SYNTHESIS AND CHARACTERIZATION OF CURCUMINOIDS BY CLAISEN-SCHMIDT CONDENSATION AND THEIR CYTOTOXIC EFFECTS ON HELA AND K562 CANCER CELL LINES

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SUPERVISOR'S DECLARATION

We hereby declare that we have checked this thesis and in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Master of Science in Industrial Chemistry.

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STUDENT'S DECLARATION

I hereby declare that the work in this thesis is based on my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Malaysia Pahang or any other institutions.

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LIST OF SYMBOLS

α	Alpha
β	Beta
δ	Chemical shift
ºC	Degree celcius
g/mol	Gram per mol
Hz	Hertz
hr	Hours
J	Joule
L	Litre
MHz	Megahertz
µg/ml	Microgram per ml
µM	Micromolar
mg	Milligram
ml	Millilitre
mm	Millimetre
min	Minute
nm	Nanometer
N	Normality
ppm	Parts per milliom
%	Percentage
λ	Wavelength
W	Watt

LIST OF ABBREVIATIONS

MTT	3-(4,5-Dimethythiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
ABL	Abelson murine leukemia
CH_3COOH	Acetic acid
AML	Acute myeloid leukimias
NH_4Cl	Ammonium chloride
BDMC	*Bis*-demethoxycurcumin
B_2O_3	Boron oxide
Br	Bromine
CO_2	Carbon dioxide
^{13}C-NMR	Carbon nuclear magnetic resonance
cm	Centimetre
$CHCI_3$	Chloroform
Cl	Chlorine
CC	Column chromatography
DMC	Demethoxycurcumin
CH_2Cl_2	Dichloromethane
DMSO	Dimethyl sulfoxide
DMEM	Dulbecco's Modified Eagle's Medium
EtOAc	Ethyl acetate
FBS	Fetal bovine serum
F	Fluorine
FTIR	Fourier transform infrared spectroscopy
GC-MS	Gas chromatography-mass spectroscopy
g	Gram
Hex	Hexane
HPV	Human papillomavirus
NH_2NH_2	Hydrazine
kg	Kilogram
HCI	Hydrogen chloride
MS	Mass spectroscopy
MeOH	Methanol

OCH_3	Methoxy
MWI	Microwave irradiation
MACs	Mono-carbonyl
n-$BuNH_2$	n-butylamine
NMR	Nuclear magnetic resonance
OD	Optical density
cm^{-1}	Per centimetre
KBr	Potassium bromide
^{1}H NMR	Proton nuclear magnetic resonance
QSAR	Quantitative structure-activity relationship
rt	Room temperature
SARs	Structure-activity relationship
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulphate
H_2SO_4	Sulphuric acid
TMS	Tetramethylsilane
TLC	Thin layer chromatography
UV-Vis	Ultraviolet-visible spectroscopy
v-Scr	Rous sarcoma virus

