The Synthesis and Antioxidant Capacities of a range of Resveratrol and Related Phenolic Glucosides.

A thesis presented in fulfilment of the requirements for the degree of

Doctor of Philosophy

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Abstract

The resveratrol analogues have attracted great attension by scientists as these compounds exhibit numerous bioactive properties due to their outstanding antioxidant capacity. However, the role of the antioxidant activity of these molecules is still not quite clear. This thesis details the development and biological evaluation of a library of resveratrol analogues in order to provide a better understanding of their pharmaceutical value.

This thesis begins with an overview of an important hydroxylated stilbene (resveratrol) and its analogues present in natural plants, food and beverage. Consequently, these studies are summarised and aided in the selection of a new library of substrates to be synthesised herein and biologically evaluated.

Chapter two details the successful synthesis of resveratrol glycosides from resveratrol. Pleasingly, all chemical transformations carried out herein were performed in excellent yields. *In-vitro* anti-oxidant studies on these substrates revealed glycosylation of resveratrol leads to a decreased antioxidant capacity. In addition, these studies suggested the para hydroxyl group on resveratrol has a higher reactivity than the meta hydroxyl group.

Chapter three details the synthesis of a hydroxylated resveratrol (piceatannol) and many of its glycosides. Almost all of the targeted compounds were prepared by applying a modified strategy designed for resveratrol glycosides in high efficiency. The anti-oxidant assays suggested that piceatannol is a more powerful antioxidant than resveratrol. The assays also revealed that the antioxidant activity of piceatannol glycosides is quite dependent on the glycosylation position.

Chapter four then details the preparation of several common resveratrol dimers. The individual products were obtained via a one step oxidation of resveratrol followed by acetylation of the products, separation, and base hydrolysis. In addition, successful isomerisation of some of the *trans*-dimers into their *cis* forms was achieved in this study. With a simple protocol now in place to synthesise such resveratrol dimers, it paves the way for future work on the synthesis of glucosylated dimers of resveratrol. Such compounds would be expected to have a diverse range of antioxidant properties and other related bioactivities and are worthy of further exploration.

Finally, Chapter five contains the associated experimental procedures and characterisation data for all synthesised resveratrol and piceatannol analogues along with a range of oligomers.

List of publications

1. Fragmentation Patterns of Monomeric and Oligomeric Wine Stilbenoids by UHPLC-ESI-QTOFMS. Moss, R.; Mao, Q.; Taylor, D.; Saucier, C. *Rapid Communications in Mass Spectrometry*, **2013**, *27*, 1815-1827.

2. Pallidol hexaacetate ethyl acetate monosolvate. Mao, Q.; Taylor, D. K.; Ng, S. W.; Tiekink, E. R. T. *Acta Crystallographica Section E*, **2013**, *E69*, 1155-1156.

3. Synthesis and Antioxidant Capacity Studies of Resveratrol of all Possible Glucosides. Mao, Q.; Skouroumounis, G.; Taylor, D. K. *Natural Products*. **2015**, *In Preparation*.

4. Synthesis and Antioxidant Capacity Studies of Piceatannol Glucosides. Mao, Q.; Skouroumounis, G.; Taylor, D. K. *Natural Products*. **2015**, *In Preparation*.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Abbreviations

ABS	Absorbance
br	Broad
COSY	Correlation spectroscopy
cm	Centimetres
d	Doublet
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DPPH	2,2-Diphenyl-1-picrylhydrazyl-1,1-diphenyl-2-picrylhydrazyl
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
$FeCl_3$	Ferric chloride
FRAP	Ferric cyanide reducing antioxidant power assay
g	Grams
GC	Gas chromatography
GCMS	Gas chromatography mass spectrometry
h	Hours
HCl	Hydrochloric acid
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum coherence
HPLC-DAD	High-Performance Liquid Chromatography-Diode-Array Detection
HRMS	High resolution mass spectrometry
Hz	Hertz
$h\nu$	Light/irradiation
J	Coupling constant
K_2CO_3	Potassium carbonate
L	Litre
LC-MS	Liquid chromatography-mass spectrometry
Lit.	Literature

m	Multiplet
M	Molar (moles/litre)
min.	Minutes
m/z	Mass to charge ratio
MeOH	Methanol
$MgSO_4$	Magnesium sulphate
mg	Milligrams
MHz	Megahertz
mL	Millilitre
mmol	Millimoles
mol	Moles
Mpt.	Melting point
MS	Mass spectrometry
nm	Nanometres
Na	Sodium
$NaHCO_3$	Sodium bicarbonate
NMR	Nuclear magnetic resonance
OAc	Acetate
Piv	Pivaloyl
ppm	Parts per million
psi	Pounds per square inch
q	Quartet
R_f	Retension factor
rt	Room temperature
s	Singlet
t	Triplet
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TPTZ	2,4,6-Tripyridyl-1,3,5-triazin
UV	Ultra-violet
d	Chemical shift
m	Micro

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"God in his goodness sent the grapes, to cheer both great and small; little fools drink too much, and great fools not at all."

-Anonymous

'Wine is a biochemical challenge. It is a daunting task to probe the alchemy of this elixir and to determine what lies 'at the heart of the matter'.'

-Goldberg