Angular Naphthopyrones as Antibacterial Agents:
Investigations into the antibacterial activity of
benzo[f]chromanones and related compounds

By Simone A. Ward

A thesis submitted for the degree of Master of Philosophy of
The Australian National University

THE AUSTRALIAN NATIONAL UNIVERSITY

Department of Chemistry
The Australian National University
Canberra, Australia

October, 2009
Author’s Declaration

The work described in this thesis is original work of the author, except where due references are stated. This material has not been submitted for any other degree at any other university.

Simone A. Ward
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I am also grateful to the ANU and RSC for the scholarships which funded this profound adventure.
Abstract

Antibiotics have been hailed as one of medicine’s greatest achievements, but the effectiveness of current drugs is waning. Chapter 1 introduces the need for novel antibacterials, current approaches towards drug discovery, and the suitability of benzo[f]chromanone as a scaffold for antibacterial drug development.

A summary of synthetic methods for the preparation of benzo[f]chromanones is presented in Chapter 2.

The suitability of polyphosphoric acid (PPA) cyclisation methodology was investigated for the preparation of a library of benzo[f]chromanones. Of the 19 naphthalene-based compounds synthesized and characterised in Section 3.1, six were novel naphthopyrones ((±)-84, (±)-85, (±)-103, (±)-112, (±)-113 and (±)-115) and two were novel naphthocyclopentanones ((±)-96 and (±)-101).

A reproducible synthetic route for the preparation of alkylated 2-hydroxybenzo[f]chromanones was developed and described in Section 3.2. Through this route 2-hydroxybenzo[f]chromanones ((±)-37 and (±)-136) were prepared and characterized. Other previously unreported compounds prepared via this route included two naphthofuranones (120, (±)-137), an epoxide ((±)-135), and an α,β-unsaturated ketone (134). Section 3.3 details investigations into alternative synthetic routes for the preparation of 2-hydroxybenzo[f]chromanones.

30 Compounds prepared in this work were subjected to antibacterial testing. The results of the microbial assays are detailed in Section 3.4. The majority of the compounds tested were found to exhibit antibacterial activity towards Gram-positive bacteria, including Mycobacterium smegmatis, a non virulent model organism for M. tuberculosis. The compounds identified with the greatest zones of inhibition against M. smegmatis included the novel naphthofuranone 120, naphthocyclopentanone (±)-96 and α,β-unsaturated ketone 79. These compounds represent leads in the development of drugs for the treatment for tuberculosis.

The experimental details are provided in Chapter 4.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>ANGP</td>
<td>Angular naphtho-(\gamma)-pyrone</td>
</tr>
<tr>
<td>ANU</td>
<td>Australian National University</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>BuLi</td>
<td>Butyllithium</td>
</tr>
<tr>
<td>ca.</td>
<td><em>circa</em> (approximately)</td>
</tr>
<tr>
<td>calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstracts Service</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COSY</td>
<td>(^1)H-(^1)H Correlation Spectroscopy</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>Community-acquired methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>(\delta)</td>
<td>Chemical Shift (parts per million)</td>
</tr>
<tr>
<td>d</td>
<td>Day(s)</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>e.g.</td>
<td><em>Exempli gratia</em> (for example)</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>et. al.</td>
<td><em>et alia</em> (and others)</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (US)</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>Bacteria that stain dark blue in the Gram staining process, due to large amounts of peptidoglycan in the cell wall</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>Bacteria that resist the Gram stain, and stain pink from a counter stain, due to an outer membrane surrounding the cell wall</td>
</tr>
<tr>
<td>GPC</td>
<td>Gel Permeation Chromatography</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>HR</td>
<td>High Resolution</td>
</tr>
<tr>
<td>HTS</td>
<td>High throughput screening</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared (Spectroscopy)</td>
</tr>
<tr>
<td>IUPAC</td>
<td>The International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>LR</td>
<td>Low Resolution</td>
</tr>
<tr>
<td>m</td>
<td>Meta</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-Chloroperbenzoic Acid</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi-drug resistant</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Mel</td>
<td>Methyl iodide</td>
</tr>
<tr>
<td>MHz</td>
<td>Mega Hertz</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Mole(s)</td>
</tr>
<tr>
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<td>Molecular</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>MW</td>
<td>Molecular Weight</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass to charge ratio</td>
</tr>
<tr>
<td>n</td>
<td>Normal</td>
</tr>
<tr>
<td>N</td>
<td>Normality</td>
</tr>
<tr>
<td>NA</td>
<td>Nutrient agar</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>NP</td>
<td>Natural product</td>
</tr>
<tr>
<td>o</td>
<td>Ortho</td>
</tr>
<tr>
<td>p</td>
<td>Para</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric acid</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PS</td>
<td>Petroleum Spirit (60-80°C fraction)</td>
</tr>
<tr>
<td>p-TSA</td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td>R</td>
<td>Alkyl group</td>
</tr>
<tr>
<td>RSC</td>
<td>Research School of Chemistry</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure activity relationship</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>temp</td>
<td>Temperature</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
</tbody>
</table>
UV  Ultraviolet (spectroscopy)
Wt.  Weight
# Table of Contents

Author’s Declaration .............................................................................................................. ii  
Acknowledgements .................................................................................................................. iii  
Abstract ......................................................................................................................................... iv  
Glossary, Abbreviations and Acronyms ...................................................................................... v  
Table of Contents ......................................................................................................................... ix  

1 Introduction ................................................................................................................................. 1  

1.1 Terms and Definitions .................................................................................................................. 1  

1.2 The Need for Novel Antibacterial Agents .................................................................................. 2  

1.3 Resistance .................................................................................................................................... 4  

1.4 Drug discovery ............................................................................................................................... 6  

1.4.1 Natural Product Screening ........................................................................................................ 6  
1.4.2 Semi-synthetic Improvement ....................................................................................................... 7  
1.4.3 Combinatorial Chemistry ........................................................................................................... 8  
1.4.4 High Throughput Screening ....................................................................................................... 9  
1.4.5 Structure-Activity Relationships ............................................................................................. 9  
1.4.6 Privileged Structures ............................................................................................................... 10  

1.5 Nomenclature ............................................................................................................................... 12  

1.6 The Bioactivities of Benzopyrones and Naphthopyrones ........................................................... 14  

1.6.1 Benzopyrones ............................................................................................................................ 14  

1.6.1.1 Chromones ............................................................................................................................ 15  
1.6.1.2 Coumarin ............................................................................................................................... 15  
1.6.1.3 Chromanones ......................................................................................................................... 16  
1.6.2 Naphthopyrones ....................................................................................................................... 16  

1.6.2.1 Benzocoumarin ....................................................................................................................... 16  
1.6.2.2 Benzochromones ..................................................................................................................... 17  
1.6.3 Drug Suitability of Benzo[j]chromanones ................................................................................. 19  

2 Summary of Benzochromanone Syntheses ................................................................................. 21  

2.1 Scope and Overview ..................................................................................................................... 21  

2.2 Cyclisation of 3-Aryloxypropanoic Acids and Derivatives ......................................................... 21  

2.3 Alkylation and Acylation of Naphthol ......................................................................................... 24  

2.3.1 Polyphosphoric Acid Condensations ......................................................................................... 25  

2.4 The Fries Rearrangement ........................................................................................................... 27
2.5 Condensations of 1-(2-Hydroxynaphthalen-1-yl)ethanone .......... 28
  2.5.1 Claisen Condensation ................................................................. 29
  2.5.2 Kostanecki-Robinson and Allan-Robinson Reaction ................. 30

2.6 Baker-Venkataraman Rearrangement ........................................ 31

2.7 Pechmann Condensation .............................................................. 32

2.8 Hydrogenation and Dehydrogenation ........................................... 33

2.9 Hydroxychroman-4-ones ............................................................... 34

2.10 Project Aims .............................................................................. 37

3 Results and Discussion .................................................................. 38

3.1 Synthesis of Benzo[j]chromanones by Polyphosphoric Acid
  Cyclisation ....................................................................................... 38
  3.1.1 2-Naphthol Condensation .......................................................... 38
  3.1.2 1-Naphthol Condensation ......................................................... 45
  3.1.3 Naphthoresorcinol Condensation .............................................. 47
  3.1.4 2,6-Dihydroxynaphthalene Condensation .................................. 53

3.2 Syntheses of 2-Hydroxy Benzo[j]chromanones ......................... 60
  3.2.1 Introduction .............................................................................. 60
  3.2.2 Synthesis of 2-Hydroxy-3-methylbenzo[j]chromanone (±)-37 .... 61
  3.2.3 Synthesis of 2-Hydroxy-2,3-dimethylbenzo[j]chromanone 136 .. 72
  3.2.4 Attempted Synthesis of 2-Hydroxybenzo[j]flavanone 145 ......... 75
  3.2.5 Attempted Synthesis of 2-Hydroxybenzo[j]chromanone 154 ...... 79

3.3 Towards 2-Hydroxybenzo[j]chromanones .................................. 85
  3.3.1 Attempted Benzo[j]chromone Epoxidation ................................ 85
  3.3.2 Attempted Benzo[j]chromanone Acetoxylation ......................... 88
  3.3.3 Attempted Benzo[j]chromanone Enol Protection ....................... 89

3.4 Testing for Antibacterial Activity ............................................... 92

3.5 Conclusion, and Future Work ..................................................... 97

4 Experimental ................................................................................. 100

4.1 General Experimental Procedures .............................................. 100
  4.1.1 General Method of Cyclisation of α,β-Unsaturated Acids with
        2-Naphthol Utilising Polyphosphoric Acid ................................... 101
    4.1.1.1 Preparation of polyphosphoric acid (PPA) ......................... 101
    4.1.1.2 General Polyphosphoric Acid (PPA) Cyclisation Method ....... 101
        4.1.1.2.1 (±)-3-Methyl-2,3-dihydro-1H-benzo[j]chromen-1-one (±)-53 .. 101
        4.1.1.2.2 (±)-2,3-Dimethyl-2,3-dihydro-1H-benzo[j]chromen-1-one (±)-84 .. 102

x
4.1.2 Synthesis of 2,3-Dihydro-1H-benzo[f]chromen-1-one 106

4.1.3 Cyclisations with Crotonic Acid and 1-Naphthol in PPA 107

4.1.3.1 Synthesis of (±)-2,3-Dihydro-2-methylbenzo[h]chromen-4-one (±)-95 107

4.1.3.2 Synthesis of (±)-5-Methoxy-3-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-1-one (±)-101 108

4.1.4 Cyclisations of Crotonic Acid with Naphthalendiol Utilising PPA 109

4.1.4.1 Synthesis of 6-Hydroxy-3-methyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-103 109

4.1.4.2 Synthesis of 3-Methoxynaphthalen-1-ol 110 110

4.1.4.3 Synthesis of 6-Hydroxy-1-methyl-1H-benzo[f]chromen-3(2H)-one (±)-112 111

4.1.4.4 Synthesis of (±)-6-Methoxy-1-methyl-1H-benzo[f]furan-3(2H)-one (±)-113 112

4.1.4.5 Synthesis of 8-Hydroxy-3-methyl-2,3-1H-benzo[f]chromen-1-one (±)-115 112
4.1.5 Synthesis of 1-Bromo-2-methoxynaphthalene 116 ........................................ 113
4.1.5.1 1-Bromo-2-methoxynaphthalene 116 .................................................. 113
4.1.6 Synthesis of Crotonic Anhydride ........................................................... 113
4.1.6.1 Crotonic Anhydride ........................................................................... 114
4.1.7 General Synthesis of Acylated Methoxynaphthalenes ...................... 114
4.1.7.1 (E)-1-(2-Methoxynaphthalen-1-yl)but-2-en-1-one 79 ..................... 114
4.1.7.2 (E)-1-(2-Methoxynaphthalen-1-yl)-2-methylbut-2-en-1-one 134 .... 115
4.1.7.3 (E)-1-(2-Hydroxynaphthalen-1-yl)-3-phenylprop-2-en-1-one 55 ...... 115
4.1.7.4 (E)-1-(2-Methoxynaphthalen-1-yl)-3-phenylprop-2-en-1-one 145 .... 116
4.1.7.5 2,3-Dihydro-9-methoxynaphthalen-1-one 158 ..................................... 116
4.1.8 General Method of Nucleophilic Epoxidation of the (Naphthylen-1-yl)-2-ene-1-ones ................................................................. 117
4.1.8.1 (±)-(2-Methoxynaphthalen-1-yl)(3-methyloxiran-2-yl)methanone (±)-80 .............................................................................................. 117
4.1.8.2 (±)-(2-Methoxynaphthalen-1-yl)(2,3-dimethyloxiran-2-yl)methanone (±)-135 ................................................................. 118
4.1.8.3 (±)-(2-Methoxynaphthalen-1-yl)(3-phenyloxiran-2-yl)methanone (±)-146 ................................................................. 118
4.1.9 Cyclisation of Epoxides ...................................................................... 119
4.1.9.1 Synthesis of 2-Hydroxy-3-methyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-37 ................................................................. 119
4.1.9.1.1 (±)-2-Hydroxy-3-methyl-2,3-dihydro-1H-benzo[f]chromen-1-one 37 ................................................................. 119
4.1.9.1.2 2-(1-Hydroxyethyl)naphtho[2,1-b]furan-1(2H)-one 120 .................. 119
4.1.9.1.3 (Z)-2-Ethylidenenaphtho[2,1-b]furan-1(2H)-one 128 ................... 120
4.1.9.2 Synthesis of 2,3-Dihydro-3-methyl-1-oxo-1H-benzo[f]chromen-2-yl Acetate 169 ................................................................. 120
4.1.9.2.1 (±)-2,3-Dihydro-3-methyl-1-oxo-1H-benzo[f]chromen-2-yl Acetate 169 ................................................................. 121
4.1.9.3 Synthesis of 2,3-Dihydro-2-hydroxy-2,3-dimethylbenzof[f]chromen-1-one (±)-136 ................................................................. 121
4.1.9.3.1 (±)-2,3-Dihydro-2-hydroxy-2,3-dimethylbenzof[f]chromen-1-one (±)-136 ................................................................. 121
4.1.9.3.2 (±)-2-(1-Hydroxyethyl)-2-methylnaphtho[2,1-b]furan-1(2H)-one (±)-137 ................................................................. 122
4.1.10 Synthesis of 3-Methyl-1H-benzo[f]chromen-1-one 58 ................. 122
4.1.10.1 3-Methyl-1H-benzo[f]chromen-1-one 58 ........................................ 123
4.1.10.2 General Method for the Attempted Epoxidation of 3-Methyl-1H-benzo[f]chromen-1-one 58 ........................................ 123
4.1.10.2.1 2-Hydroxy-1-naphthoic acid 166.....................................................123
4.1.10.3 Preparation of 1-Butyl-3-methyl Imidazolium Tetrafluoroborate 165........................................................... 124
4.1.10.4 Preparation of Manganic Acetate. ............................................ 124
4.1.10.5 Attempted Acetoxylation of benzo[\]chromanone (±)-53 .... 124

4.2 Antibacterial Screening ............................................................... 124
4.2.1 Preparation of Nutrient Agar (NA) ............................................ 124

5 References ...............................................................................................125
1 Introduction

Antibiotics have been hailed as one of modern medicine’s greatest achievements. By effectively controlling bacterial infections, antibiotics have eased the suffering of patients and saved millions of lives.

Before the introduction of antibiotics, patients with bacterial infections had low survival rates. It was the introduction of antibacterial agents, such as the sulphonamides in the 1930s and the penicillins in the 1940s, that led to a significant decrease in fatality rates from bacterial infections. Antibiotics were proven to be so effective that by the late 1960s it was generally believed that infectious diseases could be eradicated and that research should shift away from antibiotics to focus on the treatments of other diseases. This era, known as the golden age, has now passed; many antibiotics are no longer effective. Diseases and disease agents that were once thought to be under control are returning - and with resistance to current control methods. The emergence of bacterial resistance to all commonly used antibiotics limits the effectiveness of current drugs and resistance is increasing at an alarming rate. Resistance is found in every country of the world, and as such we are potentially facing a global health problem of returning to pre-antibiotic days. Resistance is not anticipated to abate and, as antibiotics are expected to lose their effectiveness with their continued use, it is imperative to discover novel antibacterial agents that are unaffected by current and emerging resistance mechanisms.

1.1 Terms and Definitions

Before a more detailed discussion on antibiotic resistance is presented, it is important to define several terms. Common usage of the term antibiotic refers to a substance, of either natural or synthetic origin, that kills or inhibits the growth of bacteria. However, the term antibiotic was originally defined as a chemical substance of microbial origin, that selectively inhibits the growth of, or even destroys, other microorganisms. Under the latter definition, any substance that is not produced by a microorganism yet holds the same properties of microbial inhibition is termed an antimicrobial. The term antibacterial is more specific again, indicating any substance inhibiting the growth of bacteria. Bacteriostatic agents affect only bacterial growth and agents that kill bacteria are termed bactericidal. Throughout this thesis the term antibacterial will be used to describe compounds of either microbial or synthetic origin with inhibitory activity.
towards bacteria. Antimicrobial is used for microbe-derived or synthetic compounds with activity against a range of microbes such as fungi and bacteria.

1.2 The Need for Novel Antibacterial Agents

Infectious diseases are the second leading cause of death worldwide, with over 17 million deaths annually, mostly of children and the elderly.2 A decade ago, it was estimated that 90,000 die out of 2 million acquired bacterial infections in the US alone - and mortality from infectious diseases is increasing.8 Diseases that were once thought under control are re-emerging; tuberculosis incidence is on the increase owing to bacterial drug resistance, impoverished health systems and the onset of HIV/AIDS. The bacterium responsible for tuberculosis, Mycobacterium tuberculosis, is carried by over 1.9 billion people, and it is predicted that 35 million people will die from M. tuberculosis infection by 2020.9

Due to the emergence of multi-drug resistant strains and the associated toxicities of current drugs, new families of anti-infective agents are desperately required to reduce the prevalence of treatable diseases such as tuberculosis. Resistance not only affects patient morbidity and mortality, but also increases health care costs.8

Despite the concerted search for new antibiotics since the introduction of sulphonamides and penicillins, only three new classes of antibacterials have appeared on the market since 1970. In addition, there has been a 56% decline in the number of antibacterials approved by the FDA since mid 1990s.2

Antibacterial agents work by targeting essential bacterial mechanisms to halt bacterial growth e.g. β-lactams inhibit cell wall synthesis, quinolones target DNA gyrase, and macrolides affect protein synthesis3 (Table 1-1). Some antimicrobial agents act on different types of bacteria, for example, penicillin G has only a narrow range of activity and targets Gram-positive bacteria, however, ampicillin, another β-lactam, has a broad spectrum and inhibits both Gram-negative and Gram-positive bacteria. The common classes of antibiotic agents and their modes of action are presented in Table 1-1.

With the rapid development of resistance to most antibacterial drugs, many drugs have lost their effectiveness, and consequently, we need to continue to generate novel drugs with novel mechanisms of action to continue to fight the war against bacterial infection.2 New antibacterial templates and novel mechanisms of action will be
<table>
<thead>
<tr>
<th>Class</th>
<th>Year</th>
<th>Examples</th>
<th>Spectrum</th>
<th>Derivation</th>
<th>Target</th>
</tr>
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<tbody>
<tr>
<td>Sulphonamides</td>
<td>1935</td>
<td>Suphonilamide, Sulfadiazine</td>
<td>Broad-spectrum, Broad-spectrum</td>
<td>Synthetic</td>
<td>Antifolate</td>
</tr>
<tr>
<td>β-lactams</td>
<td>1941</td>
<td>Penicillins, Penicillin G, Methicillin, Ampicillin, Amoxicillin</td>
<td>Gram-positive, Gram-positive, Broad-spectrum, Broad-spectrum</td>
<td>NP-derived</td>
<td>Bacterial cell wall</td>
</tr>
<tr>
<td></td>
<td>1945</td>
<td>Cephalosporins, Cefprozil, Cefpirome</td>
<td>Broad-spectrum, Broad-spectrum</td>
<td>NP-derived</td>
<td>Bacterial cell wall</td>
</tr>
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<td>Aminoglycosides</td>
<td>1944</td>
<td>Streptomycin, Neomycin</td>
<td>Gram-negative, Broad-spectrum</td>
<td>NP-derived</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>1950</td>
<td>Tetracycline, Doxycycline</td>
<td>Broad-spectrum, Broad-spectrum</td>
<td>NP-derived</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1951</td>
<td>Isoniazid</td>
<td>Mycobacteria</td>
<td>Synthetic</td>
<td>Fatty acid biosynthesis</td>
</tr>
<tr>
<td>Macrolide</td>
<td>1952</td>
<td>Erythromycin, Clarithromycin</td>
<td>Gram-positive, Gram-positive</td>
<td>NP-derived</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>1957</td>
<td>Rifampicin</td>
<td>Mycobacteria</td>
<td>NP-derived</td>
<td>RNA synthesis</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>1956</td>
<td>Vancomycin, Teicoplanin</td>
<td>Gram-positive, Gram-positive</td>
<td>NP-derived</td>
<td>Bacterial cell wall</td>
</tr>
<tr>
<td>Quinolones</td>
<td>1962</td>
<td>Nalidixic acid, Norflaxin</td>
<td>Broad-spectrum, Broad-spectrum</td>
<td>Synthetic</td>
<td>DNA synthesis</td>
</tr>
<tr>
<td>Diaminopyrimidine</td>
<td>1968</td>
<td>Trimethoprim</td>
<td>Broad-spectrum</td>
<td>Synthetic</td>
<td>Antifolate</td>
</tr>
<tr>
<td>Pseudomonic acid</td>
<td>1985</td>
<td>Mupirocin</td>
<td>Gram-positive</td>
<td>NP-derived</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>2000</td>
<td>Linezolid</td>
<td>Gram-positive</td>
<td>Synthetic</td>
<td>Protein synthesis</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>2003</td>
<td>Daptomycin</td>
<td>Gram-positive</td>
<td>NP-derived</td>
<td>Bacterial cell membrane</td>
</tr>
</tbody>
</table>

Table 1-1 Antibiotic Classes; Year of Introduction, Examples, Derivation and Target.
advantageous over current antibacterials to treat multidrug resistant bacteria and newly emerging pathogens. Ideally, new drugs with enhanced characteristics, such as shortened treatment regimes, reduced side effects, and greater effectiveness to circumvent resistance need to be developed.

It is the emergence of resistant bacterial strains that warrants the need for novel antimicrobials. Large pharmaceutical companies, however, are closing down antibiotic discovery programs citing declining productivity. It is generally believed that economic factors are driving such decisions, as generic competition, resistance, and increased regulation have affected profit margins even though antibiotics still account for the third largest drug market segment with annual global sales over $US25 billion. The treatment of diseases associated with cardiovascular, central nervous and gastrointestinal systems are more profitable, and chronic diseases have a more rapidly growing market when compared to infection treatment. The auto-obsolescent nature of antimicrobials combined with the commercial success of chronic drugs has lured companies away from the field of antibiotics. In addition, companies that continued to identify compounds with known modes of action found that the drugs had only incremental advantages over existing drugs and as such they were difficult to progress commercially.

Smaller biotech companies have increased their interest in the development of specialist markets that are no longer commercially viable for large companies, however they can often not support the significant costs associated with drug development. They are discouraged not only by the cost and risk of entering a new drug on the market, but also by the time required for animal and in vitro studies; it is estimated that the cost of bringing a drug to market costs $US800 million, and takes longer than a decade.

There have been many proposals on how to rekindle the interest in antibiotic development, including: shortening the approval process; offering patent extensions; classifying as orphan drugs; providing tax credits; limiting liability for adverse effects; offering advance commitments by the government; and generally reducing drug development costs.

1.3 Resistance

Resistance is not a new phenomenon in the age of antibiotics, as soon after the development of sulphonamide in the 1930s, resistant strains of *Streptococcus pyogenes* were identified in military hospitals. Penicillin-resistant strains of *Staphylococcus*
*aureus* and streptomycin-resistant strains of *Mycobacterium tuberculosis* were also identified soon after the introduction of penicillin and streptomycin.\(^5\)

Resistance occurs as a consequence of gene mutation, or from the horizontal transfer of mobile genetic elements such as bacteriophages, plasmids, or naked DNA.\(^5\) The mechanisms of genetic resistance include modification of the target site of action, modification of the cell wall permeability, overproduction of the target enzyme, inactivation of the drug by metabolism, or circumvention of inhibited steps.\(^3\)

The rise in resistant bacteria is believed to stem from the use and misuse of antibacterial agents. The use of antibacterials places selection pressure on bacterial populations to select for resistant microbes,\(^1\) and exposure of bacteria to suboptimal quantities of antibiotics is an important factor leading to resistance.\(^4\) Uncontrolled, incomplete or unsuitable antibiotic treatment regimes, indiscriminate use in agriculture, and use as prophylactics, all lead to the selection and spread of resistant organisms.\(^3,4\) As such, the control of both infection and antibiotic usage are of utmost importance in preventing the emergence and spread of resistance.\(^4\)

Methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are of particular concern in hospital settings, especially in intensive care units. MRSA have increased in prevalence from 11-13% in 1986 to twice that in a 12 year period.\(^4\) Enterococci are intrinsically resistant to many antibiotics, yet are also able to acquire resistance *via* horizontal transfer of genetic material.\(^4\) Vancomycin resistance in enterococci has increased from 0.5% in 1989 to over 18% only 8 years later.\(^4\) Vancomycin has long been considered the drug of last resort for the treatment of multidrug resistant *S. aureus*, although vancomycin resistance has recently been reported.\(^3\) Even after only two years on the market, and representing an entirely new class, linezolid was found to be losing efficacy towards bacterial infections.\(^3\)

Resistance is well documented in the hospital setting, and up to 70% of nosocomial pathogens are resistant to at least one class of antimicrobial.\(^3\) However, recently there has also been an increase in the reports of resistant community-acquired pathogens.\(^8\) The prevalence of community-acquired MRSA (CA-MRSA) is raising additional concerns as CA-MRSA is more virulent in comparison to its nosocomial counterparts. Once a rarity, CA-MRSA currently poses a global threat with serious consequences.\(^12\)

Some pathogens are showing multiple resistance to several classes of antibiotics e.g. *Streptococcus pneumoniae* is resistant not only to penicillin and other β-lactams, but is also resistant to sulphonamides, tetracycline, and erythromycin.\(^4\) Multi-drug resistant
MDR tuberculosis re-emerged in the 1980s, and was aided by the prevalence of HIV. The treatment of MDR tuberculosis requires up to seven drugs administered concurrently, rendering some cases of tuberculosis almost incurable. Increased resistance, reduced efficacy of current drugs, and a lack of new drugs in the pipeline requires reassessment of the current situation. It is important to determine ways to use current antibiotics more effectively in order to minimize resistance, as well as the most appropriate therapy to maximize patient outcomes. It is necessary to try to extend the life of current drugs and increase patient compliance with education, and other methods of disease and infection control. Although the correct use of antibiotics will increase effectiveness, it will not stop resistance, and the only option is to develop new antibacterials with novel modes of action, unaffected by current and emerging resistance mechanisms. As such, it is an important objective of medicinal chemistry to discover novel antimicrobial agents, and the next section details the advantages and shortcomings of current approaches for the discovery and development of novel antibacterial agents.

1.4 Drug discovery

Current approaches towards drug discovery include natural product screening, semisynthetic improvement, combinatorial chemistry, and structure-activity relationship (SAR) studies. Advances in genome sequencing and bioinformatics have assisted the development of novel assays for high throughput screening (HTS), which is used in combination with many of the above approaches. The latest trends in drug development centre on the investigation of ‘privileged structure’ scaffolds for the development of a wide range of therapeutic compounds. All of these approaches are discussed below.

1.4.1 Natural Product Screening

Natural product screening is one of the classical methods of drug discovery. Many early antibiotics were discovered by screening methods and the multitude of natural product-derived drugs is also testimony to this approach.

The advantage of natural product screening is that biologically active natural products - rich in functional groups and of complex chemical scaffolds - are identified through library extract screening and biological assay guided isolation. Biologically active natural products are often secondary metabolites that presumably provide advantages to the organism. It has been postulated, for example, that secondary metabolites evolved to penetrate cell membranes of other organisms to interact with molecular targets.
There are many disadvantages of natural product screening; it is considered to be expensive, inefficient, ineffective, and incompatible with modern processes. The screening process, biological assay guided isolation, structure elucidation and production scale-up requires time and money. Biological assay turn around time is lengthy, as the crude extract is tested, separated, and retested – with this process repeated until the active compound is isolated. Limitations in separation and purification technology, and methods of structure determination and characterisation were once limiting factors in the isolation of compounds from natural products, but advances in HPLC compound separation and NMR structure elucidation technologies are addressing these problems. In addition, developments in high throughput screening (HTS) technology have increased the efficiency of the screening process. However, the complexity of natural product samples has challenged the robustness of HTS technology and has resulted in a diminished success rate of lead detection. Further technical improvements in HTS technology are required to circumvent these problems.

Other obstacles faced during natural product screening and isolation were those of quantity and supply. The substance of interest is commonly <1% by weight of the initial crude extract, which may lead to difficulties in structure elucidation and characterisation. Scale up procedures might not be appropriate if the source organism is rare, and compounds with structural complexity may prove to be challenging to synthesise.

Natural product screening is important for the identification of biologically active novel compounds, however, further advancements in technology are required to keep this method competitive in drug discovery.

1.4.2 Semi-synthetic Improvement

Chemical modification of existing drugs, natural products or drug leads, to improve potency, spectrum, absorption, or metabolism, is a traditional way to develop new active compounds. All of the antibacterial agents that entered the market between 1962-2000 were modifications of existing compounds, with the exception of mupirocin, a topical bactericide which entered the market in 1985. The development of new antibiotics was in response to increased resistance, and were variations on mostly β-lactam, macrolide, and quinolone classes. Semi-synthetic improvement of existing compounds is a only short term approach to circumvent the problem of resistance. Eventually all possibilities
will be exhausted and, as bacterial resistance initially developed for the parent drug, it is likely that resistance will also develop quickly to the improved antimicrobial agent.\(^3\)

Whilst this technique has been important for providing new drugs, it can not stand alone in the development of new drugs if we are to try to combat bacterial resistance. Drugs with different scaffolds are required that will interact with different molecular targets, in order to circumvent the current mechanisms of resistance. As discussed above, natural product screening can provide those scaffolds, but is an inefficient process. The development of combinatorial chemistry was promoted as the biggest new thing in drug discovery, with the promise that many new antibiotics would be discovered by this method.

1.4.3 Combinatorial Chemistry

Combinatorial chemistry is the rapid synthesis of structurally related compounds, prepared from similar starting materials, to develop large collections, or libraries, of synthetic analogues. The concept behind the development of such libraries was that systematic chemical synthesis and HTS together would uncover compounds with activity; synthesizing compounds with novel structures that act at different sites to those already targeted by existing drugs.\(^3\) In stark contrast to natural product isolation, resources did not need to be wasted on compound separation, purification, or structure elucidation, and this methodology was not subject to the same issues of yield quantity.

