

**SYNTHESIS OF BIOACTIVE CYCLOHEXENYL  
CHALCONES AND FLAVONOID DERIVATIVES**

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## Abstract

Flavonoids are a class of natural products that are well known to possess a wide range of pharmacological properties. Due to their recent discovery in modulating muscarinic receptor activity and its inhibitory effect against dengue-2 virus NS3 protease, flavonoids are idea candidates for drug development. This dissertation describes the syntheses of several flavones and some Diels-Alder adducts derived from chalcones.

A modified Baker-Venkataraman method has been developed where flavones were prepared in a one-pot procedure from the corresponding 2'-hydroxyacetophenones and acyl chlorides under different conditions. When 2'-hydroxyacetophenone is heated with a stoichiometric amount of acyl chloride, either in a DBU/pyridine system or in an open K<sub>2</sub>CO<sub>3</sub>/acetone system, only the flavone is obtained, albeit in modest yield. However, when it is heated with an excess of acyl chloride in a DBU/pyridine system, the 3-acylflavone is the only product, while treatment in an open K<sub>2</sub>CO<sub>3</sub>/acetone system afforded the flavone as the major product and a smaller amount of 3-acylflavone.

Panduratin A and its regioisomer isopanduratin A have been synthesized in four steps from (*E*)-ocimene, [(*E*)-3,7-dimethyl-1,3,6-octatriene] via a Diels–Alder cycloaddition reaction. An overall yield of 75% was achieved from 2',6'-dihydroxy,4'-methoxyacetophenone.

The mulberry Diels-Alder adducts pentamethyl ethers of the kuwanon V and dorsterone have been synthesised via a biomimetic intermolecular [4+2] cycloaddition reaction between a highly electron-rich dienophile and a Lewis acid sensitive diene derived from chalcone. Cycloaddition reaction under thermal condition afforded the

kuwanon V and dorsterone in a 3:2 ratio. Cycloaddition catalysed by AgOTf/Bu<sub>4</sub>NBH<sub>4</sub> gave higher yield of adducts.

## Abstrak

Flavonoid merupakan satu kelas sebatian semulajadi yang dikenalpasti dengan pelbagai sifat farmakologinya. Penemuan terbaru flavonoid dalam penyelarasan aktiviti reseptor muscarinik dan kesan penghambatannya terhadap protease denggi-2 virus NS3 menjadikan flavonoid sebagai suatu idea untuk menghasilkan ubat yang sesuai. Disertasi ini menggambarkan sintesis beberapa flavonoid dan produk Diels-Alder yang berasal dari chalcon.

Satu kaedah Baker-Venkataraman telah diubahsuai di mana sintesis flavon dilakukan dalam prosedur satu-bakul (one-pot) dari 2'-hidroksiasetofenon dan asid klorida di bawah keadaan-keadaan yang berbeza. Semasa 2'-hidroksiasetofenon dipanaskan dengan stoikiometri kuantiti asid klorida, baik dalam sistem DBU/piridin atau dalam sistem  $K_2CO_3$ /aseton terbuka, hanya flavon dihasilkan, walaupun dalam kuantiti yang sederhana. Namun demikian, apabila 2'-hidroksiasetofenon dipanaskan dengan asid klorida yang berlebihan dalam sistem DBU/piridin, hanya 3-asilflavon dihasilkan. Sebaliknya tindak balas yang sama dalam sistem  $K_2CO_3$ /aseton terbuka menghasilkan flavon sebagai produk utama dan 3-asilflavon sebagai hasil sampingan.

Panduratin A dan regioisomernya isopanduratin A telah disediakan dalam empat langkah dari (*E*)-ocimene, [(*E*)-3,7-dimetil-1,3,6-octatriene] melalui tindak balas Diels-Alder. Hasil keseluruhannya adalah 75% dari 2',6'-dihidroksi,4'-metoksiasetofenone.

Produk Diels-Alder kuwanon V dan dorsterone pentametil eter telah disediakan melalui biomimitik tindak balas Diels-Alder antara kedua-dua dienophile dan diene yang berasal dari chalcon dimana dienophile itu kaya dengan electron dan diene itu sensitif terhadap acid Lewis. Tindak balas Diels-Alder yang dilakukan di bawah keadaan termal menghasilkan kuwanon V dan dorsterone dalam nisbah 3:2. Tindak balas Diels-Alder yang dilakukan di bawah pemangkin  $AgOTf/Bu_4NBH_4$  memberi hasil yang lebih tinggi.

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## List of Abbreviations

Ac	Acetyl
BDNF	Brain-Derived Neurotrophic Factor
cAMP	Cyclic Adenosine MonoPhosphate
CO	Carbon monoxide
COX	Cyclo-oxygenase
CREB	cAMP Response-Element Binding protein
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
EI	Electron Ionisation
ESI	ElectroSpray Ionisation
ERK	Extracellular Signal-Regulated Kinase
GCMS	Gas Chromatography-Mass Spectrometry
KOtBu	Potassium <i>tert</i> -butoxide
MEM-Cl	Methoxyethoxymethyl chloride
mp	melting point
MW	Microwave
NaH	Sodium hydride
NMR	Nuclear Magnetic Resonance
NMS	<i>N</i> -methylnscopolamine
NOE	Nuclear Overhauser Effect
OAc	Acetate
OBz	Benzoyloxy
OTf	Trifluoromethanesulfonate

PA-Ph	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane
Pd <sub>2</sub> (dba) <sub>3</sub>	Tris[dibenzylideneacetone]dipalladium(0)
PPh <sub>3</sub>	Triphenylphosphine
SAR	Structure-Activity Relationship
TBAF	Tetra- <i>n</i> -butylammonium fluoride
THF	Tetrahydrofuran

## Research Publications

1. Chee, C. F.; Abdullah, I.; Buckle, M. J. C.; Rahman, N. A. (2010) An efficient synthesis of ( $\pm$ )-panduratin A and ( $\pm$ )-isopanduratin A, inhibitors of dengue-2 viral activity. *Tetrahedron Lett.* 51, 495-498.
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