examiners to this version of the MPhil thesis.

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APTES	3-Aminopropyltriethoxysilane
UV-Vis	Ultraviolet-Visible Spectroscopy
FTIR	Fourier Transform-Infrared
NMR	Nuclear Magnetic Resonance
SEM	Scanning Electron Microscopy
XRD	X-Ray diffraction
TGA	Thermogravimetric analysis
ATR	Attenuated total reflection
ATCC	American Type Culture Collection
S. aureus	*Staphylococcus aureus*
P. aeruginosa	*Pseudomonas aeruginosa*
E. coli	*Escherichia coli*
C. albicans	*Candida albicans*
MRSA	Methicillin Resistant Staphylococcus aureus
DPPH	(2,2-diphenyl-1-picryl-hydrazyl-hydrate)
ROS	Reactive oxygen species
DMSO	Dimethyl sulfoxide
CDCl3	Deuterated Chloroform
WHO	World Health Organization
TLC	Thin-layer chromatography
MHA	Mueller-Hinton agar
SDA	Sabouraud dextrose agar

SDB	Sabouraud dextrose broth
MIC	Minimum Inhibitory Concentration
MFC	Minimum Fungicidal Concentration

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Green Approach to Synthesis of Oxindole Derivatives and investigations of their Antimicrobial and Antioxidant Activities

Hapuhinne Pallayage Shyamali Kumari Wijekoon

ABSTRACT

Synthesis of biologically active compounds in an environmentally benign manner is a challenge. This study reports the efficient synthesis of thirteen 3-alkenyl oxindole derivatives including two novel compounds in solvent-free condition under microwave irradiation. The synthetic procedure contains two consecutive steps. In the first step, seven 3-alkenyl oxindole derivatives were synthesized from oxindole and aromatic aldehydes in the presence of (3-aminopropyl)ethoxysilane (APTES) functionalized silica as a heterogeneous catalyst. Secondly, the synthesized oxindole derivatives were acetylated using acetic anhydride in the presence of H_2SO_4 functionalized silica to obtain *N*-acetylated 3-alkenyl oxindole derivatives. The silica was extracted from the rice husk ash under microwave irradiation and functionalized with APTES and H_2SO_4 to use as heterogenous catalysts in above reactions. The catalysts were characterized by powder X-Ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), Thermo gravimetrical analysis (TGA), Scanning electron microscopy (SEM) and elemental analysis. The synthesized compounds were characterized by ^{1}H and ^{13}C Nuclear Magnetic Resonance, FTIR, UV-Visible spectrophotometry, melting point and elemental analysis. The antibacterial activity of all synthesized oxindole derivatives against *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), Methicillin-Resistant *Staphylococcus aureus* (clinical strain), *Pseudomonas aeruginosa* (ATCC 27853), *Acinetobacter baumannii* (clinical strain), and the antifungal activity against

Candida albicans (ATCC 10231), *Candida glabrata* (ATCC 90030), *Candida parapsilosis* (ATCC 22019), *Candida krusei* (ATCC 6258), three clinical isolates of *Candida albicans* were determined. The antioxidant activity was investigated using ABTS, DPPH and FRAP methods. Detailed structural characterization confirmed the formation of APTES functionalized silica, H_2SO_4 functionalized silica and the thirteen oxindole derivatives with sufficient yields (72% - 91%). Only the non-acetylated 3-alkenyl oxindole derivatives demonstrated antimicrobial activity against tested organisms and the highest antifungal activity was observed against *Candida albicans*. Among the tested bacterial species, zones of inhibition (ZOI) were observed only against Gram positive organisms. Minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values of these compounds were detected from 2 µg/ml to 125 µg/ml against tested *Candida* species. Following the *N*-acetylation of synthesized 3-substituted oxindole derivatives, the resulted antimicrobial property was diminished. The antioxidant activity of all the synthesized compounds was detected with half maximum concentration (EC_{50}) of 7±0.7 µg/ml to 326±26 µg/ml. Selected compounds with potential activities were further evaluated for their toxicity and found to have no toxicity at these concentrations. The simple work-up procedure, mild conditions, recyclability of the catalyst, shorter reaction times and high yields were advantages of this green protocol. The results of this study emphasize that these compounds can be considered as potential lead compounds for development of antioxidant and antifungals against *Candida* species.

Keywords: Microwave-Assisted, Solvent-free, 3-Alkenyl oxindole derivatives, Antifungal activity, Rice husk extracted silica