Development of combinatorial synthetic libraries resulted in great numbers of compounds for HTS, however, hits were low.\(^2\) It has been argued that too much emphasis lay on the ‘throughput rather than the output’\(^3\) whereby compounds were made by ease of preparation, but ignoring the principles that led to compounds with drug-like characteristics. As such, compounds that were identified with activity were found to be too insoluble or too toxic for further optimisation.\(^3\) Thus, the method of synthetic combinatorial chemistry has not lived up to the claims of producing new antibiotics.

It is apparent that neither extreme of the scale is ideal; natural product isolation is slow and inefficient, yet purely synthetic combinatorial chemistry produces few hits and inappropriate drug candidates. Taken together, it is apparent that future approaches towards drug discovery need to draw upon the advantages of both methods, as well as drawing on the associated technologies, such as HTS, that are making rapid advancements in drug development technology.
1.4.4 High Throughput Screening

High throughput screening (HTS), in combination with either natural product isolation or combinatorial chemistry, is anticipated to help address the need for novel antibacterials. Advances made in genomic sequencing and bioinformatics have resulted in the sequencing of over 140 bacterial genomes since the mid 1990s, with the identification of many new antibacterial drug targets that are suitable for use in HTS. By identifying compounds that interact with the new targets it may be possible to develop drugs that circumvent the existing modes of antibacterial resistance. Using targets, for example, that are vital to the survival of the bacteria, instead of targeting mechanisms that affect only growth, would have superior advantages in combating antibacterial resistance.\(^3\)

Despite these advancements in HTS, to date only one candidate identified through this technique has progressed to clinical trials.\(^2\) Previously, \textit{in vitro} based screening identified hits, which required time and resources to transform those hits into whole cell active agents.\(^5\) Now, however, the development of assays that screen for essential genes within the whole cell have resulted in the ability to not only screen for targets that affect bacterial growth, but also to target resistance mechanisms and other essential pathogenesis factors.\(^2\)

With the advances in HTS technology, it is apparent that this method will be of significant use in the search for new antibacterials. However, chemical diversity possessing drug-like characteristics is required for exposure to such novel antimicrobial screens in order to be able to generate hits and thus identify new leads.\(^2\)

1.4.5 Structure-Activity Relationships

The structure activity relationships (SAR) approach is important for hit to lead development, where structural features of a biologically active compound are systematically varied to establish the features that are important for its activity. The SAR approach may include simplification of the compound, which leads to a better understanding of the structural requirements for activity.\(^13\) SAR have traditionally been tested on \textit{in vitro} inhibition of a single target, however, cell based studies can also be used to determine structural features required for specificity.\(^14\)
Natural product scaffolds, or synthetic mimetics that resemble the overall geometry of natural products, are ideal on which to conduct SAR optimization studies. It is argued, however, that *de novo* synthesis is the best way to introduce complexity and structural variation in analogues, and serious explorations of *de novo* synthesis will yield novel drug candidates.

Taken together, it is possible that natural product analogues can be synthesized *de novo* to optimize leads to develop antibacterials that can evade resistance mechanisms, such as efflux systems or β-lactamase hydrolysis. Optimisation studies are appropriate for developing leads into potent drugs, however they need a suitable supply of appropriate scaffolds on which to base SAR studies. One new approach is the use of privileged structure-based drug design, whereby privileged structures are used as the scaffold on which to base SAR and optimization studies. It is predicted that this exploratory method will generate drugs with a wide range of bioactivity in a relatively short time frame.

### 1.4.6 Privileged Structures

When a particular type of molecular scaffold is found to exhibit activity towards many unrelated targets, it is considered to be a privileged structure. Defined by Evans *et al.* in 1988 as ‘a single molecular framework able to provide ligands for diverse receptors’, privileged structures have been found to generally be rigid, polycyclic heteroatomic systems with the ability to vary substituent patterns. As the privileged structure is usually part of a larger molecular framework, Horton, Bourne and Smythe introduced a more appropriate term of ‘privileged substructure,’ however, a substructure should contribute to a significant portion of the overall structure. It is the ability to bind to multiple receptors that makes privileged substructures an ideal starting point on which to begin to build a library of drug-like molecules for SAR and optimisation studies.

Over 20 structural scaffolds have been described as privileged structures, including isoxazole 1, diphenylmethane 2, indole 3, benzazepinone 4, benzylpiperidine 5, β-glucose 6 and monosaccharides in general, as well as cyclic peptides. Biphenyl 7 is perhaps the best example of a privileged structure as molecules containing this framework contribute to 4.3% of known drugs, with anti-amoebic, anti-fungal, anti-infective, anti-rheumatic, and analgesic properties among many more.
Compounds with the substructure of benzopyran 8 also exhibit interesting biological activities, including anti-hypertensive, anti-allergenic, hair growth stimulant, and anti-juvenile hormone activities, as well as acting as non-steroidal anti-fertility agents and photochromic properties. For example, the well known benzopyran tetrahydrocannabinol 9 has psychotropic properties, ageratochromene (Precocene) 10 is a potent insecticide, and pterocarpan 11 has phytoalexin activity.

Selenium containing naphthopyrans 12a-e were found to exhibit antimicrobial activity towards both Gram-negative and Gram-positive bacteria.

The benzopyran nucleus is found in many naturally occurring compounds including xanthone 13, flavone 14, chromone 15 and coumarin 16. The benzopyrones, chromones and coumarins, have also been described as privileged structures, although it is debated as to whether this status is due to structural commonalities, or individual molecular qualities that result in the wealth of activities associated with these types of molecules.
Basing an approach to antimicrobial drug discovery on compounds with a wide range of activities is likely to enhance the possibility of not only discovering compounds with antimicrobial activity, but discovering active compounds with novel modes of action. As such, privileged structure based drug design is well suited to the application of novel antimicrobial discovery. Considering the wealth of activities associated with the benzopyrones, chromones and coumarins, it is plausible that naphthopyrones also possess interesting biological activity that warrants further investigation. A detailed examination of the bioactivities of benzopyrones and naphthopyrones is discussed in Section 1.6, but first it is essential to take a closer look at the nomenclature of these compounds.

1.5 Nomenclature

Pyrans are six membered heterocycles containing five carbons and one oxygen, along with two double bonds. They can exist as two isomers, whereby the saturated carbon is on position 2, as described by $2H$-pyran 17, or in position 4, hence $4H$-pyran 18. When a carbonyl moiety is incorporated into the pyran ring, the resulting structure is known as a pyrone. Greek letter descriptors are used to indicate the location of the ether oxygen with respect to the carbonyl, and result mainly in the two isomers $\alpha$-, and $\gamma$-pyrone or 2-pyrone 19, and 4-pyrone 21, respectively. Much less common is $\beta$-, or 3-pyrone 20.

![Chemical structures](image.png)

When a pyrone is benzannulated, it is known as a benzopyrone. The fusion of $\alpha$-pyrone and benzene give the molecule commonly known as coumarin 16, whereas chromone 15 is generated from 4-pyrone with benzene. Named under IUPAC guidelines they are both classified as substituted chromenes, which is the fusion of pyran with benzene. For example, coumarin, under IUPAC guidelines, is named $2H$-chromen-2-one and...
chromone is \(4H\)-chromen-4-one. Saturated benzopyrones are referred to as chromanones, for example, chroman-2-one 22 and chroman-4-one 23.

![structures](image)

Compounds in which naphthalene and a pyrone ring are fused together are called naphthopyrones, which can be alternatively viewed as the fusion of benzopyrones with another benzene ring. The structural units can be arranged into 18 isomeric forms, and form either angular or linear naphthopyrones. The orientation of the pyrone ring is denoted by a letter, depending on which face is fused with naphthalene. The bond between the pyrone carbon and ether oxygen denoted as ‘a’ and, working towards the ketone around the benzopyrone nucleus, the connecting bonds are designated alphabetically (Figure 1-1).

For the angular naphthopyrones, the numbering begins above the peri-position in the naphthalene and proceeds around the pyrone ring first, regardless of whether the pyrone ether oxygen is in the peri-position or not. In the linear isomer, numbering starts at the pyrone ether oxygen (Figure 1-1).

![structures](image)

Figure 1-1 The numbering and lettering convention, and IUPAC nomenclature pertaining to benzochromones.

Naming of the naphthopyrones has varied over the years, for example \(4H\)-benzo[\(h\)]chromen-4-one 24 has had alternative names such as, 7,8-benzochromone, 1,4-\(\alpha\)-naphthopyrone, 1,2-naphtho-\(\gamma\)-pyrone, \(\alpha\)-naphthochromone, naphtho-1’,2’:2,3-pyrone-(4). 22 In use today are the International Union of Pure and Applied Chemistry (IUPAC) and Chemical Abstracts Service (CAS) nomenclature \(4H\)-benzo[\(h\)]chromen-4-one and \(4H\)-naphtho[1,2-\(b\)]pyran-4-one respectively.
The dihydro derivatives of naphthopyrone 25 can equally be seen as the fusion of benzene with chroman-4-one. The IUPAC nomenclature refers to these compounds as dihydro-1H-benzo[f]chromen-1-ones, and this convention has been used to name compounds prepared in this work when detailed in the Experimental Section 1. However, the unwieldiness of this naming system calls for an alternative system to be used in the text of this thesis. As such, dihydro-1H-benzo[f]chromen-1-ones will henceforth be referred to as benzo[f]chromanones in the main text, and 1H-benzo[f]chromen-3(2H)-ones as dihydrobenzo[f]coumarins. A change of letter within the square brackets indicates a change in the orientation of the pyrone ring. The use of the term naphthopyrones will specifically refer to benzocoumarins, benzochromones and/or their dihydro derivatives, and the term benzopyrones refers to both chromones and coumarins.

1.6 The Bioactivities of Benzopyrones and Naphthopyrones

1.6.1 Benzopyrones

Chromone 15, coumarin 16, and their dihydro derivatives chroman-2-one 22 and chroman-4-one 23, are found in a wide variety of natural sources such as plants, fungi and bacteria. They possess a range of bioactivities, yet chromone 15 and coumarin 16 have been more extensively studied than their dihydro counterparts. A comprehensive list of the observed bioactivities of benzopyrones is provided in Table 1-2.

<table>
<thead>
<tr>
<th>Observed Activities</th>
<th>Chromones</th>
<th>Coumarins</th>
<th>Chroman-4-ones</th>
<th>Chroman-2-ones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
<td>Analgesic</td>
<td>Analgesic</td>
<td>Amoebacidal</td>
<td>Anti-helmintic</td>
</tr>
<tr>
<td>Anti-allergenic</td>
<td>Anti-cancer</td>
<td>Anti-cancer</td>
<td>Anti-convulsant</td>
<td>Anti-oxidative</td>
</tr>
<tr>
<td>Anti-asthmatic</td>
<td>Anti-coagulant</td>
<td>Anti-coagulant</td>
<td>Anti-depressant</td>
<td>Fungicidal</td>
</tr>
<tr>
<td>Anti-bacterial</td>
<td>Anti-fungal</td>
<td>Anti-fungal</td>
<td>Anti-helmintic</td>
<td>Immunomodulatory</td>
</tr>
<tr>
<td>Anti-fungal</td>
<td>Anti-helmintic</td>
<td>Anti-helmintic</td>
<td>Anti-microbial</td>
<td>Narcotic</td>
</tr>
<tr>
<td>Anti-spasmodic</td>
<td>Anti-inflammatory</td>
<td>Anti-inflammatory</td>
<td>Anti-secretory</td>
<td>Pesticidal</td>
</tr>
<tr>
<td>Anti-tumor</td>
<td>Anti-microbial</td>
<td>Bronchodilatory</td>
<td>CNS depressant</td>
<td></td>
</tr>
<tr>
<td>Coagulant</td>
<td>Anti-oxidative</td>
<td>Diuretic</td>
<td>Psycho-analeptic</td>
<td></td>
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<tr>
<td>Insecticidal</td>
<td>Anti-psoriasis</td>
<td>Psychiatry</td>
<td>Vasodilatory</td>
<td></td>
</tr>
<tr>
<td>Mutagenic</td>
<td>Anti-tumor</td>
<td>Vasodilatory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotropic</td>
<td>Hypnotic</td>
<td>Vasodilatory</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1-2 Observed Bioactivities of Benzopyrones
1.6.1.1 Chromones
Chromones are widely distributed in the plant kingdom and they possess a broad range of bioactivities as detailed in Table 1-2. Well known chromone, cromoglicic acid 27, or the disodium salt known as cromolyn, is used in the treatment of asthma. It is anti-allergenic, and is almost free of side effects.23

![Chemical structure of cromoglicic acid](image)

The chromone core is central to the flavonoid class, the latter which are responsible for the colour and taste of many plants, fruit, and wine, and are believed to act in the UV and antimicrobial protection of plants.24 They also have been shown to exhibit a multitude of bioactivities including anti-tumor activity,25 antifungal activity, antiviral activity, anti-inflammatory activity, antioxidant activity and bactericidal properties.

1.6.1.2 Coumarin
Coumarin 16 was first isolated in 1820, and subsequently over 1400 natural coumarins have been identified.26 They usually occur as secondary metabolites in plant roots, seeds, leaves and flowers.27 Whilst their function in plants is still unclear, several postulates include waste products, growth regulators, fungistats, and bacteriostats.27

Coumarin and derivatives exhibit a range of biological activities as detailed in Table 1-2. Coumarin itself is a potent rodenticide, although it is only moderately toxic to humans (LD$_{50}$ 275mg/kg), while other naturally occurring coumarins are found to possess little toxicity. The coumarins are also important as pigments, food and cosmetic additives, optical brighteners, dispersed fluorescent and laser dyes, fluorescent probes and labels.28

The well know anticoagulant and rodenticide, warfarin, is formulated as 4-hydroxycoumarin 28, although it is tautomeric with 2-hydroxychromone 29. Spectroscopy has shown that the former tautomer predominates.22
1.6.1.3 Chromanones

The chromanones have been less extensively studied than their unsaturated benzopyrone counterparts, despite their wealth of bioactivities (see Table 1-2).

Naturally occurring chroman-4-ones isolated from plants have resulted in considerable interest regarding their pharmacological activity and drug potential,\(^{29}\) and chroman-2-ones are important synthetic intermediates for the pharmaceutical industry.\(^{22}\) They are found to occur naturally in bacteria and fungi.\(^{16}\) Chroman-4-ones 30a-c were identified as possessing antimicrobial activity.\(^{22}\)

\[
A = S \quad R^1 = C_6H_4-2-CO_2H \\
A = NH \quad R^1 = C_6H_4-4-OH \\
A = SO_2 \quad R^1 = C_6H_4-(2-OCH_3)
\]

1.6.2 Naphthopyrones

Naphthopyrones contain the benzopyrone privileged substructure. They have been subjected to much less scrutiny than the benzopyrones, despite possessing interesting bioactive properties.

1.6.2.1 Benzocoumarin

Dihydrobenzocoumarin 31 and, to a lesser extent benzocoumarin 32, were found to exhibit histone deacetylase activity, and as such these compounds may play a role in developing treatments for cancer and other diseases.\(^{14}\) In addition, dihydrobenzocoumarin was found to have low toxicity (IC\(_{50} = 122 \mu M\)).\(^{30}\)
1.6.2.2 Benzochromones

There are many naturally occurring naphthopyrones that have been shown to exhibit biological activity. They exist as both linear benzo[g]chromanones and angular benzo[h]chromone isomers, or even a combination of both, for example isonigerone 33a and its demethyl derivative 33b which was isolated from *Aspergillus carbonaris*, and was found to possess antibacterial activity towards *Mycobacterium tuberculosis* (MIC = 21.5\(\mu\)M). Studies have also shown that the isonigerones 33 are not cytotoxic.

The comaparvins 34a-e, isolated from sea lilies (crinoids), were found to exhibit NF-\(\kappa\)B inhibitory activity, which has implications in the treatment of cancer, inflammation, AIDS, and Alzheimers disease.

Pleuropyrone A 35a, the glycosylated derivative of eleutherinol 35b, was isolated from the root of a traditional Chinese folk medicine plant *Pleuropterus cilinervis* commonly known by the common name ‘Hasuo’. Hasuo is used to treat inflammation, gonorrhea and other bacterial infections. In addition, flavasperones 35c-d, pigments isolated from *Aspergillus niger* and plants used in traditional African medicine to treat dysentry, rheumatic pain, and chest infection, have interesting biological activities and were
shown not to be cytotoxic. The activity associated with the flavasperones also extends to 5-methyldihydroflavasperone, which is the 2,3-dihydro-analogue of flavasperone 35d.

\[
\begin{align*}
\text{a} & \quad R^1 = H \quad R^2 = \text{D-glucose} \quad R^3 = \text{CH}_3 \\
\text{b} & \quad R^1 = H \quad R^2 = H \quad R^3 = \text{CH}_3 \\
\text{c} & \quad R^1 = \text{CH}_3 \quad R^2 = \text{CH}_3 \quad R^3 = \text{OH} \\
\text{d} & \quad R^1 = \text{CH}_3 \quad R^2 = \text{CH}_3 \quad R^3 = \text{OCH}_3
\end{align*}
\]

Synthetic naphthopyrones also exhibit biological activity. Sulfur substituted benzo[\(\alpha\)]chromanones (±)-36a-d, for example, are claimed to be active towards trichomonads, Gram-positive and Gram-negative bacteria and fungi, as well as possessing low mammalian toxicity.\(^{31}\)

\[
\begin{align*}
\text{a} & \quad A = \text{SO}_2 \quad R = \text{C}_6\text{H}_4-4-\text{CH}_3 \\
\text{b} & \quad A = \text{S} \quad R = 4-\text{pyridyl} \\
\text{c} & \quad A = \text{NH} \quad R = \text{C}_6\text{H}_4-4-\text{SO}_2\text{NH}_2 \\
\text{d} & \quad A = \text{S} \quad R = \text{C}_6\text{H}_4-2-\text{CO}_2\text{H}
\end{align*}
\]

Benzoflavones are found to inhibit aryl hydrocarbon hydroxylase and to act against the carcinogenic activity of polycyclic aromatic hydrocarbons.\(^{32}\) They have also been found to exhibit good fungicidal activity.\(^{33}\)

Our interest in the antimicrobial activity of benzo[\(\alpha\)]chromanones was sparked when a small amount of novel 2-hydroxybenzo[\(\alpha\)]chromanone, with the proposed structure of (±)-37, was obtained from a synthesis being undertaken in our group. Biological testing indicated that it held antibacterial properties towards *Mycobacterium smegmatis*, a non-virulent model organism for *Mycobacterium tuberculosis*.

\[
\begin{align*}
\text{(±)-37}
\end{align*}
\]

The plethora of activities exhibited by benzopyrones extends into the realm of naphthopyrones, including that of synthetic benzo[\(\alpha\)]chromanones. The report of antimicrobial properties associated with sulfur-containing benzo[\(\alpha\)]chromanones 36a-d,
and the finding that 2-hydroxybenzo[f]chromanone (±)-37 possessed antibacterial activity, indicated that a more comprehensive examination on the antibacterial activities of benzo[f]chromanones was required. However, as discussed in the drug development Section 1.4, it is necessary that hits hold suitable properties that provide drug like character. A brief examination of these properties is discussed below.

1.6.3 Drug Suitability of Benzo[f]chromanones

Modern drug development has centered upon combinatorial chemistry and HTS, however, the hits generated through these techniques were found to be inappropriate for further optimization due to the insolubility or related toxicity of the compounds. It is thus necessary to take into account rational design of drug-like molecules, and consider the ADMET (adsorption, distribution, metabolism, excretion, and toxicity) factors early in the process of drug discovery programs.

Both chromones and coumarins are present in the human diet and they generally exhibit low toxicity. In addition, benzo[f]chromanones that were tested for antimicrobial activity were also shown to have low toxicities and few side effects. Despite possessing interesting biological properties and low toxicity, these compounds had been subjected to only a limited number of SAR studies to date, and thus, benzo[f]chromanones were suitable drug scaffolds for further investigation.

A collection of drug-like characteristics were categorised by surveying the molecular attributes of drugs. Lipinski developed The Rule of 5, which provided general criteria to determine the drug-like character of compounds. The Rule of 5 proposed that in order for a compound to be drug-like, they required:

- Less than 5 H-bond donors
- Less than 10 H-bond acceptors
- A molecular weight under 500
- A logP less than 5

It was rationalised that an excessive number of H-bond donors (i.e. the sum of both O-H and N-H bonds) impaired the molecules’ ability to cross membrane bilayers, and a low molecular weight and logP aided absorption. Exceptions to these rules are compounds that are substrates for biological transporters such as vitamins, cardiac glycosides, antibiotics and antifungals. According to these rules, naphthopyrones are ideal drug
scaffolds, as they are of low molecular weight, and generally possess no more than the recommended H-bond donors and acceptors.

Lead compounds are often simpler than their corresponding drugs, the former being low molecular weight, less complex, and less hydrophobic. Libraries with simple lead compounds resulted in modest affinities for their target, but molecular complexity reduces the likelihood of the compounds resulting in a hit. Complexity introduced and increased at a later stage improved drug-like character as well as its affinity for the target. Naphthopyrones possess a simple structure of low molecular weight, yet are a scaffold that also allows complex chemical diversity to be added.

Aligning with Lipinski’s rules of low molecular weight, and with acceptable numbers of H-bond acceptors and donors, the benzo[\(f\)]chromanones are well placed as potential drug-like molecules. As simple structures they have the ability on which to incorporate increased complexity, and as such they represent an ideal scaffold on which to base drug design.

By taking into account Lipinski’s rules, ADMET principles, the inclusion of privileged substructure, whilst maintaining a simple structure with the ability to increase complexity to potentially develop affinity and specificity, along with demonstrated bioactivity as antimicrobial action, the benzo[\(f\)]chromanones represent a suitable class of compounds on which to investigate their potential as novel antimicrobials.

The aim of this work was to generate a library of benzo[\(f\)]chromanone analogues, as pictured below, based on 2-hydroxybenzo[\(f\)]chromanone 37, to subsequently test for antimicrobial activity and start to develop a SAR.
2 Summary of Benzochromanone Syntheses

2.1 Scope and Overview

Given the prevalence of benzopyrones in nature, their inherent relationship with the ubiquitous flavonoids, as well as their relative stabilities and ease of preparation, it is not surprising that the literature pertaining to the syntheses of benzopyrones is extensive. Much less has been reported on naphthopyrones, however the methods of syntheses of benzopyrones are generally also applicable to naphthopyrones - including those with halogen, alkyl, or hydroxy substituents in the aromatic nucleus.22

With the view to identify the synthetic methods most appropriate for the development of a library of benzo[\(f\)]chromanone analogues, a summary of methods commonly used to prepare benzopyrones and naphthopyrones is presented here. Comprehensive reviews on benzopyrones are available22,35,36 and as such, this overview focuses on the syntheses of chroman-4-ones and, in particular, benzo[\(f\)]chromanones.

The synthetic routes to other related compounds, such as coumarins and flavonoids, are beyond the scope of this work, although many of these syntheses do overlap and where appropriate they are discussed below.

2.2 Cyclisation of 3-Aryloxypropanoic Acids and Derivatives

Chroman-4-ones have been successfully prepared by the cyclisation of 3-aryloxypropanoic acids, or their corresponding esters or nitriles. Cyclisation was best affected by treatment with phosphorus pentoxide or polyphosphoric acid (PPA); other dehydrating agents such as hydrogen fluoride, sulfuric acid, and the combination of phosphorus pentachloride and aluminium chloride produced chroman-4-ones with limited success.

When various 3-(naphthalen-2-yloxy)propanoic acids were cyclised under similar dehydrating conditions, the product geometry was governed by the presence of substituents in the 1-position. Cyclisation of the 3-aryloxypropanoic acid 38 (\(R = \) alkyl, halogen, NO\(_2\)) produced the linear benzo[g]chromanones 39 (\(R = \) alkyl, halogen, NO\(_2\)), however, when the 1-position was unsubstituted cyclisation of the acid 38 (\(R = H\)) afforded the angular benzo[f]chromanone 40 (Scheme 2-1).22
Scheme 2-1 Product geometry is affected by substitution in the 1-position of aryloxy acid 38.

Chakravarti and Dutta condensed 2-naphthol 41 with 3-chloro-propionic acid under alkaline conditions to prepare 3-aryloxypropanoic acid 42. The acid 42 was subsequently cyclised using phosphorus pentoxide in benzene solution to afford benzo[f]chromanone 40 (yield not quoted) as shown in Scheme 2-2.\(^{37}\)

Scheme 2-2 Chakravarti and Dutta’s two step synthesis of benzo[f]chromanone 40.

Bachman and Levine developed an alternative method to synthesise benzo[f]chromanone 40. Cyanoethylation of 2-naphthol 41 with acrylonitrile in the presence of Triton B\(^*\) afforded the 3-aryloxypropanenitrile 43, which was subsequently cyclised by treatment with 85% H\(_2\)SO\(_4\) (Scheme 2-3).\(^{38}\) Other methods have been reported for the cyclisation of the nitrile 43 utilising polyphosphoric acid\(^{39}\) and anhydrous ZnCl\(_2\).\(^{29}\)

\(^*\) Benzytrimethylammonium hydroxide in methanol (40% w/v)
Bachman and Levine’s synthesis was the preferred route for generating benzo[f]chromanone \(40\) until a high yielding ‘one pot route’ was reported in 1988. Treatment of 2-(3-bromoprop-2ynyloxy)naphthalene \(44\) with mercury(II) trifluoroacetate produced benzo[f]chromanones \(40\) in yields up to 82% (Scheme 2-4). However, this report of a ‘one pot’ transformation is misleading, as two steps are required to prepare the naphthyl ether \(44\) from 2-naphthol. Bachman and Levine’s synthesis remains the most efficient method for preparing benzo[f]chromanone \(40\) (with overall yields of ca. 80%).

Interestingly, the dihydrobenzo[f]coumarin \(31\) was also prepared by cyanoethylation and cyclisation. Hardman found that treating 2-naphthol \(41\) with equimolar quantities of sodium hydroxide, instead of catalytic amounts of Triton B, resulted in cyanoethylation in the 1-position of 2-naphthol to afford 3-(2-hydroxynaphthalen-1-yl)propanenitrile \(45\). The nitrile \(45\) was subsequently hydrolysed to the corresponding acid by continued treatment with base and cyclisation was effected by heating to give dihydrobenzo[f]coumarin \(31\) (Scheme 2-5). This synthesis had good overall yields (63-80%) but required three steps starting from 2-naphthol. Cyanoethylation and cyclisation was effected in a one-pot sequence when 2-naphthol and acrylonitrile were heated with zinc(II) chloride in an acidic medium, although the yields were lower (40%).

---

\(^1\) Benzyltrimethylammonium hydroxide in methanol (40%w/v)
Scheme 2-5 Cyanoethylation occurred in the 1-position of 2-naphthol when equimolar quantities of NaOH were used. Further treatment with NaOH and heat afforded dihydrobenzo[f]coumarin 31.

2.3 Alkylation and Acylation of Naphthol

Substituted chroman-4-ones were readily prepared by the Friedel-Crafts acylation when phenols, or their alkyl ethers, were reacted with an unsaturated acid chloride, or derivative, in the presence of a Lewis acid, \( \text{H}_2\text{SO}_4, \text{HCl, } \text{Amberlyst 15 ion exchange resin, montmorillonite, or palladium or platinum catalysts.} \) In cases when the intermediate \( \alpha \)-hydroxy unsaturated ketone was isolated, it was readily cyclised by treatment with base. The Friedel-Crafts route was successful in the synthesis of benzo[f]chromanones when 2-naphthol was reacted with either crotonic acid or 3,3-dimethylacrylic acid. However, the use of acrylic acid, or propiolic acid, under the same reaction conditions resulted in esterification and alkylation of 2-naphthol to generate dihydrobenzo[f]coumarin, or benzo[f]coumarin, respectively.

Scheme 2-6 The reaction outcome under Friedel-Crafts conditions resulted in the formation of benzo[f]chromanones or dihydrobenzo[f]coumarins.

When 2-naphthol was reacted with \( \text{trans} \)-cinnamic acid or derivatives, the products were either benzo[f]chromanones or dihydrobenzo[f]coumarins (Scheme 2-6). While the reaction outcome was usually determined by the substitution pattern of the \( \alpha,\beta \)-unsaturated acid, the catalyst in the reaction also contributed to the product distribution. For example, Anjaneyulu \textit{et al.} found that when 2-naphthol 41 and \( \text{trans} \)-cinnamic acid
were treated with either SbCl₃ or ZnCl₂ at 140-150°C, the reactions gave exclusively the dihydrobenzo[f]coumarin (±)-47 (Scheme 2-7),⁴⁷ and Neugebauer et al. generated a range of substituted dihydrobenzo[f]coumarins by refluxing substituted trans-cinnamic acids with 2-naphthol in toluene and Amberlyst 15 ion exchange resin.⁵⁵ However, when BF₃·OEt was used as the catalyst the benzo[f]chromanone (±)-48 was obtained in 44% yield.⁵¹ Benzo[f]chromanone (±)-48 and analogues were also prepared when substituted trans-cinnamic acids and 2-naphthol 41 were reacted in the presence of POCl₃ and AlCl₃ at 70°C (Scheme 2-7).³³ These results suggested that a difference in reaction temperature may have played a role in product distribution, yet despite the multitude of investigations on the cyclisation of trans-cinnamic acid 46 with 2-naphthol 41, there has been no reported study on the effect of temperature on the reaction outcome.

Scheme 2-7 The reaction outcome of 2-naphthol and trans-cinnamic acid was affected by the catalyst used in the reaction.

Friedel-Crafts reactions provide a straightforward way to generate benzo[f]chromanones as they generally involve a single step, although the yields may vary considerably (12-98%) depending on the catalyst and substrate used. Many of the catalysts are specific to certain substrates and the unpredictable product distribution has limited the usefulness of this reaction despite its simplicity. In addition, alkylation was sometimes accompanied by the competing Fries rearrangement.⁵⁶

2.3.1 Polyphosphoric Acid Condensations

Excess polyphosphoric acid (PPA) was also effective in the condensation of α,β-unsaturated acids with phenols and naphthols; chroman-4-ones and benzo[f]chromanones were formed rapidly, often in good yields. This process was patented by Bramwell, Fitton and Ramage in 1967 for the synthesis of chroman-4-ones, cyclising phenols (including 2-naphthol) with α,β-unsaturated acids - specifically citing
crotonic acid, 3,3-dimethylacrylic acid 49, and trans-cinnamic acid 46 - at temperatures up to 100°C (Scheme 2-8). Anjaneyulu et al. reported good yields using crotonic acid or 3,3-dimethyl acrylic acid 49 with either 1- or 2-naphthol to derive benzo[h]chromanone or benzo[f]chromanone products, respectively, e.g. benzo[f]chromanone 50 (Scheme 2-8), and Hasebe had success cyclising phenyl propiolic acid with 2-naphthol in PPA albeit in 22% yield.

Scheme 2-8 Benzo[f]chromanones were successfully prepared by reacting 2-naphthol with β-substituted unsaturated acids in PPA.