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ABSTRAK

Kanser adalah salah satu sebab utama kematian di seluruh dunia dengan bilangan kes dijangka meningkat sebanyak 70% dalam tempoh dua dekad akan datang. Fakta ini menyebabkan para penyelidik terus mengkaji bagaimana cara untuk merawat kanser dengan mencari ubat baru yang berpotensi untuk menggantikan ubat anti kanser seperti doxorubicin yang mempunyai pelbagai kesan sampingan. Sebilangan besar sebatian semula jadi telah dikaji secara meluas berkenaan potensi penggunaannya dalam pencegahan kanser sejak beberapa dekad. Kurkumin dari *Curcuma longa* telah menarik perhatian para penyelidik, merupakan sebatian semula jadi yang sangat menjanjikan yang berpotensi digunakan untuk kemoterapi pelbagai kanser. Kurkumin memenuhi ciri-ciri untuk agen pencegahan kimoterapi yang ideal dengan ketoksikan yang rendah, kemampuan dan akses mudah. Tetapi disebabkan ketidakstabilan struktur, keterlarutan yang rendah dan bioavailabiliti yang lemah, kurkuminoid telah disintesis untuk memperbaiki strukturnya dan bioavailibiliti yang rendah. Kira-kira 20 kurkuminoid disintesis dengan menggunakan aldehida dan ketone yang berbeza di bawah kaedah tindak balas kondensasi Claisen-Schmidt. Produk telah ditulenkan dengan menggunakan kromatografi lajur, kromatografi lapisan nipis dan proses penghabluran. Struktur kimia sebatian disintesis telah dijelaskan dengan menggunakan spektroskopi UV-VIS, spektroskopi spektrometer Massa (MS) dan spektroskopi resonans magnetik Nuklear (NMR). Derivatif telah dinilai tahap sitotosisiti terhadap karsinoma serviks manusia HeLa dan kanser sel K562 dengan menggunakan ujian MTT. Di antara derivatif ini, **21** (IC_{50} = 12.50 ± 1.30), **22** (IC_{50} = 11.00 ± 2.80), **23** (IC_{50} = 9.00 ± 1.20), **26** (IC_{50} = 12.00 ± 1.60), **28** (IC_{50} = 11.00 ± 2.10), **29** (IC_{50} = 15.00 ± 1.60), **30** (IC_{50} = 15.00 ± 1.20), **31** (IC_{50} = 14.00 ± 1.40), **32** (IC_{50} = 11.00 ± 1.30), and **33** (IC_{50} = 9.00 ± 1.20) menunjukkan kesan sitotoksik tinggi pada sel-sel karsinoma serviks manusia HeLa. Sementara itu, sebatian **22** (IC_{50} = 6.50 ± 0.80), **23** (IC_{50} = 16.00 ± 1.30), **32** (IC_{50} = 15.00 ± 1.90) dan **33** (IC_{50} = 12.50 ± 0.95) menunjukkan kesan sitotoksik yang tinggi terhadap sel kanser K562. Oleh itu, beberapa sebatian didapati menunjukkan kesan sitotoksisiti yang lebih tinggi terhadap sel-sel kanser HeLa dan K562 berbanding dengan doxorubicin yang digunakan sebagai bahan rujukan.

ABSTRACT

Cancer is one of leading causes of death worldwide with the number of cases is expected to rise by 70% over the next two decades. These facts have lead researchers to continue studying how to treat cancer by find a new potential drug to replace the standard anti-cancer drugs such as doxorubicin which has side effects. Numerous natural compounds have been extensively investigated for their potential use in cancer prevention over decades. Curcumin from *Curcuma longa* has caught attention among researchers, is a highly promising natural compound that can potentially be used for chemoprevention of various cancers. Curcumin fulfils the characteristics for an ideal chemopreventive agent with its low toxicity, affordability and easy accessibility. But due to structurally instable, low solubility and poor bioavailability, the mono-ketone of curcuminoids were synthesized to improve its structure and poor bioavailability. About 20 curcuminoids were synthesized by using different substituted aldehydes and different ketones under Claisen-Schmidt condensation reaction method. The products were purified by using column chromatography, thin layer chromatography and crystallization processes. The chemical structures of the synthesized compounds were elucidated by using UV-VIS spectroscopy, Fourier transform infrared spectrometer (FTIR), Mass spectroscopy (MS) and Nuclear magnetic resonance spectrometer (NMR) spectroscopy. The compounds were screened for their cytotoxicity effects on HeLa human cervical carcinoma and K562 cancer cell lines by using MTT assay. Among these derivatives, **21** (IC_{50} = 12.50 ± 1.30), **22** (IC_{50} = 11.00 ± 2.80), **23** (IC_{50} = 9.00 ± 1.20), **26** (IC_{50} = 12.00 ± 1.60), **28** (IC_{50} = 11.00 ± 2.10), **29** (IC_{50} = 15.00 ± 1.60), **30** (IC_{50} = 15.00 ± 1.20), **31** (IC_{50} = 14.00 ± 1.40), **32** (IC_{50} = 11.00 ± 1.30), **33** (IC_{50} = 11.00 ± 1.20) and **34** (IC_{50} = 6.00 ± 1.20) showed high cytotoxic effects on HeLa human cervical carcinoma cell lines. Meanwhile, compounds **22** (IC_{50} = 6.50 ± 0.80), **23** (IC_{50} = 16.00 ± 1.30), **32** (IC_{50} = 15.00 ± 1.90) and **33** (IC_{50} = 12.50 ± 0.95) showed high cytotoxic effects against K562 cancer cell lines. Therefore, some compounds were found to show higher cytotoxicity effect against HeLa and K562 cancer cell lines in comparison to doxorubicin used as standard.

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