The use of PPA also resulted in the formation of dihydrobenzo[f]coumarins, and some researchers found that cyclisation of trans-cinnamic acid 46 with 2-naphthol 41 under these conditions resulted in dearylation affording benzo[f]coumarin. Thus, Bhattacharjee reported dearylation and the formation of benzo[f]coumarin 32 when 2-naphthol 41 and trans-cinnamic acid 46 were condensed in the presence of PPA at 70°C (Scheme 2-9). Manimarin observed analogous results when synthesizing coumarins from phenyl cinnamates, but found that dearylation only occurred in certain solvent systems.

Scheme 2-9 The reaction of trans-cinnamic acid and 2-naphthol in PPA resulted in benzocoumarin 32.

Bramwell et al. made no mention of this phenomenon in the patent, and no data was provided to confirm the formation of benzo[f]chromanone from 2-naphthol and trans-cinnamic acid. It was also surprising that Anjaneyulu et al. made no comment on the reaction of trans-cinnamic acid with 2-naphthol despite their rigorous systematic study of the condensation of 1- and 2-naphthol with α,β-unsaturated acids in the presence of Lewis acids and PPA.
The use of PPA as a condensing agent provided an efficient means for preparing substituted benzo[f]chromanones in moderate to good yields (60-75%). Whilst the formation of chroman-4-ones is unambiguous when using crotonic acid, and other β-alkyl substituted derivatives, there exists some uncertainty of the reaction outcome when using trans-cinnamic acid (see Scheme 2-7 and Scheme 2-9). There are no reports describing the condensation of acrylic acid and derivatives with 2-naphthol in PPA.

2.4 The Fries Rearrangement

The Fries rearrangement has also been used for the preparation of chroman-4-ones, whereby phenolic esters were treated with aluminium chloride (or similar reagents) to effect intramolecular acylation followed by cyclisation. Benzo[f]flavone 52 was first synthesized in 1914, when sodium 2-naphthoxide was reacted with ethyl cinnamate to form 2-naphthyl cinnamate 51 (R = Ph) which, when treated with PCl₅ and AlCl₃, formed benzo[f]flavone 52 in almost quantitative yield. Treatment of 2-naphthyl crotonate 51 (R = CH₃) with HF afforded the corresponding benzo[f]chromanone (±)-53 in low yield (20%) (Scheme 2-10).

\[
\begin{align*}
51 & \quad \xrightarrow{PCl_5/AlCl_3} \quad 52 \\
R = Ph & \quad \text{Scheme 2-10 The Fries rearrangement prepared benzo[f]flavone 52 and benzo[f]chromanone (±)-53.}
\end{align*}
\]

The Fries rearrangement approach was limited by a competing intermolecular acylation (para-substitution), and only a few benzo[f]chromanones have been prepared by this method because of the variable, and mostly poor, yields.
2.5 Condensations of 1-(2-Hydroxynaphthalen-1-yl)ethanone

Chroman-4-ones have been prepared when o-hydroxyacetophenones were reacted with carbonyl compounds under acidic or basic conditions. However, o-hydroxyacetophenones are not common precursors for the formation of chroman-4-ones - unlike the flavanones. Nonetheless, several napthopyrones have been synthesized by an analogous method. Aldol condensations of 1-(2-hydroxynaphthalen-1-yl)ethanone 54 with benzaldehyde and substituted benzaldehydes under alkaline conditions led to the formation of benzo[f]flavanones (±)-48 (Scheme 2-11). 3,3-Dimethylbenzo[f]chromanone 50 was also prepared by treating ethanone 54 with acetone in the presence of pyrrolidine (Scheme 2-11).

![Scheme 2-11 Aldol reactions were successful for preparing benzo[f]chromanones (±)-48 and 50.](image-url)

When the reaction did not proceed directly to the chromanone, the intermediate aryl enone e.g. 55 was isolated and cyclised by treatment with n-butylamine, alkaloids, HCl, acetic acid, BF₃.OEt, AlCl₃, P₂O₅ or by photochemical conversion (Scheme 2-12).

![Scheme 2-12 Cyclisation was effected by acids, bases, and photochemical conversion.](image-url)
Intramolecular condensations have also been used to generate chromones. Thus, Bhalla achieved cyclisation of 1-acetylnaphthalen-2-yl benzoate 56 by treatment with sulfuric acid and afforded benzo[f]flavone 52 (Scheme 2-13).\(^78\)

\[
\begin{align*}
\text{H}_2\text{SO}_4 \\
\end{align*}
\]

56

52

Scheme 2-13 Intramolecular condensation produced benzo[f]flavone 52.

The Knoevenagel reaction is a modified aldol condensation whereby the electrophilic carbonyl compound is an \(o\)-hydroxyarylaldehyde. This reaction affords a range of coumarins in good yield.

The aldol approach has generated a variety of naphthopyrones, and in particular benzo[f]flavanones.

2.5.1 Claisen Condensation

One of the most common methods used to make a wide variety of chromones and benzo[f]chromanones is the Claisen condensation, where an \(o\)-hydroxyaryl alkyl ketone and a carboxylate ester are treated with a strong base. The diketone intermediate was cyclised upon heating in an acid medium and afforded chromones in good yields. Thus, the reaction of \(1-(2\text{-hydroxynaphthalen}-1\text{-yl})\text{ethanone} 54\) with ethyl acetate in the presence of sodium gave the diketone intermediate 57, which was subsequently cyclised by the action of concentrated sulfuric acid and gave benzo[f]chromone 58 (Scheme 2-14).\(^79\) Many halogenated and methylated \(2\text{-hydroxyacetophenones} were also treated with ethyl acetate in the same manner and afforded the substituted chromanones in high yield (80-97\%).\(^79\)

\[
\begin{align*}
\text{Na} \\
\end{align*}
\]

54

57

58

Scheme 2-14 The Claisen condensation was used to prepare benzo[f]chromone 58.
The use of strong acids such as sulfuric acid limited the effectiveness of the Claisen condensation reaction, although cyclisation was also effected by other means. For example, irradiation of the diketone 57 generated benzo[f]chromone 58, with the yields dependent on the solvent used. When the substrate was irradiated in Br₂/CHCl₃ the yield was 33%, whereas in I₂/MeOH 62% product was obtained. Cyclisation was also effected by indium(III) chloride via intramolecular cyclisation and dehydration.

This two-step method for preparing chromones is limited to β-substituted derivatives, where the substituent is determined by the carboxylic ester used. In order to produce chromanones, a subsequent hydrogenation step is necessary and will result only in mono-substituted products.

2.5.2 Kostanecki-Robinson and Allan-Robinson Reaction

When o-hydroxyaryl ketones were treated with acid anhydrides in the presence of sodium acetate either coumarin or chromone products resulted (Scheme 2-15). Reactions that favoured the synthesis of chromones and flavones were called Allan-Robinson reactions, while those that favoured the formation of coumarins as Kostanecki-Robinson reactions. Often both coumarins and chromones were formed in the reaction, and the use of unsymmetrical dihydroxyacetophenones resulted in isomeric products. This method has led to otherwise inaccessible chromones (such as disubstituted chromones) but the unpredictable nature of the product distribution and unsatisfactory yields limited the usefulness of this reaction.

\[
\text{Scheme 2-15 The condensation of acid anhydrides with o-hydroxyaryl ketones sometimes resulted in the formation of both chromones and coumarins.}
\]

Wittig used the Allan-Robinson reaction to synthesise 3-methylbenzo[f]chromone 58. 1-(2-Methoxynaphthalen-1-yl)ethanone 59 was treated with an excess of acetic anhydride and sodium acetate which afforded the 2-acetyl derivative 60 as well as the 3-methylbenzo[f]chromone 58 (Scheme 2-16). The acetylated derivative 60 was deacetylated to 3-methylbenzo[f]chromone 58 with ammonia.
Scheme 2-16 The Allan-Robinson reaction was used to prepare benzo[\(f\)]chromone 58.

2.6 Baker-Venkataraman Rearrangement

Many chromones and flavones have been prepared by the Baker-Venkataraman rearrangement. The rearrangement of \(o\)-acyloxyacylbenzenes in basic media formed 1,3-diketones (Scheme 2-17) which were then cyclised akin to intermediates from the Claisen condensation (Section 2.5.1, p29). Potassium carbonate was usually used to promote the intramolecular migration of the acyl group \(R^2\)CO from the oxygen to carbon (Scheme 2-17), although other reagents such as sodium, sodium alkoxide, sodium hydride, potassium hydroxide and sodium hydroxide were also effective. Migration did not occur if there was no \(ortho\) substituent.\(^{22}\)

Flavones were often prepared by the reaction of \(o\)-hydroxyacetophenone with benzoyl chloride. The resulting ester was then treated with potassium hydroxide to effect the rearrangement.\(^{81}\) Cyclisation was achieved under acidic conditions as for the Claisen condensation.

Scheme 2-17 The Baker-Venkataraman rearrangement has been used in the synthesis of chromones.

Ullal and co-workers effected the Baker-Venkataraman rearrangement by treating \(o\)-acyloxyacynaphthalene 61 with sodium ethoxide and generated benzoyl-2-hydroxy-1-naphthoylmethane 62 in a quantitative yield. Diketone 62 was cyclised to benzo[\(f\)]flavone 52 when treated with HBr in acetic acid (Scheme 2-18).\(^{85}\) The
cyclisation step faced the same problems as discussed for the Claisen condensation (Section 2.5.1, p29).

Scheme 2-18 The Baker-Venkataraman rearrangement was useful for the synthesis of benzo[f]flavone 52.

Even though the rearrangement afforded good yields and the problems of the cyclisation had been avoided, this route still required an additional reduction step in order to produce benzo[f]chromanones.

2.7 Pechmann Condensation

The reaction of phenols and 3-oxoesters in the presence of an acidic condensing agent produced chromones or coumarins directly (Scheme 2-19). Originally the Pechmann condensation used sulfuric acid as the condensing agent to generate coumarins, whereas the Simonis condensation used phosphorus pentoxide to prepare chromones. Subsequently, it was shown that both coumarins and chromones resulted from either method, and that the outcome of the reaction depended on the nature of the phenol, the 3-oxoester, and the condensing agent.\(^6\)

Scheme 2-19 The Pechmann condensation was successful for preparing benzopyrones.

The 3-methylbenzo[f]chromone \(58^{7-9}\) and its phenyl analogue \(52^{9,10}\) were synthesized from 2-naphthol \(41\) and ethyl acetoacetate (or ethyl benzoylacetae, respectively) in the presence of phosphorus pentoxide which effected condensation and cyclisation (Scheme 2-20).
Scheme 2-20 The Pechmann condensation was used to prepare benzo[f]chromone.

The advantage of this method was that the starting materials were readily available, but often the condensing agents were used in stoichiometric quantities, and strong acids and high temperatures limited the scope of this reaction. This reaction generally only afforded \( \beta \)-substituted dihydrobenzo[f]coumarins, and required an additional reduction step to afford the corresponding chromanones. The unpredictable nature of product distribution was a further drawback of this reaction.

2.8 Hydrogenation and Dehydrogenation

Hydrogenation and dehydrogenation methods were used to interconvert chroman-4-ones and chromones. Chroman-4-ones were prepared by catalytic hydrogenation of chromones but care needed to be taken to avoid reduction of the keto-group. Only chroman-4-ones with one substituent in the 2- and/or 3-position were able to be made by this method. Naphthopyrones e.g. benzo[f]coumarin 32, were reduced to benzochromanones e.g. dihydrobenzo[f]coumarins 31, by treatment with Ni-Al alloy in hot NaOH solution, followed by treatment with \( p \)-toluenesulfonic acid (Scheme 2-21).19

Scheme 2-21 The reduction of naphthopyrones to benzochromanones.

Chromanones were oxidised to chromones by treatment with lead tetraacetate, triphenylmethyl perchlorate, DDQ, and thallium(III) salts.91 Benzochromones e.g. 58 were prepared directly via dehydrogenation of benzochromanones e.g. 53, utilising DMSO-I\(_2\)-H\(_2\)SO\(_4\), DMSO-I\(_2\), 91 or with thallium(III) tosylate\(^{41}\) in almost quantitative yields (Scheme 2-22). Bachman and Levine achieved oxidation by dehydrobromination.38
2.9 Hydroxychroman-4-ones

Several approaches have been used for the preparation of 3-hydroxychroman-4-ones, via oxidation of the pyrone ring or oxidative cyclisation. The use of lead tetraacetate gave complex mixtures of flavanones, although when chroman-4-ones 63 (R = H, 7-OMe) were treated under similar conditions they furnished 3-acetoxy-derivatives 64 which were hydrolysed in warm mineral acids to afford 2-hydroxychroman-4-ones 65 (Scheme 2-23).92

Scheme 2-23 Chroman-4-ones were oxidized by treatment with lead tetraacetate.

The Algar-Flynn-Oyamada (AFO) reaction was used to prepare flavonols 68 via oxidative cyclisation by treating 2'-hydroxychalcones 66 with alkaline hydrogen peroxide. Flavanonols 67 were proposed to be intermediates in the reaction, and on some occasions were isolated from the reaction mix (Scheme 2-24).

Scheme 2-24 The Algar-Flynn-Oyamada reaction was found to generate flavanols as intermediates.

Whilst the AFO reaction was used primarily for the preparation of flavones, Dean and Podimuang were successful in the preparation of 3-hydroxychroman-4-one 70 when chalcone vinylogue 69 was treated under AFO conditions (Scheme 2-25).93
Scheme 2-25 Hydroxychromanone 70 was prepared by oxidative cyclisation.

In contrast to the selection of approaches towards 3-hydroxychroman-4-ones, there was an obvious lack of reported routes for the preparation of 2-hydroxybenzo[fl]chromanones, as evidenced by the few representatives of this particular class. A Scifinder® search based on the 2-hydroxybenzo[fl]chromanone substructure 71 resulted in only three compounds being identified; benzo[fl]flavanonol (±)-72, benzo[fl]chromanone (±)-73, and benzo[fl]isoflavanonol (±)-74. There was, however, no associated literature reference for the isoflavanonol (±)-74 identified by Scifinder®.

The benzo[fl]flavanonol (±)-72 was generated when the effect of substituents on the course of the AFO reaction was under investigation. Chalcone 75 was treated under Weitz-Scheffer conditions to afford a 1:1 mixture of the benzo[fl]flavanonol (±)-72 and the naphthofuran (±)-76 (Scheme 2-26). The stereochemistry of (±)-72 was inferred from the stereochemistry determined for the analogous flavanonol.95

Scheme 2-26 Benzo[fl]flavanonol (±)-72 was isolated from the products of an AFO reaction.

Investigations into syntheses towards cryptosporin, an antibiotic metabolite of Cryptosporium pinicol, resulted in the isolation of the benzo[fl]chromanone (±)-73. The

\[\text{Conducted May, 2009}\]
benzo[\(f\)]chromanone (\(\pm\))-73 was isolated in 3% yield, together with the acetylated benzo[\(f\)]chromandiol (\(\pm\))-78, when 2-methyl-2\(H\)-chromene (\(\pm\))-77 was treated with osmium tetroxide, and acetylated (Scheme 2-27).\(^{94}\) The stereochemistry of (\(\pm\))-73 was not reported, but determined in this work (see Section 3.2.2).

\[
\begin{align*}
\text{(\(\pm\))-77} & \xrightarrow{(1) \text{ Dioxan, OsO}_4} \text{(\(\pm\))-78} + \text{(\(\pm\))-73} \\
\end{align*}
\]

Scheme 2-27 Oxidation of chromene 77 resulted in the production of acetylated benzo[\(f\)]chromanone 73.

McCulloch synthesized 2-hydroxybenzo[\(f\)]chromanone 37 when investigating syntheses towards naphthopyrones. Nucleophilic epoxidation of 79 under Weitz-Scheffer conditions generated epoxide (\(\pm\))-80, which was cyclised with BBr\(_3\) to produce (\(\pm\))-37 (Scheme 2-28).\(^{96}\)

\[
\begin{align*}
\text{79} & \xrightarrow{H_2O_2/NaOH} \text{(\(\pm\))-80} \xrightarrow{\text{BBr}_3} \text{(\(\pm\))-37} \\
\end{align*}
\]

Scheme 2-28 McCulloch’s synthesis of 2-hydroxybenzo[\(f\)]chromanone (\(\pm\))-37.

Given the observed antibacterial activity of (\(\pm\))-37 and that fact that so few 2-hydroxybenzo[\(f\)]chromanones derivatives were reported in the literature, molecules of this type represented an interesting class of compounds which required further exploration.
2.10 Project Aims

Novel classes of antibacterial agents are desperately required to treat diseases and infections caused by bacteria with resistance to current drug regimes. To address this pressing need, this work investigated the potential of naphthopyrone compounds as a novel class of antibacterial agents. Naphthopyrones have previously shown promise in this regard (Section 1.6.2.2), but few have been systematically tested for antibacterial activity. Thus, the aim of this work was to generate a library of benzo[f]chromanone analogues, as pictured below, to subsequently test for antimicrobial activity.

\[
\begin{align*}
R^1 &= H, OH \\
R^2 &= H, CH_3 \\
R^3 &= H, CH_3, Ph \\
R^4 &= H, OH
\end{align*}
\]

The review of synthetic methods for the preparation of benzo[f]chromanones revealed that polyphosphoric acid (PPA) condensation of 2-naphthol and \(\alpha,\beta\)-unsaturated acids provided a high yielding, facile one-step method that produced benzo[f]chromanones with various alkyl substituents in the pyrone moiety. As such, the route for the preparation of a library of benzo[f]chromanones (\(R^1 = H\)) was modeled on this, with the view to prepare compounds previously synthesized by this route as well as extending the methodology to prepare other related compounds.

The review also highlighted the lack of efficient routes for the preparation of hydroxybenzo[f]chromanones (\(R^1 = OH\)), and as such another aim of this work was to develop a versatile synthetic route towards these compounds, with the view of preparing them for subsequent antibacterial activity testing.

Any compounds, known or novel, generated through the pursuit of benzo[f]chromanone analogues, were to be subjected to antibacterial testing in order to conduct structure activity relation studies and to consequently identify compounds with antibacterial activity.
3 Results and Discussion

3.1 Synthesis of Benzo[f]chromanones by Polyphosphoric Acid Cyclisation

3.1.1 2-Naphthol Condensation

Polyphosphoric acid (PPA) condensation of 2-naphthol with α,β-unsaturated acids has previously been successful for the preparation of benzo[f]chromanones (Section 2.3.1) and as such the preparation of a range of benzo[f]chromanones for the analogue library was modeled on this route. Initially, it was anticipated that the benzo[f]chromanones 40, (±)-53, 81 and (±)-48 could be prepared by this method, where variation of the substituents in the pyrone ring would effect changes in solubility and target binding and hence result in changed antibacterial activity to aid SAR studies.

40 (±)-53 81 (±)-48

Benzo[f]chromanone (±)-53 had previously been prepared by PPA cyclisation, thus following the method of Anjaneyulu et al.,47 2-naphthol 41 and crotonic acid 82 were condensed in PPA to afford a racemic mixture of benzo[f]chromanone (±)-53 in high yield (92%) as shown in Scheme 3-1. The spectral data of benzo[f]chromanone (±)-53 have previously not been reported, however the melting point was in accordance with the literature61 and the mass spectrum fragmentation pattern and HRMS supports the structure of benzo[f]chromanone (±)-53. The 1H NMR spectrum is shown in Figure 3-2 A typical 1H NMR spectrum of a benzo[f]chromanone, e.g. (±)-53 (CDCl3, 300MHz).

p.41, and the peak assignments are tabulated in Table 3-1 p.55. A distinct coupling pattern of 4 doublet-doublets and two doublet-doublet-doublets in the aromatic region of the 1H NMR spectrum indicate that substitution occurred at C-1 of 2-naphthalene. A downfield resonance was assigned to H-10 and was typical of benzo[f]chromanones systems. An absence of olefinic resonances indicated that cyclisation had occurred at C-3, and was confirmed by a resonance at 4.71ppm with coupling appropriate of an ABMXX3 system.
Scheme 3-1 Polyphosphoric acid cyclisation of 2-naphthol and crotonic acid.

Conditions: a PPA, 60°C, 1.5h, (±)-53 92%.

With the success of the cyclisation of crotonic acid with 2-naphthol, the method was extended to the cyclisation of tiglic acid 83 with 2-naphthol 41. Adapting Anjaneyulu’s protocol, 47 2-naphthol 41 and tiglic acid 83 were cyclised in PPA at 60°C until total consumption of starting material, as indicated by TLC. Purification of the crude product (83%) by column chromatography realized diastereomers (±)-84 and (±)-85, neither of which has been previously reported. The distinct coupling pattern in the aromatic region of the ¹H NMR spectrum, and the downfield resonance at 9.47ppm indicated that benzo[f]chromanones had formed. The configuration of the diastereomers was determined from the coupling observed in the ¹H NMR spectra, as the anti-product (±)-84 displayed coupling for the methine protons (J₂-₃ = 11.7Hz) characteristic of protons in axial-axial orientation. 97 The syn-product (±)-85 displayed coupling (J₂-₃ = 3.5Hz) characteristic of axial-equatorial orientation.

Scheme 3-2 Polyphosphoric acid cyclisation of 2-naphthol 41 and tiglic acid 83.

Conditions: a PPA, 60°C, 20h, (±)-84 30%, (±)-85 38%.

Bramwell, Fitton and Ramage patented PPA cyclisation for the preparation of chroman-4-ones, and claimed to have used this method using acrylic acid. 61 However, when 2-naphthol 41 was reacted with acrylic acid 86 cyclisation to benzo[f]chromanone 40 did not proceed as expected, as the spectral data of the product from this reaction did not concur with the spectral data for benzo[f]chromanone 40 as reported by Ravukimar. 29 Instead, cyclisation occurred to produce dihydrobenzocoumarin 31 in addition to a small amount of phenalenone 87 (Scheme 3-3).
The lack of a downfield resonance \( \text{ca.} \ 9\text{-}10\text{ppm} \) in the \(^1\text{H}\) NMR spectrum indicated that the benzo[f]chromanone had not formed, and the lack of a singlet in the aromatic region suggested that substitution had occurred. Analysis of the \(^1^3\text{C}\) NMR spectral data indicated that the carbonyl resonated at 168ppm, and hence a lactone had formed. It was postulated that the reaction had afforded dihydrobenzo[f]coumarin. It was found that the \(^1\text{H}\) NMR spectral data of dihydrobenzocoumarin 31, shown in Figure 3-3 p.41 and tabulated in Table 3-3 p.57, was in accordance with that reported for the dihydrobenzo[f]coumarin by Shi and He.\(^{95}\) No data was provided by Bramwell \etal\ for comparison.\(^{61}\) Nonetheless, as Bramwell \etal\ had performed the reaction at a temperature of 100°C, these reaction conditions were reproduced to determine if the chromanone resulted from an increase in temperature – however, no such change was observed.

The most distinct difference in the spectral data of a coumarin-type product and a chromanone-type product was in the shift of the respective H-10 resonance in the \(^1\text{H}\) NMR spectrum (see Figure 3-2 A typical \(^1\text{H}\) NMR spectrum of a benzo[f]chromanone, e.g. (±)-53 (CDCl\(_3\), 300MHz).

and Figure 3-3 p.40). The anisotropic shielding experienced by H-10 in benzo[f]chromanones shifts the signal downfield when compared to the same proton in benzo[f]coumarins (Figure 3-1, see also \(^1\text{H}\) NMR Spectral Comparison, Table 3-1 p.55 and Table 3-3 p.57).

Figure 3-1 The anisotropic shielding experienced by H-10 in benzo[f]chromanones shifts their signal downfield in \(^1\text{H}\) NMR spectra.
Figure 3-2 A typical $^1$H NMR spectrum of a benzo[f]chromanone, e.g. (±)-53 (CDCl$_3$, 300MHz).

Figure 3-3 A typical $^1$H NMR spectrum of a dihydrobenzo[f]coumarin, e.g. 31 (CDCl$_3$, 300MHz).
Apart from Bramwell’s patent, the cyclisation of acrylic acid and 2-naphthol in PPA had not been reported before, although Merchant and Upasani had investigated the reaction of acrylic acid with 2,7-dihydroxynaphthalene 88 in PPA. Expecting the chromanone, they also found that cyclisation took place to afford the coumarin-type product 89, and that cyclisation had occurred at both hydroxyl groups (Scheme 3-4). Merchant and Upasani also observed the formation of phenalenones in analogous experiments.

![Scheme 3-4](image)

**Scheme 3-4** Merchant and Upasani’s cyclisation of 2,7-dihydroxynaphthalene and acrylic acid in PPA afforded tetracycle 89.

It appeared that if the α,β-unsaturated acids were substituted in the β–position (e.g. crotonic acid 82 and tiglic acid 83) then cyclisation would occur to generate benzo[f]chromanones, but if the acid was unsubstituted in the β–position (e.g. acrylic acid 86) then cyclisation would occur to form the dihydrobenzo[f]coumarin. This postulation was examined by treating 2-naphthol 41 and methacrylic acid 90 in PPA, and as anticipated, the dihydrobenzo[f]coumarin (±)-91 was formed (Scheme 3-5), with the spectral data in agreement with that reported in the literature.

![Scheme 3-5](image)

**Scheme 3-5** Polyphosphoric acid cyclisation of 2-naphthol 41 and methacrylic acid 90.

**Conditions:** a PPA, 60°C, 20h (±)-91 58%.

The cyclisation of propiolic acid 92 with 2-naphthol in PPA as shown in Scheme 3-6 was also found to produce benzo[f]coumarin 32. The spectral data, tabulated in Table 3-3 p.57 and Table 3-4 p.58, were in good agreement with that in the literature.
Scheme 3-6 Polyphosphoric acid cyclisation of 2-naphthol 41 and propiolic acid 92.

Conditions: a PPA 60°C, 20h, 32 25%.

An anomaly was found when 2-naphthol 41 and *trans*-cinnamic acid 46 were cyclised with PPA at 60°C in that both the dihydrobenzo[**f**]coumarin (±)-47 and benzo[**f**]chromanone (±)-48 were produced in a 1:1 ratio (Scheme 3-7). The spectral data for benzo[**f**]chromanone (±)-48 was in accord with that provided by the literature, although similar data for dihydrobenzo[**f**]coumarin (±)-47 had not previously been reported.

Scheme 3-7 Cyclisation of 2-naphthol 41 with *trans*-cinnamic acid in PPA 60°C produces both dihydrobenzo[**f**]coumarin (±)-47 (46%) and benzo[**f**]chromanone (±)-48 (44%).

It was observed that the production of benzocoumarin (±)-47 was favoured if the reaction was conducted at a higher temperature ((±)-47 74% at 100°C). These results also parallel the findings in the literature in that Friedel-Crafts reactions with Lewis acids at higher temperatures led to dihydrobenzocoumarins, and lower temperatures result in benzochromanones (Section 2.3). This observation led to the conjecture that this was a reaction that could generate either benzo[**f**]chromanones or dihydrobenzo[**f**]coumarins depending on the temperature at which the reaction was run; dihydrobenzo[**f**]coumarins were favoured at higher temperatures, and benzo[**f**]chromanones at lower temperatures (Figure 3-4). This possibly represented a versatile, direct and facile method to produce either coumarin-type or chromanone-type products exclusively.
The results indicated that increased reaction temperatures favoured dihydrobenzocoumarins and that lower reaction temperatures favoured benzochromanones.

In order to test this supposition, reactions of 2-naphthol 41 with crotonic acid 82 in PPA at temperatures up to 200°C were conducted, however, only the production of benzo[f]chromanone (±)-53 was observed. Increasing the temperature did not allow crotonic acid and 2-naphthol to afford a dihydrobenzo[f]coumarin, but perhaps cooling the analogous reaction of acrylic acid and 2-naphthol would result in the formation of benzo[f]chromanone.

Conducting the reaction of 2-naphthol 41 with acrylic acid 86 at lower temperatures presented difficulties with PPA. The latter is a viscous liquid at room temperature, and requires a minimum temperature of 60°C at standard pressure in order to make it an effective reaction medium. To circumvent this problem Eaton’s reagent, a medium with similar properties to PPA yet suitable to use at room temperature, was prepared by a reported procedure. The cyclisation of acrylic acid and 2-naphthol in Eaton’s reagent at room temperature did not produce benzo[f]chromanone 40.

Under the conditions examined PPA cyclisation did not present a general method to prepare either a benzo[f]chromanone or a dihydrobenzo[f]coumarin from a given α,β-unsaturated acid at different temperatures.

The cyclisation of 2-naphthol with acrylic acid in PPA did not generate benzo[f]chromanone 40 and as such, it was necessary to prepare it following the method of Bachman and Levine (Scheme 2-3). 2-Naphthol was treated with acrylonitrile in the presence of Triton B** to afford the 3-aryloxynitrile 43, which was subsequently cyclised in 85% H₂SO₄ to give benzo[f]chromanone 40.

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1 Phosphorus pentoxide-methanesulfonic acid

** Benzytrimethylammonium hydroxide in methanol (40%w/v)
3.1.2 With the success of preparing benzo[f]chromanones, it was questioned as to whether the PPA 1-Naphthol Condensation cyclisation methodology could be extended to prepare natural product naphthopyrones based on the benzo[h]chromanone scaffold, such as 5-methyldihydroflavasperone 93. The simplest system on which to develop an appropriate synthetic route to these compounds was 1-naphthol 94.

![Structure of 5-methyldihydroflavasperone 93](image)

The reaction of 1-naphthol 94 and crotonic acid in PPA generated the desired benzo[h]chroman-4-one (±)-95, albeit in 20% yield, with the major product identified as the cyclopentanone (±)-96 (Scheme 3-8). The reaction of crotonic acid with 1-naphthol in PPA has previously been attempted by Anjaneyulu et al. reporting good yields of benzo[h]chroman-4-one (±)-95 (up to 70%) but with no reported side products.47

![Scheme 3-8 Polyphosphoric acid cyclisation of 1-naphthol 94. Conditions: PPA, 60°C, 3h, (±)-95 20%, (±)-96 55%](image)

The structure of benzo[h]chromanone (±)-95 was confirmed by NMR analysis. The chemical shift of carbonyl C-4 at 192.1ppm in the $^{13}$C NMR spectrum supports the formation of a γ-pyrone, and the ABMX$_3$ system of H-2 at 4.79ppm in the $^1$H NMR spectrum is typical of a proton adjacent to the pyrone ether oxygen of these systems. The presence of two aromatic protons at 7.86ppm and 7.39ppm, with ortho-coupling ($J_{5,6} = 8.9$Hz) can be assigned to H-5 and H-6, respectively, and indicates that cyclisation occurred ortho to the oxygen atom as anticipated. This data was in good agreement with that provided by the literature.25

Analysis by HRMS indicated that the product (±)-96 was isomeric to benzo[h]chromanone (±)-95 as they possessed the same molecular weight of 212.0837. The presence of a singlet resonating at 6.86Hz in the aromatic region of the $^1$H NMR
spectrum (see Figure 3-5) indicated that substitution and cyclisation of the crotonic acid had occurred on the same ring as the hydroxyl group, leaving only one uncoupled proton. In addition, the resonance at 3.37ppm was typical of a benzylic proton. It was postulated that the possible structure of product (±)-96 was likely to be one of four cyclopentanones 97-100.

The 'H NMR spectrum of product (±)-96 also presented an aromatic signal shifted significantly downfield to 8.95ppm. Of the proposed cyclopentanones, the angular cyclopentanone 100 experiences the most significant anisotropic deshielding from the orientation of the carbonyl moiety, and as such product (±)-96 was proposed to have the structure of cyclopentanone 100. The signal of 8.95ppm in the 'H NMR spectrum was assigned to H-9 due to its observed coupling and the anisotropic deshielding from the carbonyl moiety, and the doublet-doublet-quartet of the ABMX₃ system on the pyranone ring resonating at 3.37ppm was assigned as H-3. Only one anomaly existed with data for the structure proposed for (±)-96, in that the ¹³C NMR APT spectrum presented two
resonances *ca.* 160-170ppm. The resonance at 162.9ppm was assigned to C-5, appropriate for a quaternary aromatic carbon adjacent to a hydroxyl group. However, the resonance at 168.5ppm, assigned to C-3a, was *ca.* 30ppm further downfield than calculated. HMBC correlations occurred to H-3 and H-3CH₃, however, and all the other quaternary resonances in the spectrum had been accounted for. Searching the literature for analogous structures indicated that this downfield resonance had been observed previously for similar systems (see Table 3-5 for comparative spectral data).

Cyclopentanone 96 was *O*-methylated to give (±)-101 in order to confirm its identity by nOe experiments as shown in Figure 3-6. An aromatic singlet at 6.86ppm, assigned to H-4, showed a reciprocal nOe to the methoxy protons upon irradiation. In addition, irradiation of the proton assigned as H-9 showed nOe to the aromatic protons assigned as H-8 and H-7, clearly supporting the putative structure of novel compounds (±)-96 and (±)-101.

![Figure 3-6](image)

(±)-101

Figure 3-6 The nOe experiments confirmed the structure of *O*-methylated cyclopentanone 101.

3.1.3 Naphthoresorcinol Condensation

Given the reaction with both 1- and 2-naphthols had been demonstrated we wished to explore the reactivity of polyhydroxylated systems. As such, crotonic acid and naphthoresorcinol 102 were reacted to determine the effect of multiple electron donating functional groups. With two *ortho*-directing groups, it was possible that benzo[**h**]chroman-4-ones could be made, representing the natural product scaffold of angular naphtho-γ-pyrones. However, upon reaction under the standard conditions employed, only the benzo[**f**]chroman-4-one 103 was isolated in low yield from a complex mixture of products (Scheme 3-9).
Scheme 3-9 Polyphosphoric acid cyclisation of naphthoresorcinol 102. Conditions: a PPA, 60°C, 3h, 103 27%.

The mass spectrum of the product isolated showed a molecular ion (m/z = 228) that indicated only mono-substitution had occurred, and a singlet resonance (6.40ppm) in the aromatic region of the ¹H NMR spectrum (Figure 3-7) indicated that cyclisation had occurred in the hydroxylated ring.

Potentially, up to to six different isomers could result from the mono-substitution and cyclisation of crotonic acid with naphthoresorcinol, depicted by benzochromanones 104-109. The presence of a signal at 9.36ppm in the ¹H NMR spectrum of the product (±)-103 could result from anisotropic deshielding from the proximity and orientation of the carbonyl moiety, as previously observed in analogous benzo[f]chromanones.
Thus, of the possibilities presented above, the only structure that would experience strong anisotropic deshielding was benzo[f]chromanone 106. Furthermore, a doublet-doublet-quartet at 4.64ppm is typical of protons adjacent to the ether moiety in an ABMX₃ system of a γ-pyron system. Thus, cyclisation occurred around the hydroxyl group in position 3 to form the novel compound benzo[f]chromanone (±)-103 (see also NMR Spectral Comparison, Table 3-1 and Table 3-2).

In order to prepare benzo[h]chromanones, it was necessary to achieve cyclisation about the hydroxyl group of C-1 of naphthoresorcinol. It was proposed that the protection of the 3-hydroxyl group would encourage cyclisation about the hydroxyl group of C-1. Monomethylation of the 3-hydroxyl group of naphthoresorcinol 102 was achieved by treating naphthoresorcinol 102 with methanolic HCl, following the method of Bell and McCaffery,¹⁰³ which afforded 3-methoxynaphthalen-1-ol 110 and 1,3-dimethoxynaphthalene 111 (Scheme 3-10). The regioselectivity of this reaction for 3-methoxynaphthalen-1-ol 110 was confirmed by nOe experiments whereby irradiation of the methoxyl group protons of 110 resulted in the observation of nOes to H-2 and H-4 (Figure 3-8).

Scheme 3-10 O-Methylation of naphthoresorcinol. Conditions: a HCl/MeOH (1.2M), r.t. 3d, 110 70%, 111 8%.
Figure 3-8 nOe experiments confirmed the structure of 3-methoxynaphthalen-1-ol 110.

The reaction of 3-methoxynaphthalen-1-ol 110 with crotonic acid under the standard conditions resulted in the generation of α-pyrene 112. The product was isolated in only 9% yield after chromatography, and naphthoresorcinol 102 was the major product (Scheme 3-11). This was surprising that naphthoresorcinol was isolated, as it was previously shown that it reacted with crotonic acid to form benzo[f]chromanone 103 under the same reaction conditions (Scheme 3-9).

The mass spectrum of product (±)-112 showed a molecular ion of m/z of 228, indicating that only monosubstitution had occurred with concurrent demethylation, supported by the lack of signals in the region characteristic of ether groups in the ¹H NMR spectrum (ca. 3-4ppm, see Figure 3-9). In addition, there was a singlet in the aromatic region of the ¹H NMR spectrum, thus, the product was likely to be one of the structures 104-109. The spectral data of (±)-112 was not comparable to that of benzo[f]chromanone (±)-103, hence it was different to the product from the reaction of crotonic acid with naphthoresorcinol, eliminating structure 106 from the possibilities.

The methine proton (H-3) in β-substituted benzo[f]chromanones typically resonates ca. 4.3-4.7ppm, (See Benzo[f]chromanone ¹H NMR Spectral Comparison, Table 3-1, p.55), however, the methine proton of (±)-112 was observed to resonate at 3.79ppm which suggested that cyclisation had occurred to form an α-pyrene (cf. dihydrobenzo[f]coumarins 31 and (±)-91 in ¹H NMR Spectral Comparison, Table 3-3 p.57).
Analysis of the $^{13}$C NMR spectrum revealed that indeed the carbonyl moiety was resonating at 170.6ppm, which is indicative of an ester moiety, clearly supporting the formation of an $\alpha$-pyrone (cf. $^{13}$C NMR Spectral Comparison, Table 3-2 p.56 and Table 3-4 p.58). This rationale eliminated structures 104 and 105 from the selection of possible structures.

In order to determine the orientation of the $\alpha$-pyrone ring, it was necessary to methylate the remaining hydroxyl group and conduct nOe experiments. The $^1$H NMR spectrum of the O-methylated product (±)-113 is shown in Figure 3-10.
Figure 3-10 The $^1$H NMR spectrum of (±)-113 (CDCl$_3$, 300MHz).

The methoxy group of (±)-113 was irradiated and reciprocal enhancements were observed between the methoxy protons and the aromatic singlet observed at 6.57ppm in the $^1$H NMR spectrum (Figure 3-11). Enhancements were also observed to H-10, H-1, and H-2 when the methyl group of the pyranone ring was irradiated, confirming the identity of the novel dihydrobenzo[g]coumarin (±)-113 and hence the analogous structure of the parent dihydrobenzo[g]coumarin as (±)-112.

Figure 3-11 nOe experiments confirmed the structure of O-methylated naphthalene 113.
3.1.4 2,6-Dihydroxynaphthalene Condensation

The reaction of 2,6-dihydroxynaphthalene 114 with crotonic acid was explored to investigate if multiple cyclisations would occur on a less hindered system than naphthoresorcinol. When 2,6-dihydroxynaphthalene 114 and crotonic acid were treated under the standard PPA cyclisation conditions, it was found that mono-substitution of 2,6-dihydroxynaphthalene 114 occurred rapidly to afford benzo[f]chromanone (±)-115 (Scheme 3-12), and that an extended reaction period (5d) did not result in further cyclisation to produce a tetracyclic system. The racemic product was purified by column chromatography and analysis by GCMS showed a molecular ion \( m/z = 228 \) which together with the presence of 5 aromatic signals in the \(^1\text{H} \) NMR spectrum (Figure 3-12) indicated mono-substitution had occurred on the naphthalene ring.

![Scheme 3-12 Polyphosphoric acid cyclisation of 2,6-dihydroxynaphthalene 114 and crotonic acid. Conditions: a PPA, crotonic acid, 60°C, 5d, (±)-115 60%.

Figure 3-12 The \(^1\text{H} \) NMR spectrum of (CD$_3$OD, 300MHz).
Comparison of the spectral data for (±)-115 with that of benzo[f]chromanones (±)-53 and (±)-103 indicated many similarities between the compounds (see NMR Spectral Comparison, Table 3-1 p.55 and Table 3-2 p.56), including the characteristic downfield resonance at 9.20ppm which is typical of a benzo[f]chromanone H-10 experiencing anisotropic deshielding. This, and the fact that the fragmentation pattern in the mass spectrum is consistent with the proposed structure, supports the formation of the novel benzo[f]chromanone (±)-115.
Table 3-1: Benzo[f]chromanone $^1$H NMR Spectroscopic Data (300MHz, CDCl$_3$)

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* Assigned by HMBC
Table 3-3 Benzo[f]coumarin $^1$H NMR Spectroscopic Data (300 MHz, CDCl$_3$)

$\delta$, Mult. ($J$ in Hz)

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|   | (7.5)       | (15.3, 5.7) | (6.3, 2.4) | (9.6) | (7.2, 6.6, 1.8) | (7.2, 5.4, 2.0) |
| 2 | 2.94, app t. | 2.89, ddq | 3.23, dd | 6.58, d | 3.01, dd | 2.94, dd |
|   | (7.5)       | (12.0, 5.7, 6.3) | (16.1, 6.3) | (9.6) | (15.9, 6.6) | (16.1, 5.4) |
| 5 | 7.24, d     | 7.21, d   | 7.36, d  | 7.47, d | 6.57, s    | 6.59, s   |
| 6 | 7.78, d     | 7.75, d   | 7.88, d  | 7.99, d | -          | -         |
| 7 | 7.86, bd    | 7.83, bd  | 7.88, dd | 7.92, ddd | 8.23, ddd | 8.27, dd |
| 8 | 7.48, bdd   | 7.45, ddd | 7.44, ddd | 7.57, ddd | 7.41, ddd | 7.45, ddd |
| 9 | 7.59, bdd   | 7.56, ddd | 7.48, ddd | 7.69, ddd | 7.57, ddd | 7.59, ddd |
| 10| 7.90, bd    | 7.88, bd  | 7.80, dd | 8.23, bd | 7.93, bd    | 7.85, dd |
| 1' | -           | 1.46, d   | (8.4)   | (8.9, 1.7) | (8.4) | (8.2, 0.9) |
| 2' | -           | -         | 7.13, dd | -         | (7.2) | (7.2) |
| 3' | -           | -         | 7.25, m | -         | -         | -         |
| 4' | -           | -         | 7.25, m | -         | -         | -         |
Table 3-4 Benzo[f]coumarin $^{13}$C NMR Spectroscopic Data (75 MHz, CDCl$_3$)

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*Assigned by HMBC
Table 3-5 Spectroscopic Data for Benzo[h]chromanone and Cyclopentanones

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*Obtained in CD₂OD

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3.2 Syntheses of 2-Hydroxy Benzo[f]chromanones

3.2.1 Introduction

In order to prepare a diverse range of benzo[f]chromanones for antibacterial activity testing, we wanted to include several compounds that were hydroxylated in the pyranone ring. As discovered from the literature search (Section 2.9) the 2-hydroxybenzo[f]chromanone class was relatively unexplored, however, previous work within our group had led to the synthesis of 2-hydroxybenzo[f]chromanone (±)-37, which was shown to have antibacterial activity. As such, we wished to develop a series of analogues with various substituents on the pyrone ring as shown in Figure 3-13. The differences in the substituents would affect antibacterial activity by altering their solubility, as well as their ability to bind to their target site in bacteria.

McCulloch had previously synthesized the 2-hydroxybenzo[f]chromanone (±)-37 whilst investigating syntheses towards naphthopyrones. Metal halogen exchange on 1-bromo-2-methoxynaphthalene 116 with n-BuLi followed by treatment with crotonic anhydride produced acylated methoxynaphthalene 79. Nucleophilic epoxidation of 79 under Weitz-Scheffer conditions gave epoxide (±)-80, which was demethylated and cyclised with BBr₃ to afford 37 in an overall yield of 18% (Scheme 3-13).

```
116  79  (±)-80  (±)-37
```

Scheme 3-13 McCulloch's synthesis of hydroxybenzo[f]chromanone 37. Conditions: a THF, -78°C, N₂, n-BuLi (1.1eq), crotonic anhydride, 79 40%; b THF, 0°C, H₂O₂, NaOH(aq), (±)-80, 52%; c DCM, BBr₃, (±)-37 ca. 70-85%.
3.2.2 Synthesis of 2-Hydroxy-3-methylbenzo[f]chromanone (±)-37

In order to follow McCulloch's protocol, 1-bromo-2-methoxynaphthalene 116 was first prepared by dissolving 2-methoxynaphthalene 117 in AcOH and treating it with molecular bromine (Scheme 3-14). The $^1$H NMR spectral data for 116 was in accordance with the literature.\(^{105}\)

Scheme 3-14 Bromination of 2-methoxynaphthalene 117. Conditions: a AcOH, Br$_2$, r.t. 18h. 116 93%.

Brominated naphthalene 116 was dissolved in THF at -78°C and metalated by treating it with $n$-BuLi. After 10 min the lithiated intermediate was exposed to freshly distilled crotonic anhydride which had previously been prepared by dehydrating crotonic acid with dicyclohexylcarbodiimide (DCC). Analysis of the reaction mix revealed a complex mixture. Conditions were altered to a longer reaction time of 0.5h before addition of crotonic anhydride; however, this still returned a complex mixture containing 2-methoxynaphthalene 117. A more efficient route was therefore sought to generate $\alpha,\beta$-unsaturated ketone 79 despite McCulloch achieving a yield of 40% via this method (Scheme 3-15).\(^{96}\)

Scheme 3-15 McCulloch's synthesis of 79. Conditions: a THF, -78°C, N$_2$; b $n$-BuLi (1.1 eq), 10 min; c crotonic anhydride → r.t. overnight. 79 40%.

Friedel-Crafts acylation proved to be a more successful method to produce the $\alpha,\beta$-unsaturated ketone 79. Crotonyl chloride was prepared by treating crotonic acid with an excess of thionyl chloride and refluxing overnight before purification by Kügelrohr distillation.\(^{106}\) 2-Methoxynaphthalene 117 was treated with distilled crotonyl chloride 1.1 equiv.) in dry DCM at 0°C. AlCl$_3$ (1.1 equiv.) was added slowly and after 0.5h the
reaction was quenched with ice cold 1\textit{N} HCl to give the \(\alpha\beta\)-unsaturated ketone 79 in 87\% yield (Scheme 3-16).

![Scheme 3-16: Friedel-Crafts acylation of 2-methoxynaphthalene 117. Conditions: a DCM, 0\(^\circ\)C, \(\text{N}_2\), crotonyl chloride, AlCl\(_3\), 0.5h, 79 87\%.

Longer reaction times led to the formation of benzo[\(\ell\)]chromanone (±)-53. Demethylation of the \(\alpha\beta\)-unsaturated ketone 79 by AlCl\(_3\) to give intermediate 118 allowed cyclisation to occur via nucleophilic attack of the oxygen on the crotonyl substituent in a 1,4-Michael addition. Protonation of intermediate 119 on acidic work up gave benzo[\(\ell\)]chromanone (±)-53 (Scheme 3-17).

![Scheme 3-17 Proposed mechanism for the cyclisation and demethylation of 79 to give benzochromanone (±)-53.

The conjugated double bond of \(\alpha\beta\)-unsaturated ketone 79 was epoxidised under Weitz-Scheffer conditions as reported by McCulloch\(^{46}\) to give the racemic epoxide product 80 (Scheme 3-18). The trans-stereochemistry about the double bond on the crotonyl side chain has been retained, as indicated by the coupling constant (\(^3J_{2,3} = 2.0\text{Hz}\)) which is characteristic of trans disposition of protons on an epoxide bond (see NMR Spectral Comparison Table 3-8 p.81 and Table 3-9 p. 82 ).\(^{97}\)

![Scheme 3-18 Nucleophilic epoxidation of 30. Conditions: a \(\text{H}_2\text{O}_2\), NaOH\(_{\text{aq}}\), THF, 0\(^\circ\)C → r.t., 2h, (±)-80 72\%.

62
Curiously, the signals in the $^1$H NMR spectrum of epoxide 80 in CDCl$_3$ were concentration dependent. Change was most notable for the resonance of H-8' which appeared as a doublet at 7.86ppm in dilute solutions (ca. 0.16 M) but at higher concentrations (ca. 0.62 M) the resonance overlapped with the doublets for H-4' at ca. 7.92ppm (Figure 3-14). The signal from H-8' moves ca. 15Hz downfield towards the H-4' resonance. This can be explained by an increase in anisotropic effect from the carbonyl oxygen experienced by H-8' as the side chain is forced to rotate into a more planar position with respect to the naphthalene moiety with increased concentration.

Figure 3-14 (Top) A low concentration of epoxide (±)-80 (ca. 0.16M) shows 2 distinct doublets for the resonances for H-4' and H-8' in the aromatic region of the $^1$H NMR spectrum. An increased concentration (0.62M) results in the resonances for H-4 and H-8 overlapping (Bottom).

In a single previous experiment McCulloch reportedly achieved demethylation and cyclisation of epoxide (±)-80 by treatment with excess BBr$_3$ in dry DCM at 0°C for 10min before quenching with iced water. Limited supporting evidence indicated that the product had the proposed structure of 2-hydrozybenzo[f]chromanone (±)-37. For example, anisotropic deshielding of H-10 by the carbonyl moiety in the pyranone ring in the putative structure would lead to a signal further downfield than aromatic signals usually observed for naphthalene (ca. 7-8ppm) in the $^1$H NMR spectrum. A doublet
observed at 9.34ppm in the $^1$H NMR spectrum of product (±)-37 was assigned to H-10, and this, along with the absence of a singlet signal of the methoxy group (ca. 3.5-4.5ppm), provided evidence that demethylation and cyclisation has occurred to form the pyrone ring. Proton spin coupling constants of 12.2Hz in product (±)-37 indicated that the protons were aligned axial-axial in a system with no free rotation which supports the formation of a cyclised structure. In addition, the mass spectrum showed a molecular ion ($m/z = 228$) and fragmentations that were consistent with the structure of 2-hydroxybenzo[f]chromanone (±)-37.

Attempts to cyclise epoxide 80 following the same methodology resulted in a complex mixture of products, including brominated species, as observed by GCMS. Analysis of the reaction mixture by $^1$H NMR spectroscopy indicated the presence of the desired product as indicated by the appearance of a distinct doublet at 9.34ppm, although in small amount and that methoxylated species were dominant.

Further attempts utilising BBr$_3$ to cyclise epoxide (±)-80 with varying stoichiometric quantities of BBr$_3$ and reaction times continued to result in complex mixtures with only small amounts of the desired product. Previously, McCulloch estimated a yield of 70-85% for the conversion of epoxide (±)-80 to benzo[f]chromanone (±)-37, based on $^1$H NMR spectroscopy and GCMS analysis alone, and did not report the formation of any by-products.

We had previously noted that prolonged exposure to α,β-unsaturated ketones, such as 79, to AlCl$_3$ resulted in demethylation and cyclisation via Michael addition. Changing the Lewis acid from BBr$_3$ to AlCl$_3$ in the epoxide system resulted in the generation of cyclised products, however, cyclisation occurred to form both the racemic product (±)-37 and an isomeric furanone 120 (Scheme 3-19). The $^1$H NMR spectrum of (±)-37 is shown in Figure 3-15 and detailed in the NMR Spectral Comparison Table 3-10, p. 82.
Scheme 3-19 Cyclisation of epoxide 80. Conditions: a DCM, AlCl₃, N₂, 0°C → r.t. 20h, (±)-37 41%, 120 19%.

Nucleophilic attack by the demethylated oxygen in adduct 121 can occur on either carbon centre of the epoxide as depicted in Figure 3-16. Attack via path a (blue arrows), of 6-endo-tet mode, opens the epoxide with an inversion of stereochemistry at C2 in the intermediate (±)-122, which generates the pyrone (±)-37. Attack via the alternate path b (red arrows), of 5-exo-tet mode, results in the formation of intermediate (±)-123, which gives the furanone 120. Baldwin’s rules predict that 3 to 7-exo-tet processes are favoured whereas 5 to 6-endo-tet are disfavoured. Thus, the formation of the furanone 120 would be favoured, although this was not reflected in the product ratio. Baldwin also suggested, in the case of opening three membered rings to form a cyclic structure, that the rules were found to lie between those for tetrahedral and trigonal systems. As 6...
to 7-endo-trig and 3 to 7-exo-trig are favoured, the 6-endo pathway to open the epoxide may be favoured afterall.\(^{107}\)

![Figure 3-16 Proposed mechanism of formation of pyrone (±)-37, via path a (blue arrows), and furanone 120, via path b (red arrows).](image)

The magnitude of the scalar coupling between H-2 and H-3 at 12.0Hz for benzo[f]chromanone (±)-37 is indicative of protons arranged in an axial-axial configuration\(^{97}\) (Figure 3-17). The bulky methyl and hydroxyl substituents reside in the preferred equatorial positions whereby the hydroxyl group (observed by \(^1\)H NMR spectroscopy at 4.04ppm) is able to H-bond with the carbonyl oxygen. The H-bonding is maximized when the hydroxyl group is equatorial, leading to enhanced stability. Mechanistically, only a pair of enantiomers will be generated (Figure 3-16), and accordingly only a single racemate for (±)-37 was observed on purification. The acidic nature of the α-proton may lead to epimerization at C2, however epimerization would lead to a bulky substituent occupying an axial position, and as such this process is unfavoured. The remaining spectroscopic data also compares favorably to that collected by McCulloch\(^{96}\) and full characterization confirmed the assigned structure.\(^6\)}
Figure 3-17 The substituents on the pyrone ring reside in *trans* stereochemistry, indicated by $^3J_{2,3} = 12.0\text{Hz}$, as illustrated here for the (S,S) enantiomer of 2-hydroxybenzo[f]chromanone 37.

Anisotropic deshielding experienced by the proton in the peri position, H-10, results in a downfield signal at 9.34ppm in the $^1\text{H}$ NMR spectrum. The chemical shift of the analogous proton in furanone 120, H-9, is observed at 8.70ppm. The angle of the carbonyl moiety relative to the naphthalene group is more obtuse in the furanone 120 compared with the pyrone (±)-37, and as such H-9 of furanone 120 experiences less anisotropic deshielding, and hence resonates further upfield in the $^1\text{H}$ NMR spectrum (Figure 3-18, and also Figure 3-1).

Figure 3-18 A greater angle between the carbonyl moiety (blue) and the peri proton (red) results in decreased anisotropic deshielding and an upfield shift in the $^1\text{H}$ NMR spectrum of 120 (*cf.* (±)-37). (Right) The shielded (+) and deshielded zones (-) of benzo[f]furanone.

Based on the proposed mechanism of formation of 120, the compound should exist as a single pair of enantiomers (Figure 3-16). Spectral data for 120, however, suggested the product was present as two unseparated diastereomers. The high acidity of the α-proton, H-2, is believed to be responsible for epimerization, leading to the formation of both diastereomers of 120.

Villemin and co-workers have reported on the high carbon acidity of the pseudo planar structure of five membered ring compounds with a carbonyl group, and consequently used this property to synthesise naphtho-derivatives of aurone. Naphthofuranone 125 was first prepared by treatment of 2-naphthoxyacetic acid 124 with SOCl$_2$ to give the
acid chloride derivative, which was then cyclised to form naphthofuranone 125 using AlCl₃. Dry condensation of aryl aldehydes 127a-c with naphthofuranone 125 in the presence of Al₂O₃-KF under focused microwave irradiation (40W) generated arylidenenaphthofuranones 126a-c in good yield (Scheme 3-20).¹⁰⁸

Scheme 3-20 Conditions: a SOCl₂, 1 drop DMF, reflux 30min; AlCl₃, DCM, reflux 15mins, 125 41%; b KF-Al₂O₃, 40W microwave irradiation, 126a-c 73-95%.

Before full characterization data was collected, naphthofuranone 120 dehydrated to form naphthofuranone 128 (Scheme 3-21). The stereochemistry about the double bond of 128 is tentatively assigned as cis based on analogous compounds 129 and 130, prepared by Woydowski and co-workers, that have been shown to have a cis geometry by X-ray crystal analysis.¹⁰⁹

Scheme 3-21 Dehydration of naphthofuranone 120 to 128.

Comparison of ¹H NMR spectral data for naphthofuranone 128 and the analogous compounds 129 and 130 indicates the similarity in chemical shift of the olefinic proton (6.30ppm cf. 6.24ppm and 6.13ppm) and allylic protons (2.07ppm cf. 2.05ppm and...
1.94 ppm), and hence naphthofuranone 128 is tentatively assigned as cis (Figure 3-19). There were no trans analogues identified in the literature for comparison.

![Chemical structures]

Figure 3-19 Comparison of $^1$H NMR spectral data supports the assignment of cis stereochemistry of 128.

Woydowski and co-workers were developing a synthetic route towards 3-hydroxyflavanones and 3-hydroxychromanones. The cyclisation of benzoyloxiranes 131 by acidic hydrolysis afforded chromones 132 and furanones 133. The latter were observed as cis isomers, regardless of whether they were derived from cis or trans epoxide precursors 131 (Scheme 3-22).

![Chemical reactions]

Scheme 3-22 Woydowski synthesis of 3-hydroxychromanones.

In order to determine the stereochemistry about the double bond, future experiments could reduce the carbonyl under Luche conditions and subsequently conduct nOe experiments to observe the resulting enhancements (Figure 3-20).

![Chemical reactions]

Figure 3-20 nOe experiments on the Luche reduction product of 128 may define the stereochemistry of the naphthofuranone 128.
Previously in Section 2.9 an oxyacetylated benzo[f]chromanone (±)-73 - reported with undefined stereochemistry - was discussed. Benzo[f]chromanone (±)-73 was isolated in 9% from the oxidation and acetylation of benzo[f]chromene 77 (see Scheme 2-27, p26). Close inspection of the spectral data provided for benzo[f]chromanone (±)-73 suggested that it was the syn diastereomer, due to the coupling of H-2 and H-3 ($J_{2,3} = 4$Hz), which is typical for protons with an axial-equatorial disposition. In order to test this assumption, benzo[f]chromanone (±)-37, the precursor to the anti oxyacetylated diastereomer, was acetylated. A solution of benzo[f]chromanone (±)-37 in pyridine and acetic anhydride was stirred at room temperature for 16h to afford acetylated product 169 in good yield (Scheme 3-23).

![Scheme 3-23 Acetylation of benzo[f]chromanone 37. Conditions: a pyridine, Ac₂O, r.t. 16h, (±)-169 86%.

The spectral data reported by Begley and co-workers for oxyacetylated benzo[f]chromanone (±)-73' and the data obtained here for benzo[f]chromanone (±)-169, was not in agreement (Table 3-6). See also the NMR Spectral Comparison Table 3-10 and Table 3-11 for complete NMR assignments.

<table>
<thead>
<tr>
<th>Position</th>
<th>(±)-73 δ, int. mult. (J)</th>
<th>(±)-169 δ, int. mult. (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5.51, 1H, d (4Hz)</td>
<td>5.48, 1H, d (12.2Hz)</td>
</tr>
<tr>
<td>2OAc</td>
<td>2.08, 3H, s</td>
<td>2.29, 3H, s</td>
</tr>
<tr>
<td>3</td>
<td>4.48, 1H, m</td>
<td>4.71, 1H, dq (12.2, 6.3Hz)</td>
</tr>
<tr>
<td>3Me</td>
<td>1.43, 3H, d (7Hz)</td>
<td>1.59, 3H, d (6.3Hz)</td>
</tr>
<tr>
<td>Ar</td>
<td>7.66-7, 6H, m</td>
<td>9.36, 1H, d (8.7Hz)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.95-7.1 , 5H</td>
</tr>
</tbody>
</table>
The most significant difference lay in the shift of the resonance assigned to H-3 as well as the lack of a signal downfield (ca. 8.5-10 ppm) in the $^1$H NMR data of (±)-73, which was surprising for a purported benzo[f]chromanone. It was, however, the coupling of H-2 ($J_{2,3} = 4$ Hz) of (±)-73, when compared to that of (±)-169 ($J_{2,3} = 12.2$ Hz), which indicated that the compounds were not identical and were diastereomers. The coupling constant for protons of axial-equatorial disposition are in the order of 0-5 Hz, whilst those in axial-axial arrangement in the order of 6-14 Hz, thus, the acetoxybenzo[f] chromanone (±)-73 is believed to be the syn-diastereomer whereas (±)-169 is the anti-diastereomer.
3.2.3 Synthesis of 2-Hydroxy-2,3-dimethylbenzo[f]chromanone 136

The next synthetic target, 2-hydroxybenzo[f]chromanone 136, was made by deviating slightly from the method developed for the synthesis of benzo[f]chromanone (±)-37 (Scheme 3-24).

![Scheme 3-24: Sequence to generate benzo[f]chromanone 136. Conditions: a DCM, 0°C, N2, tigloyl chloride, AlCl3, 4h, 134 53%; b H2O2, NaOH(aq), THF, 0°C → r.t., 48h, (±)-135 87%; c DCM, AlCl3, N2, -20°C → r.t. 60h, (±)-136 16%.]

Acetylation of 2-methoxynaphthalene 117 with AlCl3 and freshly distilled tigloyl chloride (previously prepared by treating tiglic acid with SOCl2) gave α,β-unsaturated ketone 134 in a moderate yield of 53%, but also returned starting material 117 (39%). The fragmentation pattern and molecular ion (m/z = 240) of this novel compound was consistent with the proposed structure, and the exact mass was confirmed by HRMS.

Nucleophilic epoxidation of the conjugated double bond of α,β-unsaturated ketone 134 was executed in high yield to give epoxide (±)-135 in 87% as a racemate. The formation of this novel compound was supported by the appearance of a quartet at 3.03ppm consistent with the resonance of an epoxide proton,97 and the absence of a quartet for the olefinic proton at 6.38ppm. EIMS analysis presents a molecular ion (m/z = 256) and fragmentation pattern consistent with the compound structure, which is also confirmed by HRMS.

Epoxide (±)-135 was cyclised in dry DCM with AlCl3 (1 equiv.) at -20°C and monitored by GCMS. After 60h, all of the starting material had been consumed and the crude product was purified by flash chromatography to realize compounds (±)-136 and (±)-137 (Scheme 3-25). The low combined yield was due to loss of product during purification by column chromatography.
Scheme 3-25: Cyclisation of (±)-135. Conditions: a DCM, AlCl₃, N₂, -20°C, 60h, (±)-136 16%, (±)-137 33%.

The $^1$H NMR spectrum of (±)-136 (Figure 3-21) was very similar to that of the 2-hydroxy-benzo[f]chromanone (±)-37 (Figure 3-15, p.65) as it showed a downfield doublet at 9.35ppm, typical of benzo[f]chromanones, assigned to H-10 due to the anisotropic deshielding effect from the nearby carbonyl group. A quartet at 4.44ppm is typical of a phenol ether and has been assigned to H-3 in (±)-136. The absence of a singlet methoxy signal also suggests that epoxide (±)-135 has cyclised to form benzo[f]chromanone (±)-136. See also NMR Spectral Comparison Table 3-10 and Table 3-11. Based on the proposed mechanism of formation, as shown for benzo[f]chromanone (±)-37 in Figure 3-16, the stereochemistry of (±)-136 has been assigned as ($R^*R^*$).

Figure 3-21 $^1$H NMR spectrum of (±)-136 (CDCl₃, 300MHz).
The production of the novel benzo[f]chromanone (±)-136 was also supported by LRMS analysis whereby both the molecular ion \((m/z = 242)\) and fragmentation pattern are consistent with the structure of the desired product. HRMS analysis confirms the molecular weight of 2-hydroxybenzo[f]chromanone (±)-136.

The \(^1\)H NMR spectrum for (±)-137 shows a doublet at 8.72 ppm for the peri proton in the naphthalene system (Figure 3-22), as the deshielding is expected to be less pronounced in the furanone (±)-137 than in the pyrone (±)-136 due to the angle of the carbonyl moiety (see Figure 3-18, and also Figure 3-1).

![Figure 3-22: \(^1\)H NMR spectrum for (±)-137 (CDCl\(_3\), 300MHz).](image)

Unlike furanone 120, furanone (±)-137 was isolated as a single diastereomer. This may be explained by the lack of an epimerisable proton in the \(\alpha\)-position with respect to the carbonyl. The stereochemistry of naphthofuranone (±)-137, as \((R^*R^*)\), was assigned by the mechanism of formation as shown in Figure 3-16.
3.2.4 Attempted Synthesis of 2-Hydroxybenzo[f]flavanone 144

Flavanoids are natural products, often highly pigmented, found commonly in plants, fruit, nuts, seeds, honey, tea and wine. The class includes flavone 138, flavanone 139, flavonol 141, flavanon-3-ol 142, catechin 140 and chalcone 143. Recently, flavanoids have sparked interest in anti-infective research, with many flavanoids demonstrating antifungal, antiviral and antibacterial activity.

One of the target 2-hydroxybenzochromanones for the library of compounds for antimicrobial testing, was benzo[f]flavanol 144.

It can be seen that 144 is closely related to the flavanoids, but is based upon a naphthalene core. Despite the abundance of literature on flavanoids, benzo[f]flavanol 144 has not been reported. In order to make the flavanonol analogue, the same Friedel-Crafts methodology developed earlier was used. 2-Methoxynaphthalene 117 was acylated with AlCl₃ and freshly distilled cinnamoyl chloride (previously prepared from treating trans-cinnamic acid with SOCl₂) to return naphthochalcones 145 and 55 (Scheme 3-26). Demethylation of naphthochalcone 145 to give 55 may be averted with a shorter reaction time, however, this leads to incomplete consumption of starting material. Surprisingly, deprotection did not result in cyclisation as observed for the crotonyl analogue 79 (see Scheme 3-17).
Scheme 3-26 Friedel-Crafts acylation of 2-methoxynaphthalene. Conditions: a DCM, trans-cinnamoyl chloride, AlCl₃, N₂, 0°C→r.t. 16h, 145 34%, 55 39%.

Nucleophilic epoxidation of naphthochalcone 145 returned a racemate of epoxide 146 in good yield of 84% (Scheme 3-27). The trans-stereochemistry was retained about the epoxide bond, as indicated by the coupling between H-2' and H-3' ($^3J_{2,3} = 2.0$Hz) in the $^1$H NMR spectrum.

Scheme 3-27 Epoxidation of naphthochalcone 145. Conditions: a H₂O₂, NaOH(aq), THF, 0°C→r.t. 2h, (±)-146 84%.

Cyclisation of epoxide (±)-146 was unsuccessful. Previously cyclisations of the desphenyl epoxides analogues (±)-80 and (±)-135 were successful using AlCl₃, however, these standard conditions resulted in complex mixtures when trying to cyclise epoxide (±)-146. Changes in the amount of Lewis acid, reaction time, and temperature have been investigated, but cyclisation remained elusive and complex mixtures of methoxylated products were obtained. Table 3-7 details the experimental conditions tried for the cyclisation of epoxide (±)-146.

**Table 3-7 Reaction conditions tried for the cyclisation of epoxide (±)-146**

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Conditions</th>
<th>Time</th>
<th>Desired product detected by GCMS/NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 equiv. AlCl₃, 4°C, DCM, N₂</td>
<td>3d</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>1 equiv. AlCl₃, 0°C, DCM, N₂</td>
<td>20min</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv. AlCl₃, 4°C, DCM, N₂</td>
<td>1d</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>2 equiv. AlCl₃, r.t., DCM, N₂</td>
<td>1d</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>2 equiv. AlCl₃, -20°C, DCM, N₂</td>
<td>1d</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>Excess BBr₃, 0°C→r.t., DCM, N₂</td>
<td>3d</td>
<td>Y (&lt; 5%)</td>
</tr>
</tbody>
</table>
It has previously been observed that 1-cinnamoyl-2-methoxynaphthalene 145, when treated with AlCl₃, forms phenalenone derivative 147.⁷⁵,¹¹² Whilst no phenalenone derivatives were observed during the Friedel-Crafts acylation of 2-methoxynaphthalene 117 with trans-cinnamic acid (Scheme 3-26), it may be possible that cyclisation of the epoxide (±)-146 to form benzo[f]flavanonol 144 was prevented by preferential cyclisation to form phenalenone-type products. The complexity of the reaction mixtures, however, indicated that time would be better spent finding an alternative route to the desired benzo[f]flavanonol 144.

Scheme 3-28 Treatment of 1-cinnamoyl-2-methoxynaphthalene 145 with AlCl₃ will cyclise to form phenalenone derivative 147.⁷⁵,¹¹²

A common method of making flavonols is the Algar-Flynn-Oyamada reaction, or AFO oxidation.¹¹³ Alkaline H₂O₂ oxidation of 2'-hydroxychalcones 148 affords flavonols 150, but alternative products have been reported, including flavanonol 149 which were proposed as intermediates in the reaction (Scheme 3-29).¹¹³

Scheme 3-29 AFO oxidation of 2'-hydroxychalcones 148 affords flavonols 150.

Given that target compound 144 is a flavonoid analogue, its synthesis may be possible under AFO conditions. The appropriate starting material 2-hydroxychalcone 55 was generated in the Friedel-Crafts acylation of 2-methoxynaphthalene with cinnamoyl chloride (Scheme 3-26).

Bright yellow 2-hydroxychalcone 55 was dissolved in MeOH, and treated with 1N NaOH until a pH of 9 was reached. The reaction mixture was heated under reflux and the solution was subsequently treated with 30% v/v H₂O₂. Analysis of the reaction mixture indicated that cyclisation had occurred to form dihydrobenzo[f]chromane 48,
but oxidation had not occurred. The harsh conditions also resulted in decomposition of the starting material to 2-naphthol 41 (Scheme 3-30).

Scheme 3-30 Attempted AFO oxidation of naphthochalcone 55. Conditions: a MeOH, NaOH\textsubscript{(aq)} pH 9, H\textsubscript{2}O\textsubscript{2}, reflux 15 min, 48 45%, 41 53%.

During the course of their work on substituent effects on the AFO reaction, Cullen \textit{et al.} noticed the susceptibility of 3-phenylflavanone 151 to autooxidation. They suggested that autooxidation occurred after cyclisation of 2'-hydroxychalcone and subsequent enolisation. Their experiments showed that treatment with NaOH (1.5%) resulted only in cyclisation, however, addition of ethanol resulted in autooxidation to give flavanonol 152 (Scheme 3-31).\textsuperscript{95} When benzo[/\]flavanone 48 was treated under similar conditions, only starting material was returned.

Scheme 3-31 Autooxidation of 3-phenylflavanone 151 by Cullen \textit{et al.}\textsuperscript{95}

Due to the lack of success of preparing benzo[/\]flavanol 144, attention was turned to the preparation of 2-hydroxybenzo[/\]chromanone 153.
3.2.5 Attempted Synthesis of 2-Hydroxybenzo[f]chromanone 153

The route that was successful for the preparation of 2-hydroxybenzochromanones (±)-37 and (±)-136 was investigated for the synthesis of 2-hydroxybenzo[f]chromanone target 153.

When attempting to acylate 2-methoxynaphthalene 117 under Friedel-Crafts conditions with commercially available acryloyl chloride and AlCl₃ the reaction repeatedly generated dihydrophenalenone 158, instead of the expected α,β-unsaturated ketone 157.

Figure 3-23 Friedel-Crafts acylation of 2-naphthol 117 with acryloyl chloride 154 repeatedly generated dihydrophenalenone 155. Conditions: a AlCl₃ (1.1 equiv.), DCM, N₂, 0°C, 3h, 155 80%.

The ¹H NMR spectral data of 155 showed that the methoxy group was still present with a resonance at 3.99ppm. There were only 5 resonances in the aromatic region, indicating that substitution had occurred at two carbons on 2-methoxynaphthalene 117. Friedel-Crafts acylation would occur at C-1, ortho to the methoxy group, and should substitution occur elsewhere a singlet would be present in the aromatic region in the ¹H NMR spectrum. The lack of a singlet in the spectrum, and the coupling pattern of four doublets and one doublet-doublet, indicated that substitution had taken place at C-1 and C-8. Of the two apparent triplets (³J₂,₃ = 7.2Hz) assigned to methylene protons H-2 (2.92ppm) and H-3 (3.38ppm) the latter resonance was typical of a benzylic methylene. Characteristic mass spectrum fragmentation patterning and HRMS confirmed the structure of the dihydrophenalenone 155.
α,β-Unsaturated ketone 157 was presumably an intermediate in this reaction, as proposed in Figure 3-24, which cyclised at the activated C-8 peri position to form the dihydrophenalenone 158.

![Chemical structures](image)

**Figure 3-24 Proposed mechanism of Friedel-Crafts acylation and subsequent cyclisation.**

The formation of phenalenone 87 was observed in the reaction of 2-naphthol 41 with acrylic acid 86 in PPA (Scheme 3-3, p.40). The treatment of 1-cinnamoyl-2-methoxynaphthalene with AlCl₃ previously led to the formation of phenalenone 87, although, there were no phenalenone type products identified when 1-cinnamoyl-2-methoxynaphthalene was prepared using AlCl₃ previously in Section 3.2.4. When the respective crotonoyl and tigloyl analogues were prepared, there were no phenalenone type products isolated. The propensity for cinnamoyl and acryloyl analogues to behave differently was also observed in Section 3.1. When cyclising 2-naphthol and β-alkylated α,β-unsaturated acids in PPA, only benzo[β]chromanones formed. However, 2-naphthol and acrylic acid cyclised to form dihydrobenzocoumarin, and 2-naphthol and cinnamic acid formed a mixture of both dihydrobenzo[β]coumarin and benzo[β]chromanone products. The difference in reactivity may be explained by the possession of an electrophilic β-carbon in both acrylic acid and trans-cinnamic acid.

Despite the success in developing a reproducible sequence for the preparation of 2-hydroxybenzo[β]chromanones with alkyl substituents, such as (±)-37 and (±)-136, the same sequence was presenting difficulties for analogues with either aryl substituents, or no substituents at all.
Table 3-8 \( \alpha,\beta \)-Unsaturated Ketone and Epoxide \(^1\)H NMR Spectroscopic Data (300MHz, CDCl\(_3\))

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<th>(±)-146 (δ, Mult. (J in Hz))</th>
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Table 3-9 \( \alpha,\beta \)-Unsaturated Ketone and Epoxide \(^{13}\text{C}\) NMR Spectroscopic Data (300MHz, CDCl\(_3\))

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<td>112.4, CH</td>
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<td>129*</td>
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*Assigned by HMBC

Table 3-10 2-Hydroxybenzol[f]chromanone and Naphthofuranone \(^1\text{H}\) NMR Spectroscopic Data (300MHz, CDCl\(_3\))
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<th>(±)-136</th>
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Table 3-11 Hydroxybenzo[f]chromanone and Naphthofuranone $^{13}$C NMR Spectroscopic Data (300MHz, CDCl$_3$)
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</tr>
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<td>2'</td>
<td>16.9, CH₃</td>
<td>11.3, CH₃</td>
</tr>
<tr>
<td>2-CH₃</td>
<td>17.2, CH₃</td>
<td>-</td>
</tr>
</tbody>
</table>

84
3.3 Towards 2-Hydroxybenzo[\,f\,]chromanones

One aim of this work was to develop a general route towards these 2-hydroxybenzo[\,f\,]chromanones, and due to the problems experienced preparing targets 144 (Section 3.2.4) and 153 (Section 3.2.5), a different synthetic route was sought. Having previously identified a simple route for the preparation of a range of benzo[f]chromanones, we conjectured as to whether they could be used as the substrate on which to prepare 2-hydroxybenzo[\,f\,]chromanones. Retrosynthetic analysis of 2-hydroxybenzo[\,f\,]chromanones indicated that it could be formed from an epoxide derived from a benzo[f]chromone. Delivery of a nucleophilic reagent to the epoxide could install a side chain and open the epoxide to give 2-hydroxybenzo[\,f\,]chromanones (Scheme 3-32). This methodology, if successful, would present a general synthesis towards 2-hydroxybenzo[\,f\,]chromanones with the ability to introduce varying side chains.

![Scheme 3-32 Retrosynthetic analysis of 2-hydroxybenzo[\,f\,]chromanone.]

3.3.1 Attempted Benzo[\,f\,]chromone Epoxidation

A suitable benzo[\,f\,]chromone was prepared for subsequent epoxidation. Employing the standard polyphosphoric acid (PPA) cyclisation conditions 2-naphthol 41 and readily available crotonic acid were condensed in polyphosphoric acid (PPA) to generate benzo[\,f\,]chromanone (±)-53 in high yield. Following Bachman and Levine’s protocol\(^{38}\) (±)-53 was brominated then dehydrobrominated to afford benzo[\,f\,]chromone 58 (Scheme 3-33). The spectral data of benzo[\,f\,]chromone 58 compared favorably with that reported in the literature\(^{41}\).

![Scheme 3-33 Synthesis of unsaturated benzo[\,f\,]chromanone 58. Conditions: a PPA, crotonic acid, 60°C, 1.5h, (±)-53 92%; b Et\(_2\)O, Br\(_2\), 10min; c Et\(_3\)N, THF, 20h, 58 75%.]

85
With benzo[f]chromone 58 in hand, epoxidation experiments were conducted. Firstly, electrophilic epoxidation was tried with m-CPBA, however, no reaction occurred, returning only starting material (Table 3-12). Reasoning the double bond was electron poor due to conjugation with the carbonyl we turned our attention to nucleophilic methods. Klawonn and coworkers showed that bleach in basic conditions will epoxidise non-activated alkenes, but when tried on substrate 58 it proved ineffective (Table 3-12). Donnelly and co-workers were successful in epoxidising chromones under Weitz-Scheffer conditions. However, they found epoxidation of 2-methylchromone resulted in partial rearrangement to 2-methylchromonol 163 (Scheme 3-34).

$$\text{Scheme 3-34 The rearrangement of 2-methylchromone epoxide as proposed by Donnelly et al.}$$

Despite the problems experienced by Donnelly et al., Weitz-Scheffer conditions were tried on benzo[f]chromone 58, but resulted in decomposition of the starting material 58 (Table 3-12). When a weaker base was used, substituting NaHCO₃ for NaOH, as performed by Schuda and coworkers in the synthesis of hirsutic acid, starting material was returned. The epoxidation of chromones in ionic liquid was reported as high yielding. As a last resort, an ionic liquid 1-butyl-3-methyl imidazolium tetrafluoroborate, [bmim]BF₄, was prepared by a documented route, where 1-methylimidazole 164 and butyl chloride were refluxed overnight to give [bmim]Cl. The ionic liquid [bmim]BF₄ was prepared by treating [bmim]Cl with NaBF₄ (Scheme 3-35). Subsequent epoxidation of substrate 58 in the ionic liquid was no more effective than the other methods tried (Table 3-12).

* Sodium hypochlorite
Scheme 3-35 Synthesis of ionic liquid 1-butyl-3-methyl imidazolium tetrafluoroborate

165. Conditions: a Butyl chloride, reflux, 75°C, 16h; b NaBF₄, H₂O, 1h.

Table 3-12 Experimental Conditions for the Attempted Epoxidation of Benzo[f]chromone 58

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Solvent</th>
<th>Time</th>
<th>Epoxide detected</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 m-CPBA, r.t.</td>
<td>DCM</td>
<td>16h</td>
<td>N</td>
<td>Starting material</td>
</tr>
<tr>
<td>2 NaClO</td>
<td>Pyridine</td>
<td>16h</td>
<td>N</td>
<td>Starting material</td>
</tr>
<tr>
<td>3 H₂O₂, 1N NaOH, 0°C</td>
<td>THF</td>
<td>20h</td>
<td>N</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4 H₂O₂, 1N NaOH,</td>
<td>EtOH</td>
<td>24h</td>
<td>N</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5 H₂O₂, 4N NaOH,</td>
<td>MeOH</td>
<td>16h</td>
<td>N</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6 H₂O₂, KOH (cat)</td>
<td>THF</td>
<td>1h</td>
<td>N</td>
<td>Starting material</td>
</tr>
<tr>
<td>7 H₂O₂, NaHCO₃, 0°C</td>
<td>Acetone</td>
<td>1h</td>
<td>N</td>
<td>Starting material</td>
</tr>
<tr>
<td>8 H₂O₂, NaOH(s), 0°C</td>
<td>[bmim]BF₄</td>
<td>3h</td>
<td>N</td>
<td>Starting material</td>
</tr>
</tbody>
</table>

A lack of success in the epoxidation of the benzo[f]chromanones under a variety of conditions can be explained by the reactivity of the pyrone ring. The propensity for nucleophilic addition to occur at C-3 of benzo[f]chromones may have led to substitution by hydroxide at this position with subsequent ring-opening of the pyrone moiety. Recyclisation would have occurred on acidification to return starting material (see entries 6-8, Table 3-12). Prolonged treatment with base, however, resulted in decomposition of benzo[f]chromone 58 to 2-hydroxy-1-naphthoic acid 166 (Figure 3-25). This type of hydrolytic cleavage was acknowledged in the literature.¹¹⁹

Considering the abundance of literature on the epoxidation of chromones it is anticipated that benzo[f]chromones can be epoxidised, however, it may be necessary to use non-basic conditions. The reagent dimethyldioxirane has been used for the non-basic epoxidation of flavones, hence this reagent may be ideal to try in future reactions.
3.3.2 Attempted Benzo[\(f\)]chromanone Acetoxylation

With the lack of success in the epoxidation of benzo[\(f\)]chromone 58, an alternate method of oxidizing the pyrone ring was sought. Manganese(III) triacetate mediated direct acetoxylation was used by Demir and co-workers to produce 3-hydroxychromanone 168 from chromanone 23 in excellent yield (Scheme 3-36).\(^{120}\)

In order to attempt this method for the acetoxylation of benzo[\(f\)]chromanones it was necessary to first prepare the manganic acetate dihydrate (Mn(OAc)\(_3\).2H\(_2\)O), following the method of Andrulis.\(^{121}\) A solution of benzene and freshly prepared Mn(OAc)\(_3\).2H\(_2\)O was heated under reflux for 45 min in a Dean-Stark apparatus before the addition of benzo[\(f\)]chromanone 53. The suspension was refluxed over a period of 48 h. Work up revealed that acetoxylation had not occurred and only starting material was returned (Scheme 3-37).
The reactivity of Mn(OAc)$_3$ has been shown to depend on the way it is synthesised. As such, commercial Mn(OAc)$_3$ was obtained, and used to treat benzo[f]chromanone (±)-53 under similar conditions. Again, only starting material was returned. Demir et al. suggested that Mn(OAc)$_3$ acetoxylation can be optimized by drying the reagent extensively, and that yields can be improved by adding AcOH to the benzene.\textsuperscript{122} However, as no reaction was observed with benzochromanone (±)-53, optimization was not the issue. Despite the abundant literature on the acetoxylation of chromanones,\textsuperscript{122} there were no examples of acetoxylation of benzo[f]chromanones available. It may be possible that the angle of the carbonyl, with respect to the naphthyl group, was preventing favourable co-ordination of the manganic acetate and thus impeding acetoxylation of the α-carbon (Figure 3-26).

![Figure 3-26 Congested co-ordination of manganic acetate may prevent acetoxylation of benzochromanone (±)-53.](image)

3.3.3 Attempted Benzo[f]chromanone Enol Protection

While searching for another method to install a hydroxyl group alpha to the carbonyl moiety of benzo[f]chromanone 53, the sequence used by Wrobel and co-workers to oxidize cyclic ketone 170\textsuperscript{123} was found. Conversion of ketone 170 to the α-hydroxy ketone 171 (Scheme 3-38) was utilised in the synthetic route towards conformationally rigid analogues of Tolrestat, an aldose reductase inhibitor.\textsuperscript{123}

![Scheme 3-38 Reaction conditions: a CF$_3$SO$_2$SiMe$_3$, TEA, benzene, N$_2$, 0°C
15min→10°C 1h, 97%; b m-CPBA, hexane, N$_2$, -30°C 30min→0°C 10 min; c 1.5N HCl, ether, r.t. 17h, 171 90%.](image)
In order to follow Wrobel's synthetic sequence benzo[f]chromanone (±)-53 would need to be trapped as the silyl ether (±)-172. Electrophilic epoxidation of the silyl enol ether (±)-172 to give 173, followed by deprotection, could potentially give 2-hydroxybenzo[f]chromanone 37 (Scheme 3-39).

![Scheme 3-39 Proposed synthesis towards hydroxylated benzo[f]chromanones.](image)

Table 3-13 details the experimental conditions explored in trying to prepare the silyl enol ether 172. In all cases, the reaction was not successful, returning only starting material. Initially TEA was used as the base, however fruitless results indicated a stronger base was required. NaH was tried at both 0°C and at reflux in THF, but again only starting material was returned. The use of ZnCl₂ was employed to increase the acidity of the α-proton, but still only starting material was returned.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Solvent</th>
<th>Time</th>
<th>172 observed</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 TEA, TMSCl,</td>
<td>DCM, 0°C</td>
<td>16h</td>
<td>No</td>
<td>Starting material</td>
</tr>
<tr>
<td>2 NaH, TMSCl,</td>
<td>THF, 0°C</td>
<td>7h</td>
<td>No</td>
<td>Starting material</td>
</tr>
<tr>
<td>3 NaH, TMSCl,</td>
<td>THF, reflux</td>
<td>2h</td>
<td>No</td>
<td>Starting material</td>
</tr>
<tr>
<td>4 NaH, TMSCl, ZnCl₂</td>
<td>THF, reflux</td>
<td>48h</td>
<td>No</td>
<td>Starting material</td>
</tr>
</tbody>
</table>

The active methylene group of chroman-4-ones is evident in the facile halogenation of these compounds to prepare α-halogenated species.\(^{22}\) Direct bromination of benzo[f]chromanones readily affords 2-bromo derivatives in good yields,\(^{38,44}\) and bromination of benzo[f]chromanone (±)-53 was achieved as a precursor to benzo[f]chromone 58 (Scheme 3-33). However, the behaviour of the methylene group is often unpredictable,\(^{22}\) for example, treatment of chroman-4-one 23 with MeI and NaH failed to give the methylated derivative 174 (Scheme 3-40),\(^{22}\) and the lack of examples of 2-alkyl chromanones prepared by direct alkylation of 4-chromanone highlights the
difficulty associated with such a reaction. Colonge and Guyot, however, were able to prepare methylated benzo[f]chromanone (±)-175 by treating the benzo[f]chromanone 40 with Mel in xylene in the presence of sodium t-pentoxide (Scheme 3-41).\textsuperscript{44} 

Scheme 3-40 The difficulty of preparing alkylated chroman-4-ones by direct alkylation is illustrated by the failure to prepare chroman-4-one 174.

Scheme 3-41 Colonge and Guyot were successful in methylating benzo[f]chromanone 40 using sodium t-pentoxide and Mel in benzene.

It may be necessary to deprotonate benzo[f]chromanone (±)-53 using a stronger base, such as sodium t-pentoxide as used by Colonge and Guyot,\textsuperscript{44} in order to follow Wrobel's\textsuperscript{123} synthetic sequence. The ability of the pyrone ether oxygen of benzo[f]chromanones to delocalize electron density to the pyrone carbonyl may lower the acidity of the α-proton (Figure 3-27), thus, a stronger base is required than TEA used by Wrobel for the silylation of cyclohexanone 170. The steric bulk of the silyl group of the enol ether (±)-172 lies out of the plane of the naphthyl group, thus, steric hindrance is not considered to be problematic.

Figure 3-27 Delocalisation of electrons through the vinylogous ester moiety of benzo[f]chromanone (±)-53 may decrease the acidity of the α-proton.
3.4 Testing for Antibacterial Activity

With a collection of naphthalene based compounds in hand we were ready for antimicrobial testing. Of the compounds prepared, 31 were subjected to qualitative testing for antibacterial inhibitory activity using the disk diffusion method as detailed in the Experimental Section 4.2. The compounds were screened against Gram-negative *Pseudomonas aeruginosa* and *Escherichia coli*, and Gram-positive *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Mycobacterium smegmatis*. These organisms were selected as they represent pathogens from numerous clinical conditions and are responsible for significant morbidity. The results of the testing were summarized into tables according to the general structure of the compound: the benzochromanones, including benzo[f]chromone, benzo[f]chromanones, and benzo[h]chromanone (Table 3-14, p.95); the five membered rings structures of the cyclopentanones and naphthofuranones (Table 3-15, p.95); the benzo coumarins, including benzo[f]coumarin and dihydrobenzo[f]coumarins (Table 3-16, p.96); and the miscellaneous group of naphthyl vinyl ketones, epoxides, and phenalenone products (Table 3-17, p.96). If a compound exhibited antibacterial activity, a ring of inhibited bacterial growth was apparent around the disk impregnated with the compound of interest after 24h. If the disks were impregnated with approximately 1mg of compound. The size of the zone of inhibition was noted in the result tables and a dash (-) signified that a compound showed no activity.

The results, in general, were promising as 70% of the compounds tested were shown to exhibit antibacterial activity towards the Gram-positive species, although none showed activity towards Gram-negative *P. aeruginosa* or *E. coli*.

In general, all the groups tested showed activity, except for the epoxides (±)-80, (±)-135 and (±)-146, which, as a group, showed no activity at all. In comparison, of the miscellaneous group, the naphthyl vinyl ketones 55, 79 and 134 showed good activity, which may be attributed their α,β-unsaturated ketone side chain acting as a Michael acceptor. Of the phenalenones, the dihydrophenalenone 158 also showed a weak activity, and activity was stronger for phenalenone 87. Again, it may have been the action of a Michael acceptor in the latter phenalenone, providing the enhanced biological activity (Table 3-17). Phenalenones have previously been reported to possess antibacterial properties towards *S. aureus*.

Of the benzochromanones in general, this group showed moderate activity, although benzo[f]chromanone 40 did not show any activity towards the bacteria tested.
Benzochromone 58 did not exhibit activity, despite its ability to act as a Michael acceptor, nor did its saturated derivative 53. Modifications to this scaffold, however, such as hydroxylation on either the pyrone moiety, e.g. 37, or on the aromatic moiety, e.g. (±)-103, resulted in activity. The location of the hydroxyl moiety was found to be important, as benzochromanone (±)-115 was found not to induce inhibition. The hydroxyl groups may increase solubility, binding, or both, as it was found that when the group was protected, for example acetoxy benzochromanone (±)-169, a reduction in activity and spectrum was observed. Interestingly, diastereomers (±)-84 and (±)-85 showed a difference in activity, whereby *trans*-benzo[f]chromanone (±)-84 showed no activity towards *S. epidermidis*, unlike *syn*-benzo[f]chromanone (±)-85. Of the benzochromanones, it was the natural product analogue benzo[h]chromanone (±)-95 that showed the largest zones of inhibition. The disk diffusion method is limited by the solubility of the compounds tested, however, due to the possession of identical functional groups, the solubility of (±)-95 would not vary greatly from that of its isomer (±)-53, and as such, natural product analogue held greater promise as an antibacterial lead.

The benzocoumarins also showed general inhibitory action towards the Gram-positive bacteria. In particular, the novel dihydrobenzocoumarin (±)-112 showed the greatest zones of inhibition, with the activity diminishing slightly upon protection of the aromatic hydroxyl group, e.g. (±)-113. A decrease in activity, as indicated by a decreased zone of inhibition, was also observed for cyclopentanone (±)-96 and its O-protected derivative (±)-101. The spectrum was also reduced to activity towards only *S. epidermidis* and *M. smegmatis* for the latter. Lastly, the naphthofuranone compounds also showed activity, with large zones of inhibition around 128 especially. The activity associated with this compound may stem from its ability to act as a Michael acceptor. Interestingly, rifampicin, a potent antibiotic for the treatment of tuberculosis, also contains a naphthofuranone core (Figure 3-28).

![Figure 3-28 Potent antimycobacterial rifampicin possesses a naphthofuranone core (red).](image-url)
In summary, naphthalene based compounds showed promise as antibacterial agents, with both benzochromanones and benzocoumarins exhibiting activity towards Gram-positive bacteria. However, in general, it appears that of the compounds observed in this study, the compounds that can act as Michael acceptors resulted in the greatest zones of inhibition e.g. 128 and 79, and interestingly, compounds that are hydroxylated para to C-1 of the naphthyl moiety, e.g. (±)-112, (±)-103, and (±)-96 also show good activity. In addition, the natural product analogue benzo[h]chromanone (±)-95 also showed interesting activity. Hence, this study has shown that benzo[h]chromanones possess antibacterial activity, although activity is not just limited to chromanones, but also to related compounds such as coumarins and furanones. Pentanones, as well as vinyl ketones, with a naphthyl moiety also possess activity.
Table 3-14 Results from Preliminary Antibacterial Testing: Benzochromanones.

<table>
<thead>
<tr>
<th>P. aeruginosa</th>
<th>E. coli</th>
<th>S. aureus</th>
<th>S. epidermidis</th>
<th>M. smegmatis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-85</td>
<td>1mm</td>
<td>1mm</td>
<td>1mm</td>
<td>1mm</td>
</tr>
<tr>
<td>(±)-84</td>
<td></td>
<td>1mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(±)-48</td>
<td>1mm</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(±)-103</td>
<td></td>
<td>-</td>
<td>1mm</td>
<td>2mm</td>
</tr>
<tr>
<td>(±)-115</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(±)-37</td>
<td>1mm</td>
<td>1mm</td>
<td>1mm</td>
<td></td>
</tr>
<tr>
<td>(±)-136</td>
<td></td>
<td>-</td>
<td>1mm</td>
<td></td>
</tr>
<tr>
<td>(±)-169</td>
<td></td>
<td>-</td>
<td></td>
<td>1mm</td>
</tr>
<tr>
<td>(±)-95</td>
<td></td>
<td>-</td>
<td>1mm</td>
<td>3mm</td>
</tr>
</tbody>
</table>

Table 3-15 Results from Preliminary Antibacterial Testing: Indanone and Furanones.

<table>
<thead>
<tr>
<th>P. aeruginosa</th>
<th>E. coli</th>
<th>S. aureus</th>
<th>S. epidermidis</th>
<th>M. smegmatis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-137</td>
<td></td>
<td>1mm</td>
<td>1mm</td>
<td>1mm</td>
</tr>
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<td>(±)-101</td>
<td></td>
<td>-</td>
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### Table 3-16 Results from Preliminary Antibacterial Testing: Benzocoumarins

<table>
<thead>
<tr>
<th>Compound</th>
<th>P. aeruginosa</th>
<th>E. coli</th>
<th>S. aureus</th>
<th>S. epidermidis</th>
<th>M. smegmatis</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(±)-91</td>
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<td>1 mm</td>
</tr>
<tr>
<td>(±)-112</td>
<td>-</td>
<td>-</td>
<td>2 mm</td>
<td>5 mm</td>
<td>4 mm</td>
</tr>
<tr>
<td>(±)-113</td>
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<td>-</td>
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<td>4 mm</td>
<td>3 mm</td>
</tr>
<tr>
<td>32</td>
<td>-</td>
<td>-</td>
<td>(4 mm)‡‡</td>
<td>-</td>
<td>1 mm</td>
</tr>
</tbody>
</table>

### Table 3-17 Results from Preliminary Antibacterial Testing: Miscellaneous

<table>
<thead>
<tr>
<th>Compound</th>
<th>P. aeruginosa</th>
<th>E. coli</th>
<th>S. aureus</th>
<th>S. epidermidis</th>
<th>M. smegmatis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
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<td>(±)-135</td>
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<td>(±)-146</td>
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<td>79</td>
<td>-</td>
<td>-</td>
<td>3 mm</td>
<td>3 mm</td>
<td>5 mm</td>
</tr>
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<td>-</td>
<td>2 mm</td>
<td>2 mm</td>
<td>3 mm</td>
</tr>
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<td>145</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<td>158</td>
<td>-</td>
<td>-</td>
<td>1 mm</td>
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<td>2 mm</td>
</tr>
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<td>87</td>
<td>-</td>
<td>-</td>
<td>1 mm</td>
<td>3 mm</td>
<td>3 mm</td>
</tr>
</tbody>
</table>

‡‡ After 48h
3.5 Conclusion, and Future Work

The polyphosphoric acid (PPA) cyclisation method was chosen for the preparation of the library of benzo[f]chromanones because of its high yielding, one-pot simplicity. It was found that PPA cyclisation was suitable for the preparation of alkylated benzo[f]chromanones when reacting β-alkylated-α,β-unsaturated acids with 2-naphthol, and resulted in the isolation of 2 novel diastereomeric compounds. Complications arose when using acrylic acid and derivatives, or trans-cinnamic acid, for PPA cyclisation with 2-naphthol as these substrates gave coumarin-type products, or a mixture of coumarins and chromanones. Investigations were initiated to determine whether the reaction conditions could be manipulated to generate a specific outcome, however under the conditions examined, this was found not to be the case.

PPA cyclisation was also investigated for its applicability for the synthesis of natural product benzo[f]chromanones. Whilst cyclisation of 1-naphthol with α,β-unsaturated acids was as expected, complications arose with increasing complexity of the naphthalene substrate. The general propensity of reagents to react in the peri position of polyfunctionalised naphthalene limits the usefulness of this method. However, investigations down this path led to the isolation of 5 novel compounds.

Preparation of 2-hydroxybenzo[f]chromanones began with several unsuccessful attempts following the McCulloch approach. Modification of his method resulted in a reproducible sequence with an increased total yield of (±)-37, and spectral analysis allowed the putative structure to be confirmed. The generality of this method for the preparation of 2-hydroxybenzo[f]chromanones was demonstrated for alkylated analogues with the subsequent preparation of (±)-136. Problems arose when using this method for the preparation of the phenyl analogue, as well as the unsubstituted analogue. Nonetheless, 8 novel compounds were prepared, isolated, and characterised during the course of these investigations. In addition, the unanticipated preparation of both naphthocyclopentanone and naphthofuranones led to the identification of novel routes towards these types of compounds. Further work is required to confirm the stereochemistry of naphthofuranone 128. This could be achieved by Luche reduction of the carbonyl moiety, followed by nOe experiments. Observation of the resulting enhancements would indicate the stereochemistry about the double bond.
Investigations into alternative synthetic methods for the preparation of 2-hydroxybenzo[f]chromanones via epoxidation of the chromone derivative, or acetoxylation or silylation of the chromanone were unfruitful. Epoxidation may be possible using an alternative reagent, such as dimethyldioxirane, that does not require the presence of base. Silylation of benzo[f]chromanones may be possible if a strong base such as sodium t-pentoxide is used to promote enolisation.

With a library consisting of not only 9 benzo[f]chromanones, but also related compounds benzo[f]chromone, benzo[h]chromanone, dihydrobenzo[f]coumarins, benzo[f]coumarin, phenalenone, dihydrophenalenone, naphthocyclopentanones, naphthofuranones, naphthyl vinyl ketones and epoxides, we undertook biological testing. Of the compounds prepared in this work, 30 were subjected to qualitative antibacterial testing against Gram-negative Pseudomonas aeruginosa and Escherichia coli, and Gram-positive Staphylococcus aureus, Staphylococcus epidermidis and Mycobacterium smegmatis. The outcome was very optimistic with 70% of compounds exhibiting activity towards Gram-positive bacteria. None showed activity towards P. aeruginosa or E. coli.

Benzochromanones in general exhibited moderate activity, with a slight increase in activity when they contain a hydroxyl group in the pyranone ring. SAR investigations revealed that compounds based on the naphthalene scaffold do not necessarily require a pyrone ring for activity, and that activity was enhanced for compounds possessing a Michael acceptor functionality or a hydroxyl group para to C-1. The greatest zones of inhibition were observed for natural product analogue benzo[h]chromanone (±)-95, and novel compounds dihydrocoumarin (±)-112, naphthofuranone 128, and αβ-unsaturated ketone 79.
It would be an interesting exercise to prepare naphthofuranone analogues possessing a Michael acceptor and a hydroxyl group *para* to C-1. These could potentially be made by subjecting naphthoresorcinol to similar reaction conditions used for the preparation of naphthofuranone128 (Figure 3-29).

Of the compounds shown to exhibit activity, those possessing a free hydroxyl group would be ideal targets to glycosylate. Glycosylation can often improve drug solubility without altering activity, however activity and biotargeting is often improved.

Further optimization and investigation of the active compounds is required, as with good activities towards *M. smegmatis*, a non virulent model organism for *M. tuberculosis*, they currently represent leads towards novel antibacterial agents with implications in the treatment of tuberculosis.
4 Experimental

4.1 General Experimental Procedures

$^1$H NMR spectra were recorded on a Varian Inova 300 spectrometer operating at 300MHz or, where indicated, a Varian Inova 500 spectrometer operating at 500MHz. When run in deuterated methanol (CD$_3$OD), the chemical shifts (δ) are expressed in ppm, relative to the central peak of the residual protonated solvent resonance at 3.30ppm. When run in deuterated chloroform (CDCl$_3$), the chemical shifts (δ) are expressed in ppm, relative to the residual protonated solvent resonance at 7.26ppm. The following abbreviations are used to describe the multiplicity of the observed resonances: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), appt. (apparent), co-in (coincidental), and shoulder (sh).

$^{13}$C NMR spectra were recorded using the Attached Proton Test (APT) on a Varian Inova 300 spectrometer operating at 75MHz, or a Varian Inova 500 spectrometer operating at 125MHz. Chemical shifts (δ) are expressed in ppm relative to the central peak of CD$_3$OD (49.0ppm) or the central peak of CDCl$_3$ (77.0ppm) as appropriate.

Two-dimensional NMR experiments (COSY, HMQC, HMBC) were recorded on a Varian Inova 300 spectrometer operating at 300MHz, or a Varian Inova 500 spectrometer operating at 500MHz, and were used to support assignments made.

Analytical TLC was carried out on aluminium backed Merck silica gel 60 F$_{254}$ and visualised using visible light and/or short-wave UV light and/or by development utilising ceric phosphomolybdic acid dip where appropriate.

Melting points (m.p.) stand uncorrected and were recorded with a Leica Galen III microscope. The compounds tested were amorphous (amorph.) or crystalline whereby the solvent, from which the crystals formed, is quoted.

IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR as a thin film on NaCl plates. Peak strength is described using the above abbreviations: s (strong), m (medium), w (weak), br (broad), sh (shoulder).
UV spectra were measured on a Cary 4G UV-Visible Spectrophotometer using a 1cm solution cell in the solvent indicated. Spectra maxima, $\lambda_{\text{max}}$, were given in nm, with the extinction coefficients ($\log \epsilon$). The abbreviation “sh” is used to describe absorbances that appear as a shoulder.

EI-MS and HREI-MS were recorded on a VG autospec mass spectrometer, operating at 70eV using positive ion detection. Mass spectra are recorded in mass/charge ratios ($m/z$) and relative abundance (% intensity of most intense peak).

Compounds are reported based on the name generated by the software package ChemBioDraw Ultra® v11.0. The numbering system has remained consistent with the literature conventions.

4.1.1 General Method of Cyclisation of $\alpha,\beta$-Unsaturated Acids with 2-Naphthol Utilising Polyphosphoric Acid

4.1.1.1 Preparation of polyphosphoric acid (PPA).
$\text{P}_2\text{O}_5$ (8.15g) stirred with $\text{H}_2\text{PO}_4$ (5mL) at 60°C until dissolved.47

4.1.1.2 General Polyphosphoric Acid (PPA) Cyclisation Method.
A solution of sublimed 2-naphthol 41 (2.0mmol) and $\alpha,\beta$-unsaturated acid (2.30mmol) in PPA (5g) was stirred at 60°C until all of the starting material had been consumed. The solution was diluted with ice and $\text{H}_2\text{O}$, and extracted exhaustively with DCM. The organic phase was dried (MgSO$_4$), filtered, and concentrated in vacuo to give crude product which was purified by flash column chromatography (silica gel (0.040-0.063mm).

4.1.1.2.1 (±)-3-Methyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-53
Light yellow amorphous solid, yield 92% (crotonic acid 82, stirring time 1.5h), recrystallised (PS).
M.p.: 74-75°C (from PS).
IR: $\nu$ (cm$^{-1}$): 2924 m, 1667 s, 1512 s, 1435 s, 1373 s. EIMS $m/z$ 212 [M$^+$] (76), 197 (8), 170 (100), 142 (22), 114 (35). HREI-MS $m/z$ 212.0838 (calcd for C$_{14}$H$_{12}$O$_{2}$, 212.0837). UV (DCM) $\lambda_{\text{max}}$ (log $\epsilon$): 225 (4.5), 241 sh (4.37), 264 sh (4.01), 313 (3.89).
NMR (CDCl$_3$, 300MHz): $\delta 9.45$ (1H, d, $J = 8.1$Hz, H-10), 7.91 (1H, d, $J = 9.0$Hz, H-6), 7.74 (1H, d, $J = 7.8$Hz, H-7), 7.63 (1H, dd, $J = 8.1$, 7.8Hz, H-9), 7.42 (1H, dd, $J = 7.8$, 7.8Hz, H-8), 7.10 (1H, d, $J = 9.0$Hz, H-5), 4.71 (1H, ddq, $J = 12.0$, 4.2, 6.6Hz, H-3), 2.83 (1H, dd, $J = 16.2$, 12.0Hz, H$_a$-2), 2.75 (1H, dd, $J = 16.2$, 4.2Hz, H$_b$-2), 1.56 (3H, d, $J = 6.6$Hz, H-3 CH$_3$).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) $\delta 195.8$ (qC, C-1), 162.9 (qC, C-4a), 137.0 (CH, C-6), 131.6 (qC, C-10a), 129.4 (CH, C-9), 129.1 (qC, C-6a), 128.3 (CH, C-7), 125.6 (CH, C-10), 124.6 (CH, C-8), 118.7 (CH, C-5), 111.6 (qC, C-10b), 79.0 (CH, C-3), 47.3 (CH, C-2), 19.6 (CH$_3$, C-3 CH$_3$).

4.1.1.2.2 (±)-2,3-Dimethyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-84

Off white needles, yield 30% (tiglic acid 83, stirred 20h), purified by flash column chromatography on silica gel (DCM) with (±)-85.

M.p.: 41-43°C (DCM).

IR: $\nu$ (cm$^{-1}$): 2978 m, 1670 s, 1616 m, 1597 m, 1512 s, 1512 s, 1276 m.

EIMS $m/z$ 226 [M$^+$] (50), 170 (100), 142 (20), 114 (30).

HREI-MS $m/z$ 226.0997 (calcd for C$_{12}$H$_{14}$O$_2$, 226.0994).

UV (DCM) $\lambda_{max}$ (log $\varepsilon$): 226 (4.52), 241 sh (4.40), 265 sh (4.03), 312 (3.92).

1H NMR (CDCl$_3$, 300MHz): $\delta 9.47$ (1H, dd, $J = 8.7$, 0.9Hz, H-10), 7.89 (1H, d, $J = 9.0$Hz, H-6), 7.73 (1H, dd, $J = 8.1$, 1.4Hz, H-7), 7.62 (1H, ddd, $J = 8.7$, 7.1, 1.4Hz, H-9), 7.41 (1H, ddd, $J = 8.1$, 7.1, 0.9Hz, H-8), 7.08 (1H, d, $J = 9.0$Hz, H-5), 4.73 (1H, dq, $J = 11.7$, 6.3Hz, H-3), 2.66 (1H, dq, $J = 11.7$, 7.1Hz, H-2), 1.56 (3H, d, $J = 6.3$Hz, H-3 CH$_3$), 1.27 (3H, d, $J = 7.1$Hz, H-2 CH$_3$).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) $\delta 195.8$ (qC, C-1), 162.9 (qC, C-4a), 137.0 (CH, C-6), 131.6 (qC, C-10a), 129.4 (CH, C-9), 129.1 (qC, C-6a), 128.3 (CH, C-7), 125.6 (CH, C-10), 124.6 (CH, C-8), 118.7 (CH, C-5), 111.6 (qC, C-10b), 79.0 (CH, C-3), 47.3 (CH, C-2), 19.6 (CH$_3$, C-3 CH$_3$), 10.7 (CH$_3$, C-2 CH$_3$).

4.1.1.2.3 (±)-2,3-Dimethyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-85

Light tan oil, yield 38% (tiglic acid 83, stirred 20h), purified by flash column chromatography on silica gel (DCM) with (±)-84.

M.p.: 41-43°C (DCM).

IR: $\nu$ (cm$^{-1}$): 2978 m, 1670 s, 1620 m, 1597 m, 1273 m, 1234 s.

EIMS $m/z$ 226 [M$^+$] (50), 170 (100), 142 (20), 114 (30).
HREI-MS m/z 226.0997 (calcd for C_{15}H_{14}O_{2}, 226.0994).

UV (DCM) $\lambda_{\text{max}}$ (log $\varepsilon$): 225 (4.50), 240 sh (4.40), 264 sh (4.01), 312 (3.91).

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 9.47 (1H, dd, $J = 8.6$, 0.9Hz, H-10), 7.89 (1H, d, $J = 9.0$Hz, H-6), 7.73 (1H, dd, $J = 8.3$, 1.4Hz, H-7), 7.62 (1H, ddd, $J = 8.3$, 7.1, 0.9Hz, H-9), 7.40 (1H, ddd, $J = 8.3$, 7.1, 0.9Hz, H-8), 7.08 (1H, d, $J = 9.0$Hz, H-5), 4.73 (1H, dq, $J = 3.5$, 6.6Hz, H-3), 2.70 (1H, dq, $J = 3.5$, 7.2Hz, H-2), 1.45 (3H, d, $J = 6.6$Hz, H-3CH$_3$), 1.19 (3H, d, $J = 7.2$Hz, H-2 CH$_3$).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) $\delta$ 197.6 (qC, C-1), 162.8 (qC, C-4a), 137.1 (CH, C-6), 131.8 (qC, C-10a), 129.4 (CH, C-9), 129.1 (qC, C-6a), 128.3 (CH, C-7), 125.6 (CH, C-10), 124.6 (CH, C-8), 118.7 (CH, C-5), 110.9 (qC, C-10b), 76.4 (CH, C-3), 46.2 (CH, C-2), 16.0 (CH$_3$, C-3 CH$_3$), 9.3 (CH$_3$, C-2 CH$_3$).

4.1.1.2.4 1H-benzo[f]chromen-3(2H)-one 31

Tan oil, yield 53% (acrylic acid 86, stirred 20h), purified by flash column chromatography on silica gel (DCM) with 87.

IR: $\nu$ (cm$^{-1}$): 3063 w, 1767 s, 1627 m, 1358 m, 1265 m, 1223 s.

EIMS m/z 198 [M$^+$] (100), 182 (21), 170 (88), 169 (88), 156 (80), 141 (58), 128 (90), 115 (51), 102 (28).

HREI-MS m/z 198.0682 (calcd for C$_{13}$H$_{10}$O$_2$, 198.0681).

UV (DCM) $\lambda_{\text{max}}$ (log $\varepsilon$): 231 (4.74), 280 (3.75).

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.90 (1H, bd, $J = 8.4$Hz, H-10), 7.86 (1H, bd $J = 8.0$Hz, H-7), 7.78 (1H, d, $J = 9.1$Hz, H-6), 7.59 (1H, bdd, $J = 8.4$, 7.1Hz, H-9), 7.48 (1H, bdd, $J = 8.0$, 7.1Hz, H-8), 7.24 (1H, d, $J = 9.1$Hz, H-5), 3.38 (2H, appt. t, $J = 7.5$Hz, H-1), 2.94 (2H, appt. t, $J = 7.5$Hz, H-2).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) $\delta$ 168.0 (qC, C-3), 149.2 (qC, C-4a), 130.7 (qC, C-10a), 130.4 (qC, 6a), 128.5 (CH, C-7), 128.4 (CH, C-6), 126.8 (CH, C-9), 124.8 (CH, C-8), 122.5 (CH, C-10), 117.0 (CH, C-5), 115.2 (qC, C-10b), 28.1 (CH$_2$, C-2), 19.4 (CH$_2$, C-1).

4.1.1.2.5 1H-Phenalen-1-one 87

Bright yellow amorphous solid, yield 5% (acrylic acid 86, stirred 20h), purified by flash column chromatography on silica gel (DCM) with 31.

M.p.: 152-154°C (amorph.).

IR: $\nu$ (cm$^{-1}$): 3059 w, 1643 s, 1620 m, 1578 s, 1393 m, 1358 m, 1099 m.
EIMS \textit{m/z} 180 [M$^+$] (88), 152 (100), 126 (10), 98 (6), 87 (6), 76 (25).
HREI-MS \textit{m/z} 180.0575 (calcd for C$_{13}$H$_8$O$_0$, 180.0575).
UV (DCM) $\lambda$ \text{max} (log $e$): 228 (4.06), 248 (4.22), 359 (3.86).
$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 8.58 (1H, dd, $J$ = 7.5, 1.2Hz, H-2), 8.14 (1H, dd $J$ = 8.3, 1.2Hz, H-4), 7.97 (1H, d, $J$ = 8.3Hz), 7.72 (1H, dd, $J$ = 8.3, 7.5Hz, H-3), 7.69 (1H, d, $J$ = 6.8Hz, H-7), 7.69 (1H, d, $J$ = 9.9Hz, H-3'), 7.54 (1H, dd, $J$ = 8.3, 6.8Hz, H-6), 6.69 (1H, d, $J$ = 9.9Hz, H-2').
$^{13}$C APT-NMR (CDCl$_3$, 75MHz) $\delta$ 185.6 (qC, C-1'), 141.7 (CH, C-3'), 134.8 (CH, C-4), 132.0 (qC, C-4a), 131.9 (CH, C-5), 131.3, (CH, C-7), 130.2 (CH, C-2), 129.3 (qC, C-1), 129.1 (CH, C-2'), 127.7 (qC, C-8), 127.4 (qC, C-8a), 127.0 (CH, C-3), 126.5 (CH, C-6).

4.1.1.2.6 (±)-2-Methyl-1H-benzof[\textit{f}]chromen-3(2H)-one (±)-91

Light tan oil, yield 58% (2-methylacrylic acid 90, stirred 20h), purified by flash column chromatography on silica gel (DCM).
IR: v (cm$^{-1}$): 3055 w, 1767 s, 1516 m, 1343 w, 1265m, 737 s.
EIMS \textit{m/z} 212 [M$^+$] (100), 197 (20), 184 (57), 169 (91), 156 (30), 141 (24), 128 (70).
HREI-MS \textit{m/z} 212.0838 (calcd for C$_{14}$H$_{12}$O$_2$, 212.0837).
UV (DCM) $\lambda$ \text{max} (log $e$): 230 (4.71), 280 sh (3.80).
$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.88 (1H, bd, $J$ = 8.4Hz, H-10), 7.83 (1H, bd, $J$ = 8.1Hz, H-7), 7.75 (1H, d, $J$ = 8.9Hz, H-6), 7.56 (1H, ddd, $J$ = 8.4, 6.9, 1.5Hz, H-9), 7.45 (1H, ddd, $J$ = 8.1, 6.9, 1.1Hz, H-8), 7.21 (1H, d, $J$ = 8.9Hz, H-5), 3.51 (1H, dd, $J$ = 15.3, 5.7Hz, H$_a$-1), 2.99 (1H, dd, $J$ = 15.3, 12.0Hz, H$_b$-1), 2.89 (1H, ddq, $J$ = 12.0, 6.3, 5.7Hz, H-2), 1.46 (3H, d, $J$ = 6.3Hz, H-2 CH$_3$).
$^{13}$C APT-NMR (CDCl$_3$, 75MHz) $\delta$ 177.5 (qC, C-3), 149.4 (qC, C-4a), 131.1 (qC, C-10a), 130.7 (qC, C-6a), 128.8 (CH, C-6), 128.7 (CH, C-7), 127.0 (CH, C-9), 125.0 (CH, C-8), 122.8 (CH, C-10), 117.2 (CH, C-5), 115.7 (qC, C-10b), 33.6 (CH, C-2), 27.9 (CH$_2$, C-1), 15.6 (CH$_3$, C-2 CH$_3$).

4.1.1.2.7 3H-Benzof[\textit{f}]chromen-3-one 32

Red amorphous solid, yield 25% (propiolic acid 92, stirred 20h), purified by flash column chromatography on silica gel (DCM).

104
M.p.: 113-114°C (amorph.).
IR: ν (cm⁻¹): 3059 w, 1728 s, 1566 m, 1335 w, 1265 m. EIMS m/z 196 [M⁺]
(94), 168 (100), 139 (45).
HREI-MS m/z 196.0523 (calcd for C₁₃H₉O₂, 196.0524).
UV (DCM) λ max (log ε): 233 (4.67), 249 sh (4.04), 316 (3.84), 348 (3.84).
¹H NMR (CDCl₃, 300MHz): δ 8.49 (1H, d, J = 9.6Hz, H-1), 8.32 (1H, bd, J = 8.4Hz, H-
10), 7.99 (1H, d, J = 9.3Hz, H-6), 7.92 (1H, ddd, J = 8.1, 1.5, 0.6Hz, H-7), 7.69 (1H, ddd, J = 8.4, 7.1, 1.5Hz, H-9), 7.57 (1H, ddd, J = 8.1, 7.1, 1.2Hz, H-8), 7.47 (1H, d, J = 9.3Hz, H-5), 6.58 (1H, d, J = 9.6Hz, H-2).
¹³C APT-NMR (CDCl₃, 75MHz) δ 160.9 (qC, C-3), 147.7 (qC, C-4a), 139.1 (CH, C-1),
133.1 (CH, C-6), 130.3 (qC, C-10a), 129.1 (qC, C-6a), 129.0 (CH, C-7), 128.3 (CH, C-
9), 126.0 (CH, C-8), 121.3 (CH, C-10), 117.1 (CH, C-5), 115.6 (C-2), 113.0 (qC, C-
10b).

4.1.1.2.8 (±)-3-Phenyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-48

Light tan oil, yield 44% (trans-cinnamic acid 46, stirred 20h), purified by flash column chromatography on silica gel (DCM) with (±)-47.
IR: ν (cm⁻¹): 3059 w, 1778 br m, 1670 s, 1597 m, 1234 s,
1207 m, 1123 m, 1072 br m.
EIMS m/z 274 [M⁺] (82), 256 (8), 245 (9), 231 (20), 215 (10), 197 (15), 170 (100), 142
(25), 114 (18).
HREI-MS m/z 274.0953 (calcd for C₁₉H₁₄O₂, 274.0994).
UV (DCM) λ max (log ε): 225 (4.47), 38 sh (4.35), 265 sh (3.94), 315 (3.76).
¹H NMR (CDCl₃, 300MHz): δ 9.50 (1H, bd, J = 8.7Hz, H-10), 7.96 (1H, d, J = 9.0Hz,
H-6), 7.78 (1H, dd, J = 8.1, 1.4Hz, H-7), 7.66 (1H, ddd, J = 8.7, 6.9, 1.4Hz, H-9), 7.53
(2H, dd, J = 8.4, 1.7Hz, H-2'), 7.43 (4H, m, H-8, H-3', H-4'), 7.17 (1H, d, J = 9.0Hz,
H-5), 5.61 (1H, dd, J = 13.7, 3.3Hz, H-3), 3.24 (1H, dd, 16.5, 13.7Hz, H-2'), 2.99 (1H,
dd, 16.5, 3.3Hz, H-2).
¹³C APT-NMR (CDCl₃, 75MHz) δ 193.0 (qC, C-1), 163.7 (qC, C-4a), 138.5 (qC, C-1’),
137.6 (CH, C-6), 131.4 (qC, C-10a), 129.7 (CH, C-9), 129.3 (qC, C-6a), 128.83 (CH, C-
3’), 128.79 (CH, C-4’), 128.4 (CH, C-7), 126.2 (CH, C-2'), 125.9 (CH, C-10), 124.9
(CH, C-8), 118.8 (CH, C-5), 112.6 (qC, C-10b), 79.6 (CH, C-3), 45.7 (CH₂, C-2).
4.1.1.2.9 (±)-1-Phenyl-1H-benzo[f]chromen-3(2H)-one (±)-47

Light tan oil, yield 48% (trans-cinnamic acid 46, stirred 20h) purified by flash column chromatography on silica gel (DCM) with (±)-48.

IR: v (cm⁻¹): 3055 m, 1778 br s, 1709 br s, 1636 m, 1601 m, 1419m, 1265 s, 1184 m, 740 s, 702 s.

EIMS m/z 274 [M⁺] (90), 256 (15), 245 (20), 231 (100), 202 (30).

HREI-MS m/z 274.0994 (calcd for C₁₉H₁₄O₂, 274.0994).

UV (DCM) λ_max (log ε): 235 (4.49), 281 sh (3.69).

¹H NMR (CDCl₃, 300MHz): δ 7.88 (1H, d, J = 8.9Hz, H-6), 7.88 (1H, dd, J = 8.7, 2.0, H-7), 7.80 (1H, dd, J = 8.9, 1.7Hz, H-10), 7.48 (1H, ddd, J = 8.9, 6.9, 2.0Hz, H-9), 7.44 (1H, ddd, J = 8.7, 6.9, 1.7Hz, H-8), 7.36 (1H, d, J = 8.9Hz, H-5), 7.25 (3H, m, H-3', H-4'), 7.13 (2H, dd, J = 8.4, 1.8Hz, H-2'), 4.96 (1H, dd, J = 6.3, 2.4Hz, H-1), 3.23 (1H, dd, 16.1, 6.3Hz, H₃-2), 3.15 (1H, dd, J = 16.1, 2.4Hz, H₃-2).

¹³C APT-NMR (CDCl₃, 75MHz) δ 167.1 (qC, C-3), 149.8 (qC, C-4a), 140.5 (qC, C-1'), 131.1 (qC, C-10a), 131.0 (qC, C-6a), 129.9 (CH, C-7), 129.2 (CH, C-3'), 128.7 (CH, C-6), 127.6 (CH, C-4'), 127.5 (CH, C-9), 126.9 (CH, C-7), 125.2 (CH, C-8), 123.0 (CH, C-10), 117.6 (qC, C-10b), 117.5 (CH, C-5), 37.6 (CH, C-1), 37.5 (CH₂, C-2).

4.1.2 Synthesis of 2,3-Dihydro-1H-benzo[f]chromen-1-one 40

A solution of 2-naphthol 41 (1.01g, 7.0mmol), acrylonitrile (2.5mL), and Triton B* (22 drops) was refluxed. The reaction was monitored by TLC and after 3d the reaction mix was extracted exhaustively with DCM. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to yield the crude 3-aryloxynitrile 43 (0.477g, 2.4mmol, 35%) which crystallised as yellow crystals from Et₂O. 3-Aryloxynitrile 43 (0.339g, 1.7mmol) in H₂SO₄ (85%, 10mL) was stirred for 3h before 20g of ice was added then extracted exhaustively with DCM. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to realize the title compound 40 (0.095g, 0.48mmol, 28%).

4.1.2.1 2,3-Dihydro-1H-benzo[f]chromen-1-one 40

IR: v (cm⁻¹): 3055 w, 1674 s, 1616 m, 1597 s, 1238 s, 1080 m, 991 m, 825 s, 736 s.

EIMS m/z 198 [M⁺⁺] (97), 170 (100), 156 (15), 142 (60), 128 (20),

*Benzyltrimethyl ammonium hydroxide in methanol (40% w/v)
114 (80), 99 (18), 88 (20), 75 (10), 63 (22).

HREI-MS m/z 198.0683 (calcd for C_{13}H_{10}O_{2}, 198.0681).

UV (DCM) $\lambda_{\text{max}}$ (log $\varepsilon$): 227 (4.74), 239 sh (4.64), 265 sh (3.23), 313 (4.15).

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 9.45 (1H, d, $J = 8.6$Hz, H-10), 7.89 (1H, d, $J = 9.3$Hz, H-6), 7.72 (1H, d, $J = 8.1$Hz, H-7), 7.62 (1H, ddd, $J = 8.6$, 6.8, 1.5Hz, H-9), 7.41 (1H, ddd, 8.1, 6.8, 0.9Hz, H-8), 7.08 (1H, d, $J = 9.3$Hz, H-5), 4.59 (2H, appt. t, $J = 6.0$Hz, H-3), 2.89 (2H, appt. t, $J = 6.0$Hz, H-2).

4.1.3 Cyclisations with Crotonic Acid and 1-Naphthol in PPA

4.1.3.1 Synthesis of (±)-2,3-Dihydro-2-methylbenzo[h]chromen-4-one (±)-95

A solution of 1-naphthol 94 (33.0mg, 0.23mmol) and crotonic acid (22.0mg, 0.26mmol) in polyphosphoric acid (2mL) was stirred at 60°C for 3h. The bright red solution was diluted with iced water and extracted exhaustively with DCM. The organic phase was dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting product present as a red glass was purified by flash chromatography (silica gel 0.040-0.063mm; DCM:EtOAc 100:0→50:50) to return starting material (4mg, 28$\mu$mol, 12%), (±)-95 (10.0mg, 47$\mu$mol, 20%) as a tan oil, and (±)-96 (27.0mg, 127$\mu$mol, 55%) as a light yellow oil.

4.1.3.1.1 (±)-2,3-Dihydro-2-methylbenzo[h]chromen-4-one (±)-95

IR: v (cm$^{-1}$): 3059 w, 1681 m, 1573 m, 1573 m, 1508 m, 1342 s, 1199 m, 1122 s.

EIMS m/z 212.1 [M$^{+*}$] (70), 197 (25), 170 (100), 142 (8), 114 (55).

HREI-MS m/z 212.0837 (calcd for C_{14}H_{12}O_2, 212.0837).

UV (DCM) $\lambda_{\text{max}}$ (log $\varepsilon$): 226 (4.27), 262 (4.56).

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 8.32 (1H, m, $J = 7.8$, 1.4, 0.6Hz, H-10), 7.86 (1H, d, $J = 8.9$Hz, H-5), 7.78 (1H, bd, $J = 8.0$Hz, H-7), 7.61 (1H, ddd, $J = 8.0$, 6.9, 1.4Hz, H-8), 7.53 (1H, ddd, $J = 7.8$, 6.9, 1.2Hz, H-9), 7.39 (1H, d, $J = 8.9$Hz, H-6), 4.79 (1H, ddq, $J = 16.8$, 6.2, 6.2Hz, H-2), 2.79 (2H, m, H$_a$-3, H$_b$-3), 1.66 (3H, d, $J = 6.2$Hz, H-2 CH$_3$).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) $\delta$ 192.1 (qC, C-3), 160.0 (qC, C-10b), 137.5 (qC, C-6a), 129.5 (CH, C-8), 127.8 (CH, C-7), 126.1 (CH, C-9), 124.8 (qC, C-10a), 123.5 (CH, C-10), 121.7 (CH, C-5), 120.8 (CH, C-6), 115.3 (qC, C-4a), 75.3 (CH, C-2), 44.0 (CH$_2$, C-3), 21.0 (CH$_3$, C-2 CH$_3$).
4.1.3.1.2 (±)-5-Hydroxy-3-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-1-one
(±)-96

IR: ν (cm⁻¹): 3190 w br, 2928 w, 1662 m sh, 1570 s, 1350 m, 1253 m.

EIMS m/z 212 [M⁺] (100), 197 (95), 184 (10), 169 (10), 152(8), 139 (13), 127 (7), 115 (18).

HREI-MS m/z 212.0837 (calcd for C₁₄H₁₂O₂, 212.0837).

UV (MeOH) λ_max (log ε): 224 (4.42), 333 (3.93).

¹H NMR (CD₃OD, 300MHz): δ 8.95 (1H, ddd, J = 8.3, 1.2, 0.6Hz, H-9), 8.24 (1H, ddd, J = 8.3, 1.2, 0.6Hz, H-6), 7.60 (1H, ddd, J = 8.3, 6.9, 1.2Hz, H-8), 7.48 (1H, ddd, J = 8.3, 6.9, 1.2Hz, H-7), 6.86 (1H, s, H-4), 3.37 (1H, ddq, J = 7.1, 2.8, 7.1Hz, H-3), 2.92 (1H, dd, J = 18.6, 7.1Hz, H₉-2), 2.26 (1H, dd, J = 18.6, 2.8Hz, H₉-2), 1.38 (3H, d, J = 7.2Hz, H-3 CH₃).

¹³C APT-NMR (CDCl₃, 75MHz) δ 207.4 (qC, C-1), 168.5 (qC, C-3a) 162.9 (qC, C-5), 132.1 (qC, C-9a), 130.3 (CH, C-8), 126.5 (CH, C-7), 125.8 (qC, C-9b), 124.0 (CH, C-6, C-9 co-in), 122.9 (qC, C-5a), 105.0 (CH, C-4), 46.7 (CH₂, C-2), 34.2 (CH, C-3), 21.4 (CH₃, C-3 CH₃).

4.1.3.2 Synthesis of (±)-5-Methoxy-3-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-1-one (±)-101

A stirred suspension of cyclopentanone (±)-96 (5.0mg, 24μmol), K₂CO₃ (3.5mg, 25μmol) and excess MeI, in acetone (5mL), was refluxed. The reaction was monitored by TLC, and additional MeI was added. After 16h the solvent was removed in vacuo, and the residue was exhaustively extracted with DCM/H₂O. The combined organic phases were dried (MgSO₄), filtered, and concentrated in vacuo to give (±)-101 (5.0mg, 22μmol, 92%) as light yellow oil.

4.1.3.2.1 (±)-5-Methoxy-3-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-1-one (±)-101

IR: ν (cm⁻¹): 3055 w, 1685 m, 1573 m, 1265 s, 1249 m sh, 1195 w, 740 s, 705 m sh.

EIMS m/z 226 [M⁺⁺] (100), 211 (75), 198 (12), 183 (18), 198 (15), 152 (17), 139 (20), 127 (10), 113 (12).

HREI-MS m/z 226.0995 (calcd for C₁₅H₁₄O₂, 226.0994).

UV (MeOH) λ_max (log ε): 212 (4.02), 242 (4.30), 312 (3.74).
1H NMR (CDCl₃, 300MHz): δ 9.13 (1H, dd, J = 8.1, 0.9Hz, H-9), 8.26 (1H, dd, J = 8.1, 0.9Hz, H-6), 7.67 (1H, ddd, J = 8.1, 6.9, 0.9Hz, H-8), 7.53 (1H, ddd, J = 8.1, 6.9, 0.9Hz, H-7), 6.82 (1H, s, H-4), 4.11 (3H, s, H-50CH₃), 3.45 (1H, dd, J = 17.2, 7.2Hz, H-3), 3.02 (1H, dd, J = 18.2, 7.2Hz, H₆-2), 2.37 (1H, dd, J = 18.2, 2.7Hz, H₇b-2), 1.45 (3H, d, J = 7.2Hz, H-3CH₃).

13C APT-NMR (CDCl₃, 75MHz) δ 205.1 (qC, C-1), 165.5 (qC, C-3a), 161.8 (qC, C-5), 130.3 (qC, C-9a), 129.4 (CH, C-8), 126.0 (CH, C-7), 125.0 (qC, C-9b), 124.0 (CH, C-9), 123.7 (qC, C-5a), 122.4 (CH, C-6), 100.1 (CH, C-4), 56.0 (CH₃, C-50CH₃), 45.9 (CH₂, C-2), 33.2 (CH, C-3), 21.2 (CH₃, C-3CH₃).

4.1.4 Cyclisations of Crotonic Acid with Naphthalendiol Utilising PPA

4.1.4.1 Synthesis of 6-Hydroxy-3-methyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-103

Naphthoresorcinol 102 (27mg, 0.17mmol) and crotonic acid 82 (15mg, 0.17mmol) were stirred in 2mL PPA at 60°C for 28h. The reaction mix was diluted with water and extracted exhaustively with DCM. The organic extracts where combined, dried (MgSO₄), filtered then concentrated to present a yellow amorphous solid (crude yield 22mg). The crude product was purified by flash chromatography (silica gel, 0.040-0.063mm; 100% Et₂O) to yield the title compound as a yellow oil (±)-103 (10.5mg, 27%).

4.1.4.1.1 (±)-6-Hydroxy-3-methyl-2,3-dihydro-1H-benzo[f]chromen-1-one (±)-103

IR: v (cm⁻¹): 3078 w, 1627 m, 1554 s, 1408 m, 1350 m, 1253 m, 1199 m, 1149 w, 844 w, 721 w, 670 m.

EIMS m/z 228 [M⁺] (100%), 213 (7), 186 (98), 158 (53), 130 (35), 114 (7), 102 (33).

HREI-MS m/z 228.0786 (calcd for C₁₄H₁₂O₃, 228.0786).

UV (MeOH) λ_max (log ε): 222 (4.50) 233 sh (4.49), 252 (4.44), 314 (4.07), 361 (4.13).

1H NMR (CDCl₃, 300MHz): δ 9.36 (1H, dd, J = 8.7, 0.9Hz, H-10), 8.16 (1H, dd, J = 8.0, 1.1Hz, H-7), 7.56 (1H, ddd, J = 8.0, 7.1, 0.9Hz, H-9), 7.35 (1H, ddd, J = 8.0, 7.1, 0.9Hz, H-8), 6.40 (1H, s, H-5), 4.64 (1H, dd, J = 12.3, 6.2, 4.1Hz, H-3), 2.71 (1H, dd, J = 16.5, 12.3Hz, H₆a-2), 2.64 (1H, dd, J = 16.5, 4.1Hz, H₇b-2), 1.50 (3H, d, J = 6.2Hz, H-3CH₃).

13C APT-NMR (CD₃OD, 75MHz); δ 194* (qC, C-1), 168.1 (qC, C-6), 163.2 (qC, C-4a), 134.6 (qC, C-10a), 130.8 (CH, C-9), 127.5 (CH, C-10), 124.8 (CH, C-8), 123.6 (CH, C-

109
7), 123.3 (qC, C-6a), 107.1 (qC, C-10b), 100.2 (CH, C-5), 75.6 (CH, C-3), 46.3 (CH₂, C-2), 20.9 (CH₃, C-3CH₃).

*Assigned by HMBC

4.1.4.2 Synthesis of 3-Methoxynaphthalen-1-ol 110
A solution of naphthoresorcinol 102 (0.104g, 0.65mmol) in methanolic HCl (3ml, 1.2M) was stirred under N₂. The reaction was complete after 3 days, and the solvent was removed in vacuo. The orange oil was purified by column chromatography (silica gel 0.040-0.063mm; DCM) to give 3-methoxynaphthalen-1-ol 110 (79.5mg, 0.46mmol, 70%) and 1,3-dimethoxynaphthalene 111 (9.4mg, 0.05mmol, 8%).

4.1.4.2.1 3-Methoxynaphthalen-1-ol 110

IR: v (cm⁻¹): 3394 w br, 3067 w, 1681 m, 1631 m, 1608 m, 1519 w, 1458 w, 1408 m, 1265 m, 1242 s, 1215 m, 1161 m.

EIMS m/z 174 [M⁺] (100), 145 (10), 131 (45), 115 (15) 103 (20), 83 (12), 73 (20).

HREI-MS m/z 174.0681 (calcd for C₁₁H₁₀O₂, 174.0681).

UV (MeOH) λ max (log ε): 237 (4.55), 278 (3.97), 333 (3.44).

¹H NMR (CDCl₃, 500MHz): δ 8.07 (1H, d, J = 8.3Hz, H-8), 7.70 (1H, dd, J = 8.0, 1.0Hz, H-5), 7.45 (1H, dd, J = 8.0, 7.3Hz, H-6), 7.34 (1H, ddd, J = 8.3, 7.3, 1.0Hz, H-7), 6.77 (1H, d, J = 2.3Hz, H-4), 6.54 (1H, d, J = 2.3Hz, H-2), 3.91 (3H, s, H-3OCH₃).

¹³C APT-NMR (CDCl₃, 125MHz) δ 157.7 (qC, C-1), 152.5 (qC, C-3), 135.4 (qC, C-8a), 127.1 (CH, C-6), 126.6 (CH, C-5), 122.9 (CH, C-7), 121.5 (CH, C-8), 120.5 (qC, C-4a), 101.4 (CH, C-2), 98.8 (CH, C-4), 55.3 (CH₃, C-3OCH₃).

4.1.4.2.2 1,3-Dimethoxynaphthalene 111

IR: v (cm⁻¹): 3070 w, 2847 w, 1685 m, 1631 m, 1608 s, 1512 w, 1454 m, 1408 w, 1242 m, 1215 m, 1161 m, 1045 m, 825 w br.

EIMS m/z 188 [M⁺] (100), 173 (20), 145 (22), 130 (15), 121 (10), 115 (15), 102 (21).

HREI-MS m/z 188.0836 (calcd for C₁₂H₁₂O₂, 188.0837).

UV (MeOH) λ max (log ε): 238 (4.51), 280 (4.11), 331 (3.53).

¹H NMR (CDCl₃, 300MHz): δ 8.14 (1H, dd, J = 8.3, 1.2, 0.5Hz, H-8), 7.68 (1H, ddd, J = 8.4, 1.2, 0.5Hz, H-5), 7.44 (1H, ddd, J = 8.4, 7.1, 1.2Hz, H-6), 7.32 (1H, ddd, J = 8.3,
7.1, 1.2Hz, H-7), 6.74 (1H, d, J = 2.1Hz, H-4), 6.51 (1H, d, J = 2.1Hz, H-2), 3.98 (3H, s, H-1OCH3), 3.92 (3H, s, H-3OCH3).

13C APT-NMR (CDCl3, 75MHz) δ 158.1 (qC, C-3), 156.5 (qC, C-1), 135.0 (qC, C-8a), 127.0 (CH, C-5), 126.4 (CH, C-6), 122.9 (CH, C-7), 121.9 (CH, C-8), 121.7 (qC, C-4a), 97.9 (CH, C-4), 97.6 (CH, C-2), 55.5 (CH3, C-1OCH3), 55.3 (CH3, C-3OCH3).

4.1.4.3 Synthesis of 6-Hydroxy-1-methyl-1H-benzo[f]chromen-3(2H)-one (±)-112

3-Methoxynaphthalen-1-ol 110 (27mg, 0.15mmol) and crotonic acid (14mg, 0.16mmol) were stirred in 1mL PPA at 60°C for 20h. The reaction mix was diluted with water and extracted exhaustively with DCM. The organic extracts were combined, dried (MgSO4), filtered then concentrated to present crude product (19mg) which was purified by flash column chromatography (silica gel 0.040-0.063mm; EtOAc/PS 60:40) to return the title compound (±)-112 as a brown oil (3mg, 13µmol, 9%) and naphthoresorcinol 102 (14mg, 87µmol, 58%)

4.1.4.3.1 (±)-6-Hydroxy-1-methyl-1H-benzo[f]chromen-3(2H)-one (±)-112

IR: v (cm⁻¹): 3344 w br, 3066 w, 1766 s, 1732 s, 1631 m, 1593 s, 1269 s, 1161 s, 1122 s, 1080 m, 763 m, 729 m, 540 m.

EIMS m/z 228 [M⁺] (60), 213 (100), 199 (7), 185 (30), 169 (5), 157 (10), 139 (6), 128 (15), 115 (12).

HREI-MS m/z 228.0790 (calcd for C14H12O3, 228.0786).

UV (MeOH) λ_max (log ε): 223 (478), 250 sh (4.57).

1H NMR (CD3OD, 300MHz): δ 8.23 (1H, ddd, J = 8.4, 1.2, 0.9Hz, H-7), 7.93 (1H, bd, J = 8.4Hz, H-10), 7.57 (1H, ddd, J = 8.4, 6.9, 1.2Hz, H-9), 7.41 (1H, ddd, J = 8.4, 6.9, 1.2Hz, H-8), 6.57 (1H, s, H-5), 3.79 (1H, ddq, J = 7.2, 6.6, 1.8Hz, H-1), 3.01 (1H, dd, J = 15.9, 6.6Hz, H-2a) 2.80 (1H, dd, J =15.9, 1.8Hz, H-2b), 1.30 (3H, d, J = 7.2Hz, H-1CH3).

13C APT-NMR (CD3OD, 75MHz) δ 170.6 (qC, C-3), 150.9 (qC, C-6), 149.9 (qC, C-4a), 132.6 (qC, C-10a), 128.6 (CH, C-9), 124.8 (CH, C-8), 124.4 (qC, C-6a), 124.1 (CH, C-7), 123.5 (CH, C-10), 113.0 (qC, C-10b), 100.0 (CH, C-5), 37.3 (CH2, C-2), 27.3 (CH, C-1), 20.6 (CH3, C-1CH3).
4.1.4.4 Synthesis of (±)-6-Methoxy-1-methyl-1H-benzo[f]furan-3(2H)-one (±)-113

A stirred suspension of benzo[f]coumarin (±)-112 (5.0mg, 22μmol), K₂CO₃ (3mg, 22μmol) and excess MeI, in acetone (2mL), was refluxed for 20h. The solvent was removed in vacuo, and the residue was exhaustively extracted with DCM/H₂O. The combined organic phases were dried (MgSO₄), filtered, and concentrated in vacuo to give (±)-113 (5.0mg, 21μmol, 95%) as a tan oil.

4.1.4.4.1 (±)-6-Methoxy-1-methyl-1H-benzo[f]furan-3(2H)-one (±)-113

IR: v (cm⁻¹): 3359 w br, 2974 w, 1766 m, 1720 m, 1627 m, 1597 m, 1454 w, 1423 w, 1269 m, 1087 s, 1049 s, 879 m, 737 m.

EIMS m/z 242 [M⁺] (55), 227 (100), 212 (8), 199 (20), 171 (10), 128 (15), 115 (10).

HREI-MS m/z 242.0941 (calcd for C₁₅H₁₄O₃, 242.0943).

UV (DCM) λ_max (log ε): 240 (4.53), 301 (3.72).

¹H NMR (CDCl₃, 300MHz): δ 8.27 (1H, dd, J = 8.1, 1.0Hz, H-7), 7.85 (1H, dd, J = 8.2, 0.9Hz, H-10), 7.59 (1H, ddd, J = 8.2, 7.1, 1.0Hz, H-9), 7.45 (1H, ddd, J = 8.1, 7.1, 0.9Hz, H-8), 6.59 (1H, s, H-5), 3.99 (3H, s, 6OCH₃), 2.94 (1H, dd, J = 16.1, 5.4Hz, H-2a), 1.35 (3H, d, J = 7.2Hz, H-1CH₃).

¹³C APT-NMR (CDCl₃, 75MHz) δ 168* (qC, C3), 156* (qC, C-6), 148* (qC, C-4a), 132* (qC, C-10a), 127.8 (CH, C-9), 124.3 (CH, C-8), 123.6 (qC, C-6a), 122.9 (CH, C-7), 122.2 (CH, C-10), 113 (qC, C-10b), 96.4 (CH, C-5), 55.8 (CH₃, C-6OCH₃), 37.5 (CH₂, C-2), 26.2 (CH, C-1), 20.3 (CH₃, C-1CH₃). *Assigned by HMBC.

4.1.4.5 Synthesis of 8-Hydroxy-3-methyl-2,3-1H-benzo[f]chromen-1-one (±)-115

2,6-Dihydroxynaphthalene 114 (163mg, 1.02mmol) and crotonic acid 82 (173mg, 2.01mmol) in PPA (3.2g) at 60°C was stirred for 5 days. The reaction mix was diluted with water and extracted exhaustively with DCM. The organic extracts where combined, dried (MgSO₄), filtered then concentrated to present crude product (142mg) which was purified by flash column chromatography (silica gel 0.040-0.063mm; EtOAc/PS 60:40) to return the title compound (±)-115 as a yellow oil (139mg, 0.61mmol, 60%).

4.1.4.5.1 (±)-8-Hydroxy-3-methyl-2,3-1H-benzo[f]chromen-1-one (±)-115
4.1.4.4 Synthesis of (±)-6-Methoxy-1-methyl-1H-benzo[f]furan-3(2H)-one (±)-113

A stirred suspension of benzo[f]coumarin (±)-112 (5.0mg, 22μmol), K₂CO₃ (3mg, 22μmol) and excess Mel, in acetone (2mL), was refluxed for 20h. The solvent was removed in vacuo, and the residue was exhaustively extracted with DCM/H₂O. The combined organic phases were dried (MgSO₄), filtered, and concentrated in vacuo to give (±)-113 (5.0mg, 21μmol, 95%) as a tan oil.

4.1.4.4.1 (±)-6-Methoxy-1-methyl-1H-benzo[f]furan-3(2H)-one (±)-113

IR: v (cm⁻¹): 3359 w br, 2974 w, 1766 m, 1720 m, 1627 m, 1597 m, 1454 w, 1423 w, 1269 m, 1087 s, 1049 s, 879 m, 737 m.
EIMS m/z 242 [M⁺⁺] (55), 227 (100), 212 (8), 199 (20), 171 (10), 128 (15), 115 (10).

HREI-MS m/z 242.0941 (calcd for C₁₅H₁₄O₃, 242.0943).
UV (DCM) λ_max (log ε): 240 (4.53), 301 (3.72).

¹H NMR (CDCl₃, 300MHz): δ 8.27 (1H, dd, J = 8.1, 1.0Hz, H-7), 7.85 (1H, dd, J = 8.2, 0.9Hz, H-10), 7.59 (1H, ddd, J = 8.2, 7.1, 1.0Hz, H-9), 7.45 (1H, ddd, J = 8.1, 7.1, 0.9Hz, H-8), 6.59 (1H, s, H-5), 3.99 (3H, s, 6OCH₃), 3.73 (1H, ddd, J = 7.2, 5.4, 2.0Hz, H-1), 2.94 (1H, dd, J = 16.1, 5.4Hz, H-2a), 2.85 (1H, dd, J = 16.1, 2.0Hz, H-2b), 1.35 (3H, d, J = 7.2Hz, H-1CH₃).

¹³C APT-NMR (CDCl₃, 75MHz) δ 168* (qC, C3), 156* (qC, C-6), 148* (qC, C-4a), 132* (qC, C-10a), 127.8 (CH, C-9), 124.3 (CH, C-8), 123.6 (qC, C-6a), 122.9 (CH, C-7), 122.2 (CH, C-10), 113 (qC, C-10b), 96.4 (CH, C-5), 55.8 (CH₃, C-6OCH₃), 37.5 (CH₂, C-2), 26.2 (CH, C-1), 20.3 (CH₃, C-1CH₃). *Assigned by HMBC.

4.1.4.5 Synthesis of 8-Hydroxy-3-methyl-2,3-1H-benzo[f]chromen-1-one (±)-115

2,6-Dihydroxynaphthalene 114 (163mg, 1.02mmol) and crotonic acid 82 (173mg, 2.01mmol) in PPA (3.2g) at 60°C was stirred for 5 days. The reaction mix was diluted with water and extracted exhaustively with DCM. The organic extracts were combined, dried (MgSO₄), filtered then concentrated to present crude product (142mg) which was purified by flash column chromatography (silica gel 0.040-0.063mm; EtOAc/PS 60:40) to return the title compound (±)-115 as a yellow oil (139mg, 0.61mmol, 60%).

4.1.4.5.1 (±)-8-Hydroxy-3-methyl-2,3-1H-benzo[f]chromen-1-one (±)-115
4.1.6.1 Crotonic Anhydride

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\text{EIMS } m/z \; 126 \; (10), \; 69 \; (100), \; 41 \; (40), \; 39 \; (40).
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^1\text{H NMR (CDCl}_3, \; 300\text{MHz): } \delta \; 7.09 \; (2\text{H, dq, } J = 15.3, \; 6.9, \; \text{H-3}), \; 5.87 \; (2\text{H, dd, } J = 15.3, \; 1.5\text{Hz, H-2}), \; 1.90 \; (6\text{H, dd, } J = 6.9, \; 1.5\text{Hz, H-4}).
\]

4.1.7 General Synthesis of Acylated Methoxynaphthalenes

To an ice cooled solution of acid chloride (5.0mmol) in distilled DCM (4mL) under N\(_2\), was added AlCl\(_3\) (4.5mmol) and 2-methoxynaphthalene 117 (4.0mmol). The reaction mixture was left to stir and monitored by TLC until total consumption of starting material had occurred. The reaction mix was quenched with 40mL of ice cooled 1\(N\) HCl and was exhaustively extracted with DCM/5\% NaHCO\(_3/\)H\(_2\)O. The organic phase was dried (MgSO\(_4\)), filtered, and concentrated \textit{in vacuo} to give acylated methoxynaphthalene.

4.1.7.1 \((E)-1\)-(2-Methoxynaphthalen-1-yl)but-2-en-1-one 79

Brown amorphous solid, yield 86\% (crotonoyl chloride, stirring period 0.5h).

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\text{M.p.: 58-60°C (amorph.).}
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\text{TLC: } R_f \; 0.34 \; [\text{DCM } 100\%].
\]

IR: \(v\) (cm\(^{-1}\)): 3055 w, 1651 s, 1620 m, 1593 m, 1508 m, 1465 m, 1435 m, 1253 s.

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\text{EIMS } m/z \; 226 \; [M^+] \; (98), \; 211 \; (32), \; 195 \; (38), \; 185 \; (100), \; 170 \; (27), \; 158 \; (19), \; 142 \; (47), \; 127 \; (50), \; 114 \; (58).
\]

\[
\text{HREI-MS } m/z \; 226.0995 \; (\text{calcd for } \text{C}_{15}\text{H}_{14}\text{O}_2, \; 226.0994).
\]

\[
\text{UV (DCM) } \lambda_{\text{max}} \; (\log \epsilon): \; 229 \; (4.83), \; 280 \; (3.74), \; 334 \; (3.48).
\]

\[
^1\text{H NMR (CDCl}_3, \; 300\text{MHz): } \delta \; 7.88 \; (1\text{H, d, } J = 9.0\text{Hz, H-4'}), \; 7.81 \; (1\text{H, bd, } J = 8.1\text{Hz, H-5'}), \; 7.61 \; (1\text{H, dd, } J = 8.4, \; 1.2\text{Hz, H-8'}), \; 7.44 \; (1\text{H, bdd, } J = 8.4, \; 6.9\text{Hz, H-7'}), \; 7.35 \; (1\text{H, ddd, } J = 8.1, \; 6.9, \; 1.2\text{Hz, H-6'}), \; 7.28 \; (1\text{H, d, } J = 9.0\text{Hz, H-3'}), \; 6.61 \; (1\text{H, dq, } J = 16.2, \; 6.3\text{Hz, H-3}), \; 6.51 \; (1\text{H, d, } J = 16.2\text{Hz, H-2}), \; 3.90 \; (3\text{H, s, 2'OCH}_3), \; 1.90 \; (3\text{H, d, } J = 6.3\text{Hz, H-4}).
\]

\[
^{13}\text{C'APT-NMR (CDCl}_3, \; 75\text{MHz)} \; \delta 197.7 \; (\text{qC, C-1}), \; 153.7 \; (\text{qC, C-2'}), \; 147.3 \; (\text{CH, C-3}), \; 134.2 \; (\text{CH, C-2}), \; 131.4 \; (\text{qC, C-8a'}), \; 130.9 \; (\text{CH, C-4'}), \; 128.7 \; (\text{qC, C-4a'}), \; 128.0 \; (\text{CH, C-5'}), \; 127.2 \; (\text{CH, C-7'}), \; 124.0 \; (\text{CH, C-8'}), \; 123.9 \; (\text{CH, C-6'}), \; 123.5 \; (\text{qC, C-1'}), \; 113.1 \; (\text{CH, C-3'}), \; 56.6 \; (\text{CH}_3, \; 2'OCH}_3), \; 18.4 \; (\text{CH}_3, \; C-4).}
\]
4.1.7.2 (E)-1-(2-Methoxynaphthalen-1-yl)-2-methylbut-2-en-1-one 134

Brown oil, yield 53% (tigloyl chloride, stirring period 4h), purified by flash column chromatography on silica gel (DCM).

TLC: Rf 0.45 [DCM 100%].

IR: v (cm$^{-1}$): 3363 w br, 3055 w, 1639 s br, 1593 s, 1508 s, 1469 m, 1435 m, 1253 m, 1149 m, 1084 m, 964 m, 817 m.

EIMS m/z 240 [M$^+$] (83), 225 (31), 209 (28), 197 (30), 185 (100), 170 (24), 158 (15), 152 (10), 142, (48), 127 (45), 114 (49).

HREI-MS m/z 240.1155 (calcd for C$_{16}$H$_{14}$O$_2$, 240.1150).

UV (DCM) $\lambda_{max}$ (log e): 230 (4.84), 280 (3.79).

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.86 (1H, d, $J = 9.3$Hz, H-4'), 7.79 (1H, d, $J = 8.1$Hz, H-5'), 7.44 (1H, dd, $J = 8.4, 7.5$Hz, H-6'), 7.41 (1H, d, $J = 8.4$Hz, H-8'), 7.35 (1H, ddd, $J = 8.1, 7.5, 2.0$Hz, H-6'), 7.28 (1H, d, $J = 9.3$Hz, H-3'), 6.38 (1H, q, $J = 6.9$Hz, H-3), 2.05 (3H, s, H-2Me), 1.80 (3H, d, $J = 6.9$Hz, H-4).

$^{13}$C APT-NMR (CDCl$_3$, 75 MHz) $\delta$ 199.6 (C, C-1), 153.4 (C, C-2'), 143.7 (CH, C-3), 139.7 (C, C-2), 131.9 (C, C-8a'), 130.9 (CH, C-4'), 128.6 (C, C-4a'), 127.9 (CH, C-5'), 127.0 (CH, C-7'), 124.1 (CH, C-8'), 123.9 (qC, C-1'), 123.8 (CH, C-6'), 113.2 (CH, C-3'), 56.6 (CH$_3$, C-9'), 15.1 (CH$_3$, C-4), 10.5 (CH$_3$, C-2Me).

4.1.7.3 (E)-1-(2-Hydroxynaphthalen-1-yl)-3-phenylprop-2-en-1-one 55

Yellow solid, 39% yield (trans-cinnamoyl chloride, stirred 16h). Purified by flash chromatography on silica gel (DCM$\rightarrow$EtOAc) with 145.

M.p.: 104-106°C (amorph.).

TLC: Rf 0.57 [DCM 100%].

IR: v (cm$^{-1}$): 3059 w, 1670 m, 1635 s, 1595 s, 1570 s, 1462 m, 1338 s, 1234 m, 825 m.

EIMS m/z 274 [M$^+$] (100), 257 (20), 245 (245), 226 (14), 215 (12), 197 (62), 170 (100), 142 (24), 115 (55), 103 (35).

HREI-MS m/z 274.0993 (calcd for C$_{19}$H$_{14}$O$_2$, 274.0994).

UV (DCM) $\lambda_{max}$ (log e): 227 (4.71), 316 (4.20), 391 (4.01).

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 12.58 (1H, s, 2'-OH), 8.07 (1H, bd, $J = 8.4$Hz, H-8'); 7.93 (1H, d, $J = 15.9$Hz, H-3), 7.93 (1H, d, $J = 8.9$Hz, H-4'), 7.82 (1H, bd, $J = 7.5$Hz, H-5'), 7.63 (2H, m, H-5), 7.54 (1H, m, H-7'), 7.51 (1H, d, $J = 15.9$Hz, H-2), 7.43 (3H, m, H-6, H-7), 7.41 (1H, m, H-6'), 7.19 (1H, d, $J = 8.9$Hz, H-3').
$^{13}$C APT-NMR (CDCl$_3$, 75MHz) δ 194.5 (qC, C-1), 162.8 (qC, C-2'), 143.1 (CH, C-3), 136.8 (CH, C-4'), 134.8 (qC, C-4), 131.5 (qC, C-8a''), 130.7 (CH, C-7), 129.3 (CH, C-5'), 129.1 (CH, C-6), 128.7 (CH, C-5), 127.9 (CH, C-7'), 127.1 (CH, C-2), 125.1 (CH, C-8'), 124.0 (CH, C-6'), 119.4 (CH, C-3'), 115.9 (qC, C-1'). C-4a' not observed.

4.1.7.4 (E)-1-(2-Methoxynaphthalen-1-yl)-3-phenylprop-2-en-1-one 145

Yellow solid, 34% yield (cinnamoyl chloride, stirred 16h).

Purified by flash chromatography on silica gel (DCM→EtOAc) with 55.

M.p.: 132-133°C (EtOAc).

TLC: $R_f$ 0.4 [DCM 100%].

IR: $\nu$ (cm$^{-1}$): 3059 w, 1712 w, 1643 s sh, 1631 s, 1600 s, 1508 s, 1388 m, 1279 m, 1220 m, 1172 m, 1072 m, 1030 m,

EIMS $m/z$ 288 [M$^+$] (90), 271 (15), 260 (22), 229 (25), 185 (73), 170 (18), 142 (22), 127 (25), 114 (31), 81 (48), 69 (100).

HREI-MS $m/z$ 288.1151 (calcd for C$_{20}$H$_{16}$O$_2$, 288.1150).

UV (DCM) $\lambda_{max}$ (log $\epsilon$): 229 (5.01), 288 (4.14).

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.95 (1H, d, $J = 8.9$Hz, H-4'), 7.84 (1H, bd, $J = 7.8$Hz, H-5'), 7.72 (1H, bd, $J = 8.7$Hz, H-8'), 7.50 (2H, m, H-5), 7.38 (1H, m, H-6'), 7.45 (1H, m, H-7'), 7.37 (3H, m, H-6, H-7 co-in.), 7.36 (1H, d, $J = 16.4$Hz, H-2), 7.34 (1H, d, $J = 8.9$Hz, H-3'), 7.15 (1H, d, $J = 16.4$Hz, H-3), 3.90 (3H, s, H-2'OCH$_3$).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) δ 197.4 (qC, C-1), 154.1 (qC, C-2'), 145.7 (CH, C-3), 134.6 (qC, C-4), 131.5 (qC, C-8a'') 131.3 (CH, C-4'), 130.5 (CH, C-7), 128.8 (CH, C-2, C-6(sh) co-in.), 128.4 (CH, C-5), 128.0 (CH, C-5'), 127.5 (CH, C-7'), 124.1 (CH, C-6', C-8' co-in.), 123.4 (qC, C-1'), 113.1 (CH, C-3'), 56.6 (CH$_3$, C-2'OCH$_3$). C-4a' not observed.

4.1.7.5 2,3-Dihydro-9-methoxynaphthalen-1-one 158

Yellow oil, yield 80% (acryloyl chloride, stirred 16h). Purified by flash chromatography on silica gel (DCM).

IR: $\nu$ (cm$^{-1}$): 3055 w, 1685 s, 1577 m, 1508 m, 1334 m, 1261 s, 1080 m, 829 m, 759 m.

EIMS $m/z$ 212 [M$^+$] (100), 197 (26), 181 (20), 169 (22), 152 (20), 141 (24), 129 (14), 115 (20), 87 (40), 71 (50).

HREI-MS $m/z$ 212.0837 (calcd for C$_{14}$H$_{12}$O$_2$, 212.0837).

UV (DCM) $\lambda_{max}$ (log $\epsilon$): 225 (4.61), 251 (4.39).
$^1$H NMR (CDCl$_3$, 300MHz): δ 8.16 (1H, d, J = 7.5Hz, H-6), 8.00 (1H, d, J = 7.5Hz, H-4), 7.81 (1H, d, J = 9.3Hz, H-7), 7.42 (1H, dd, J = 7.5, 7.5Hz, H-5), 7.32 (1H, d, J = 9.3Hz, H-8), 3.99 (3H, s, H-9OMe), 3.38 (2H, bt, J = 7.2Hz, H-3), 2.92 (2H, bt, J = 7.2Hz, H-2).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) δ 198.9 (qC, C-1), 154.5 (qC, C-9), 134.0 (CH, C-4), 133.0 (qC, C-3a), 129.0 (qC, C-6a), 128.6 (qC, C-9b), 127.6 (CH, C-7), 125.6 (CH, C-6), 123.1 (CH, C-5), 117.6 (qC, C-9a), 113.2 (CH, C-8), 56.1 (CH$_3$, C-9OMe), 37.6 (CH$_2$, C-2), 21.5 (CH$_2$, C-3).

4.1.8 General Method of Nucleophilic Epoxidation of the (Naphthyl-en-1-yl)-2-ene-1-ones

To a stirred solution of acylated methoxynaphthalene (2.0mmol) in THF (5mL), at 0°C, was added H$_2$O$_2$ (30% w/v, 2mL) and NaOH (1N, 2mL). After total consumption of starting material the solution was diluted with H$_2$O and extracted exhaustively with Et$_2$O/5% NaHCO$_3$/H$_2$O. The organic phase was dried (MgSO$_4$), filtered and concentrated in vacuo to realize the epoxide.

4.1.8.1 ($\pm$)-(2-Methoxynaphthalen-1-yl)(3-methyloxiran-2-yl)methanone ($\pm$)-80

Off white solid, yield 72% (stirred for 2h).

M.p.: 126-127°C (amorph.).

IR: ν (cm$^{-1}$): 2962 m, 1689 m br, 1620 m, 1593 m, 1465 m, 1415 m, 1257 s, 1188 m, 1107 s, 1072 s, 1026 s, 810 s br.

EIMS m/z 242 [M$^+$] (95), 226 (12), 185 (100), 170 (50), 155 (20), 142 (80), 127 (80), 114 (75).

HREI-MS m/z 242.0944 (calcd for C$_{15}$H$_{14}$O$_3$, 242.0943).

UV (DCM) λ$_{\text{max}}$ (log ε): 226 (4.67), 350 sh (4.17).

$^1$H NMR (CDCl$_3$, 300MHz): δ 7.94 (1H, d, J = 9.0Hz, H-4'), 7.86 (1H, ddd, J = 8.4, 1.2, 0.6Hz, H-8'), 7.79 (1H, bdd, J = 8.1. 0.6Hz, H-5'), 7.49 (1H, ddd, J = 8.4, 6.9, 1.5Hz, H-7'), 7.38 (1H, dd, J = 8.1, 6.9, 1.2Hz, H-6'), 7.29 (1H, d, J = 9.0Hz, H-3'), 4.00 (3H, s, 2'OCH$_3$), 3.79 (1H, d, J = 2.0Hz, H-2), 3.23 (1H, dq, J = 2.0, 5.1Hz, H-3), 1.44 (3H, d, J = 5.1Hz, H-4).

$^{13}$C APT-NMR (CDCl$_3$, 75MHz) δ 201.5 (qC, C-1), 156.6 (qC, C-2'), 133.1 (CH, C-4'), 131.1 (qC, C-8a'), 128.8 (qC, C-4a'), 128.8 (CH, C-5', C-7' co-in), 124.3 (CH, C-6'), 123.6 (CH, C-8'), 120.8 (qC, C-1'), 112.5 (CH, C-3'), 61.6 (CH, C-2), 56.6 (CH, 2'OCH$_3$), 56.1 (CH$_3$, C-3), 17.6 (CH$_3$, C-4).
4.1.8.2 (±)-(2-Methoxynaphthalen-1-yl)(2,3-dimethyloxiran-2-yl)methanone (±)-135

Brown solid, yield 87% (stirred for 48h).
M.p.: 68-70°C (amorph.).
IR: v (cm⁻¹): 3001 w, 1689 s, 1624 m, 1593 m, 1469 m, 1435 m, 1342 m, 1257 s, 1176 m, 1149 m, 1091 m, 1068 m, 813 m.
EIMS m/z 256 [M⁺] (74), 240 (10), 185 (100), 170 (40), 152 (18), 142 (62), 127 (48), 114 (46).
HREI-MS m/z 256.1100 (calcd for C₁₆H₁₆O₃, 256.1099).
UV (DCM) λ max (log ε): 228 (4.71), 290 (3.55), 334 (3.44).
¹H NMR (CDCl₃, 300MHz): δ 7.90 (1H, d, J = 9.0Hz, H-4'), 7.78(1H, d, J = 8.4Hz, H-8'), 7.61 (1H, d, J = 8.4Hz, H-5'), 7.46 (1H, dd, J = 8.4, 8.1Hz, H-7'), 7.35 (1H, dd, J = 8.4, 8.1Hz, H-6'), 3.98 (3H, s, H-2'OMe), 3.03 (1H, q, J = 5.4Hz, H-3), 1.66 (3H, s, H-2Me), 1.34 (3H, d, J = 5.4Hz, H-4).
¹³C APT-NMR (CDCl₃, 75MHz) δ 207.0 (qC, C-l), 155.2 (qC, C-2'), 131.9 (CH, C-4'), 131.5 (qC, C-8a'), 128.7 (qC, C-4a'), 128.2 (CH, C-8'), 127.7 (CH, C-6'), 124.0 (CH, C-7'), 123.4 (CH, C-5'), 120.5 (qC, C-1'), 112.6 (CH, C-3'), 64.7 (qC, C-2), 57.6 (CH, C-3), 56.7 (CH₃, C-2'OMe), 13.7 (CH₃, C-4), 12.8 (CH₃, C-2Me).

4.1.8.3 (±)-(2-Methoxynaphthalen-1-yl)(3-phenyloxiran-2-yl)methanone (±)-146

Off white plate crystals, yield 84% (stirred 2h).
M.p.: 127-129°C (amorph.).
IR: v (cm⁻¹): 3039 w, 1666 s, 1512 m, 1440 m, 1276 m, 1253 m, 1184 m, 1157 m, 1068 m, 875 m, 821 m, 744 m.
EIMS m/z 304 [M⁺] (20), 288 (7), 273 (12), 185 (100), 170 (11), 158 (23), 142 (22), 127 (23), 114 (21).
HREI-MS m/z 304.1100 (calcd for C₂₀H₁₆O₃, 304.1099).
UV (DCM) λ max (log ε): 229 (4.81), 281 (3.95), 333 (3.84).
¹H NMR (CDCl₃, 300MHz): δ 8.03 (1H, dd, J = 8.7, 1.1Hz, H-8'), 7.96 (1H, d, J = 9.0Hz, H-4'), 7.86 (1H, bd, J = 8.1Hz, H-5'), 7.54 (1H, ddd, J = 8.7, 7.0, 1.4Hz, H-7'), 7.40 (1H, ddd, J = 8.1, 7.0, 1.1Hz, H-6'), 7.36 (5H, m, H-5, H-6, H-7), 7.27 (1H, d, J = 9.0Hz, H-3'), 4.11 (1H, d, J = 2.0Hz, H-3) 4.39 (1H, d, J= 2.0Hz, H-2), 3.86 (3H, s, H-2'OMe).
¹³C APT-NMR (CDCl₃, 75MHz) δ 199.4 (qC, C-1), 157* (qC, C-2'), 136.1 (qC, C-4), 133.6 (CH, C-4'), 131.2 (qC, C-8a'), 128.9 (qC, C-4a'), 128.7 (CH, C-7'), 128.6 (CH, C-6), 128.5 (CH, C-5'), 128.3 (CH, C-7), 125.8 (CH, C-5), 124.4 (CH, H-6'), 123.8
(CH, C-8'), 117* (qC, C-1'), 112.4 (CH, C-3'), 64.6 (CH, C-2), 59.9 (CH, C-3), 56.5 (CH₃, C-2'OMe).

*Assigned by HMBC

4.1.9 Cyclisation of Epoxides

4.1.9.1 Synthesis of 2-Hydroxy-3-methyl-2,3-dihydro-1H-benzo[\]chromen-1-one (±)-37

To a stirred solution of epoxide (±)-80 (958mg, 3.96mmol) in DCM (10mL), cooled in ice and under N₂ atmosphere, was added AlCl₃ (531mg, 3.98mmol). After 20h the reaction was diluted with H₂O and extracted exhaustively with DCM. The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to give a light tan oil (849mg) which was purified by flash column chromatography (silica gel 0.040-0.063mm; DCM→EtOAc) to realize (±)-37 (375mg, 1.64mmol, 41%) as an off white amorphous solid, and 120 (137mg, 0.75mmol, 19%) as a mixture of diastereomers which subsequently dehydrated to 128.

4.1.9.1.1 (±)-2-Hydroxy-3-methyl-2,3-dihydro-1H-benzo[\]chromen-1-one 37

[Chemical structure image]

Off white needles, yield 41%.

M.p.: 115-117°C (EtOAc).

IR: ν (cm⁻¹): 3475 m, 1662 s, 1616 m, 1597 m, 1566 m, 1438 m, 1315 m, 1234 m, 1087 s, 1041 m, 1022 m, 933 m, 829 m, 752 m.

EI MS m/z 228 [M⁺] (33), 171 (100), 142 (18), 127 (8), 114 (32).

HREI-MS m/z 228.0784 (calcd for C₁₄H₁₂O₃, 228.0786).

UV (DCM) λ_max (log ε): 224 (4.38), 241 sh (4.22), 267 sh (3.63), 317 (3.74).

¹H NMR (CDCl₃, 300MHz): δ 9.34 (1H, bdd, J = 8.4, 0.6Hz, H-10), 7.96 (1H, d, J = 9.0Hz, H-6), 7.77 (1H, bdd, J = 8.1, 0.6Hz, H-7), 7.66 (1H, ddd, J = 8.4, 7.2, 1.5Hz, H-9), 7.45 (1H, ddd, 8.1, 7.2, 0.6Hz, H-8), 7.09 (1H, d, J = 9.0Hz, H-5), 4.39 (1H, dq, J = 12.2, 6.0Hz, H-3), 4.24 (1H, d, J = 12.2Hz, H-2), 4.04 (1H, bs, 2-OH), 1.69 (3H, d, J = 6.0Hz, 3Me).

¹³C APT-NMR (CDCl₃, 75MHz) δ 195.1 (qC, C-1) 164.0 (qC, C-4a), 138.2 (CH, C-6), 131.2 (qC, C-10a), 129.9 (CH, C-9), 129.0 (qC, C-6a), 128.5 (CH, C-7), 125.1 (CH, C-8), 124.9 (CH, C-10), 118.5 (CH, C-5), 109.7 (qC, C-10b), 78.6 (CH, C-3), 73.5 (CH, C-2), 18.5 (CH₃, 3Me).

4.1.9.1.2 2-(1-Hydroxyethyl)naphtho[2,1-b]furan-1(2H)-one 120
Obtained as a pair of diastereomers in ~2:1 ratio.

EIMS m/z 228 [M⁺] (20), 210 (25), 184 (100), 155 (60), 126 (55).

HREI-MS m/z 228.0785 (calcd for C₁₄H₁₂O₃, 228.0789).

¹H NMR (CDCl₃, 300MHz) [chemical shift of the minor diastereomer]: δ 8.72 [8.74] (1H, bd, J = 8.3Hz, H-9), 8.11 [8.09] (1H, d, J = 9.0Hz, H-5), 7.85 [7.84] (1H, bd, J = 8.3Hz, H-6), 7.67 [7.67] (1H, ddd, J = 8.3, 6.3, 1.5Hz, H-8), 7.48 [7.48] (1H, ddd, J = 8.3, 6.3, 1.5Hz, H-7), 7.29 [7.30] (1H, d, J = 9.0Hz, H-4), 4.55 [4.62] (1H, d, J = 5.8 [4.7]Hz, H-2), 4.13 [4.39] (1H, dq, J = 7.0, 5.8 [4.7]Hz, H-1’), 1.37 [1.44] (3H, d, J = 7.0Hz, H-2’).

4.1.9.1.3 (Z)-2-Ethylidenenaphtho[2,1-b]furan-1(2H)-one 128

Brown oil (obtained from the decomposition of 120).

IR: ν (cm⁻¹): 3055 w, 1712 s br, 1631 m, 1581 m, 1512 m, 1377 w, 1342 w, 1253 s, 1207 m, 1130 m, 1072 m.

EIMS m/z 210 [M⁺] (100), 181 (14), 170 (10), 155 (22), 126 (28), 114 (20), 87(26), 71 (45).

HREI-MS m/z 210.0680 (calcd for C₁₄H₁₀O₂, 210.0681).

UV (DCM) λmax (log ε): 227 (4.40), 316 (3.74).

¹H NMR (CDCl₃, 300MHz): δ 8.81 (1H, bd, J = 8.1Hz, H-9), 8.08 (1H, d, J = 9.2Hz, H-5), 7.85 (1H, bd, J = 8.1Hz, H-6), 7.67 (1H, ddd, J = 8.1, 7.1, 1.2Hz, H-8), 7.49 (1H, ddd, J = 8.1, 7.1, 1.2Hz, H-7), 7.35 (1H, d, J = 9.2Hz, H-4), 6.30 (1H, q, J = 7.5Hz, 2H-1’), 2.07 (3H, d, J = 2.07Hz, H-2’).

¹³C APT-NMR (CDCl₃, 75MHz) δ 183.4 (qC, C-1), 167.0 (qC, C-3a), 150.5 (qC, C-2), 138.9 (CH, C-5), 129.7 (CH, C-8), 129.7 (qC, C-9a), 129.4 (qC, C-5a), 128.5 (CH, C-6), 125.6 (CH, C-7), 123.6 (CH, C-9), 114.8 (qC, C-9b), 113.0 (CH, C-4), 112.7 (CH, C-1’), 11.3 (CH₃, C-2’).

4.1.9.2 Synthesis of 2,3-Dihydro-3-methyl-1-oxo-1H-benzo[f]chromen-2-yl Acetate 169

A solution of 2-hydroxybenzo[f]chromanone (±)-37 (32mg, 0.14mmol) in pyridine (0.5mL) and Ac₂O (0.5mL) was stirred at room temperature. After 16h the solution was diluted with H₂O, and extracted exhaustively with Et₂O. The combined organic fractions were washed with 1N HCl/5% NaHCO₃/H₂O, then dried (MgSO₄), filtered and concentrated in vacuo to yield 169 (32mg, 0.12mmol, 86%).
4.1.9.2.1 (±)-2,3-Dihydro-3-methyl-1-oxo-1H-benzo[f]chromen-2-yl Acetate 169

M.p.: 125-127°C (amorph.).

IR: ν (cm⁻¹): 2982 w, 1747 s, 1681 s, 1620 m, 1597 m, 1512 m, 1438 m, 1377 m, 1226 s, 1080 m, 829 m, 759 m.

EIMS m/z 270 [M⁺] (55), 226 (10), 210 (90), 184 (31), 171 (100), 155 (8), 142 (30), 127 (29), 114 (42), 95 (10).

HREI-MS m/z 270.0892 (calcd for C₁₆H₁₄O₄, 270.0892).

UV (DCM) λ_max (log ε): 225 (4.41), 240 sh (4.22), 265 sh (3.82), 317 (3.75).

¹H NMR (CDCl₃, 300MHz): δ 9.36 (1H, d, J = 8.7Hz, H-10), 7.95 (1H, d, J = 9.0Hz, H-6), 7.76 (1H, d, J = 8.1Hz, H-7), 7.63 (1H, dd, J = 8.7, 7.1Hz, H-9), 7.44 (1H, dd, J = 8.1, 7.1Hz, H-8), 7.10 (1H, d, J = 9.0Hz, H-5), 5.48 (1H, d, J = 12.2Hz, H-2), 4.71 (1H, dq, J = 12.2, 6.3Hz, H-3), 2.29 (3H, s, H-2'), 1.59 (3H, d, J = 6.3Hz, H-3Me).

¹³C APT-NMR (CDCl₃, 75MHz) δ 189.1 (qC, C-1), 169.8 (qC, C-1'), 163.0 (qC, C-4a), 137.9 (CH, C-6), 131.3 (qC, C-10a), 129.8 (CH, C-9), 129.2 (qC, C-6a), 128.4 (CH, C-7), 125.3 (CH, C-10), 125.1 (CH, C-8), 118.3 (CH, C-5), 110.9 (qC, C-10b), 75.9 (CH, C-3), 74.6 (CH, C-2), 20.6 (CH₃, C-2'), 18.1 (CH₃, C-3Me).

4.1.9.3 Synthesis of 2,3-Dihydro-2-hydroxy-2,3-dimethylbenzo[f]chromen-1-one (±)-136

To a stirred solution of epoxide (±)-135 (71 mg, 0.28mmol) in distilled DCM (5mL) cooled in an ice/NaCl bath, was added AlCl₃ (42 mg, 0.31 mmol). The solution was kept at -20°C and quenched with ice cooled 1N HCl (20mL) after 60h, then extracted exhaustively with Et₂O. The organic phase was washed with 5% NaHCO₃/THO, dried (MgSO₄), filtered, and concentrated in vacuo to yield the crude product (42 mg) which was purified by flash column chromatography (silica gel 0.040-0.063mm; DCM/EtOAc 100:0—80:20) realizing (±)-136 (11 mg, 45 μmol, 16%) and (±)-137 (22 mg, 91 μmol, 33%) as off white amorphous solids.

4.1.9.3.1 (±)-2,3-Dihydro-2-hydroxy-2,3-dimethylbenzo[f]chromen-1-one (±)-136

M.p.: 65-68°C (amorph.).

IR: ν (cm⁻¹): 3468 wbr2877 w, 1666 s br, 1620 m, 1597 m, 1566 m, 1516 m, 1438 m, 1377 m, 1153 m, 1090 m, 1018 m, 825 m, 756 m.

EIMS m/z 242 [M⁺⁺] (55), 225 (8), 199 (20), 185 (30), 171 (100), 153 (7), 142 (25), 127 (25), 115 (50).
HREI-MS m/z 242.0938 (calcd for C_{15}H_{14}O_{3}, 242.0943).

UV (DCM) \( \lambda_{\text{max}} \) (log \( e \)): 225 (4.41), 240 sh (4.21), 266 sh (3.68), 316 (3.70).

\(^1\)H NMR (CDCl\(_3\), 300MHz): \( \delta \) 9.35 (1H, dd, \( J = 8.4, 0.9\)Hz, H-10), 7.96 (1H, d, \( J = 9.0\)Hz, H-6), 7.78 (1H, dd, \( J = 8.1, 1.4\)Hz, H-7), 7.66 (1H, ddd, \( J = 8.4, 7.1, 1.4\)Hz, H-9), 7.46 (1H, ddd, \( J = 8.1, 7.1, 0.9\)Hz, H-8), 7.14 (1H, d, \( J = 9.0\)Hz, H-5), 4.44 (1H, q, \( J = 6.6\)Hz, H-3), 4.11, (1H, bs, 2-OH), 1.58 (3H, d, \( J = 6.6\)Hz, 3Me), 1.32 (3H, s, 2Me).

\(^{13}\)C APT-NMR (CDCl\(_3\), 75MHz) \( \delta \) 198.5 (qC, C-1), 163.5 (qC, C-4a), 138.1 (CH, C-6), 131.6 (qC, C-10a), 129.8 (CH, C-9), 129.1 (qC, C-6a), 128.5 (CH, C-7), 125.1 (CH, C-8), 125.0 (CH, C-10), 118.5 (CH, C-5), 109.0 (qC, C-10b), 79.5 (CH, C-3), 72.4 (qC, C-2), 17.7 (CH\(_3\), 3Me), 13.9 (CH\(_3\), 2Me).

4.1.9.3.2 (±)-2-(1-Hydroxyethyl)-2-methylnaphtho[2,1-b]furan-1(2H)-one (±)-137

M.p.: 116-118°C (amorph.).

IR: \( v \) (cm\(^{-1}\)): 3444 w br, 2978 w, 1685 s br, 1581 m, 1373 w, 1284 m, 1257 m, 1211 w, 1157 w, 1068 m, 1010 w, 933 w, 821 m, 752 m.

EIMS m/z 242 [M\(^{+}\)] (28), 198 (100), 183 (18), 171 (25), 155 (41), 141 (20), 126 (70), 115 (31).

HREI-MS m/z 242.0944 (calcd for C\(_{15}\)H\(_{14}\)O\(_3\), 242.0943).

UV (DCM) \( \lambda_{\text{max}} \) (log \( e \)): 225 (4.40), 238 (4.33), 265 sh (3.76), 310 (4.82).

\(^1\)H NMR (CDCl\(_3\), 300MHz): \( \delta \) 8.72 (1H, dd, \( J = 8.3, 1.0\)Hz, H-9), 8.09 (1H, d, \( J = 9.0\)Hz, H-5), 7.84 (1H, d, \( J = 8.1\)Hz, H-6), 7.67 (1H, dd, \( J = 8.3, 7.0\)Hz, H-8), 7.48 (1H, ddd, \( J = 8.1, 7.0, 1.0\)Hz, H-7), 7.26 (1H, d, \( J = 9.0\)Hz, H-4), 4.00 (1H, q, \( J = 6.5\)Hz, H-1'), 1.58 (3H, s, H-2Me), 1.25 (3H, d, \( J = 6.5\)Hz, H-2').

\(^{13}\)C APT-NMR (CDCl\(_3\), 75MHz) \( \delta \) 203.5 (qC, C-1), 174.6 (qC, C-3a), 140.3 (CH, C-5), 129.9 (CH, C-8), 129.4 (qC, C-9a), 129.2 (qC, C-5a), 128.5 (CH, C-6), 125.4 (CH, C-7); 123.1 (CH, C-9), 113.8 (CH, C-4), 112.3 (qC, C-9b), 91.6 (qC, C-2), 70.0 (CH, C-1'), 17.2 (CH\(_3\), 2Me), 16.9 (CH\(_3\), 2').

4.1.10 Synthesis of 3-Methyl-1H-benzo[\( f\)]chromen-1-one 58

To a stirred solution of benzo[\( f\)]chromanone (±)-53 (113mg, 0.533mmol) in Et\(_2\)O (20mL) was added dropwise Br\(_2\) (90mg, 0.53mmol). After 10min the solution was concentrated \textit{in vacuo} and taken up in DCM to be washed with 1N NaOH and H\(_2\)O. The organic phase was dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo} to yield the crude product (96mg, 0.33mmol, 62%) which was directly reacted with Et\(_3\)N (1mL) in THF.
(2mL). After 20h the solution was extracted exhaustively with Et₂O/1N HCl/H₂O to afford benzo[f]chromone 58 as a buff amorphous solid (48mg, 0.23mmol, 43%).

4.1.10.1 3-Methyl-1H-benzo[f]chromonen-1-one 58

M.p.: 163-165°C (amorph.).
IR: ν (cm⁻¹): 3059 w, 1651 s, 1616 m, 1238 m, 953 m, 817 m.
EIMS m/z 210 [M⁺] (100), 182 (50), 170 (40), 152 (18), 142 (20), 114 (45), 69 (45).
HREI-MS m/z 210.0681 (calcd for C₁₄H₁₀O₂, 210.0681).
UV (DCM) λmax (log ε): 224 (4.42), 254 (4.30), 302 (3.97).
¹H NMR (CDCl₃, 300MHz): δ 10.04 (1H, bd, J = 8.3Hz, H-10), 8.05 (1H, d, J = 9.2Hz, H-6), 7.89 (1H, bd, J = 8.0Hz, H-7), 7.74 (1H, ddd, J = 8.3, 6.8, 1.2Hz, H-9), 7.60 (1H, ddd, J = 8.0, 6.8, 1.2Hz, H-8), 7.48 (1H, d, J = 9.2Hz, H-5), 6.33 (1H, s, H-2), 2.43 (3H, s, H-3 CH₃).
¹³C APT-NMR (CDCl₃, 75MHz) δ 180.2 (qC, C-1), 163.3 (qC, C-3), 157.6 (qC, C-4a), 135.1 (CH, C-6), 130.5 (qC, C-10a), 129.1 (CH, C-9), 128.1 (CH, C-7), 127.1 (CH, C-10), 126.4 (CH, C-8), 117.5 (CH, C-5), 116.8 (qC, C-10b), 113.5 (CH, C-2), 19.9 (CH₃, C-3 CH₃).

4.1.10.2 General Method for the Attempted Epoxidation of 3-Methyl-1H-benzo[f]chromonen-1-one 58

To a solution of benzo[f]chromone 58 (0.053g, 0.25mmol) in solvent (3mL) was added H₂O₂ (30%v/v, 1mL) and 1N NaOH (0.5mL). The reaction was left to stir 20hr, at 0°C, under N₂, monitored by TLC and/or GCMS. The reaction mixture was extracted exhaustively with Et₂O. The organic phase was washed with 5% NaHCO₃/H₂O, dried (MgSO₄), filtered, and concentrated in vacuo to yield 2-hydroxy-1-naphthoic acid 166 (25.7mg, 55%). Other reagents and conditions were as listed in Table 3-12.

4.1.10.2.1 2-Hydroxy-1-naphthoic acid 166

EIMS m/z 188[M⁺] (70), 170 (100), 144 (70), 114 (75).
¹H NMR (CD₃OD, 300MHz): δ 8.85 (1H, d, J = 8.9Hz, H-4), 7.91 (1H, d, J = 8.7Hz, H-8), 7.45 (1H, d, J = 8.4Hz, H-5), 7.50 (bdd, J = 8.4, 8.4Hz, H-7) 7.32 (bdd, J = 8.7, 8.4Hz, H-6); 7.10 (1H, d, J = 8.9Hz, H-3).
13C APT-NMR (CD3OD, 75MHz) δ 137.5 (C-4), 129.9 (C-5), 129.2 (C-7), 126.5 (C-8), 124.5 (C-6), 119.9 (C-3).

4.1.10.3 Preparation of 1-Butyl-3-methyl Imidazolium Tetrafluoroborate 165
1-Butyl-3-methyl imidazolium tetrafluoroborate 165 was prepared by the literature method.118

4.1.10.4 Preparation of Manganic Acetate.
Manganic acetate was prepared in accordance with the literature.121

4.1.10.5 Attempted Acetoxylation of benzo[f]chromanone (±)-53
Following the method of Demir et al.120 a suspension of Mn(OAc)3 (0.22g, 1mmol) in benzene (60mL) in a Dean-Stark apparatus was refluxed for 45min. Benzo[f]chromanone (±)-53 (91mg, 0.4mmol) was added, and the suspension was left to reflux for 48h, monitoring by TLC. The suspension cooled, filtered, and washed with 5% NaHCO3 solution, and dried to return starting material.

4.2 Antibacterial Screening
Bioassays were performed to identify compounds with antibiotic activity. This was achieved by inoculation of a 83mm plate with 200µL suspension of bacterial cells in sterilized deionised H2O, and spreading this suspension over the agar surface with a flame sterilized glass spreader. The isolates used were clinically derived and used under appropriate physical containment levels. The isolates were stored in a glycerol-water matrix (1:4) at -20°C. The plate was dried for 10min in the laminar flow hood, while 5mm (φ) paper disks cut from filter paper were impregnated with a solution of the compound of interest, dissolved in a volatile solvent. The disks were impregnated with approximately 1mg of compound. The disks were allowed to air dry, and then pressed onto the agar surface. The plates were incubated for 24h and examined for growth inhibition around the disks.124

4.2.1 Preparation of Nutrient Agar (NA)
8g Nutrient Broth (Difco) and 20g agar per 1L was suspended in 1L tap water and autoclaved for 121°C for 20min.
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