

DESIGN, SYNTHESIS, AND ANTI-INFLUENZA ACTIVITY OF SUBSTITUTED
QUERCETINS AND PROGRESS TOWARDS THE SYNTHESIS OF MINI GRAPHENES
LIKE HEXA-PERI-BENZOCORONENE CYCLOPHANE

by

MAHENDRA THAPA

M.Sc., TRIBHUVAN UNIVERSITY, 2004

AN ABSTRACT OF A DISSERTATION

Submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry
College of Arts and Sciences

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2012

Abstract

The first chapter of the thesis involves the design, synthesis, and anti-influenza activity of quercetin derivatives. Influenza viruses are important pathogens that cause respiratory infections in humans and animals. In addition to vaccination, antiviral drugs against influenza virus play a significant role in controlling viral infections by reducing disease progression and virus transmission. Plant derived polyphenols are associated with antioxidant activity, anti-carcinogenic, and cardio- and neuro-protective actions. Some polyphenols, such as resveratrol and epigallocatechin gallate (EGCG), showed significant anti-influenza activity *in vitro*. The antiviral effects of isoquercetin were greater than that of quercetin with lower IC₅₀ values and higher *in vitro* therapeutic index. Various phenolic esters, alkoxy and aminoalkoxy derivatives of quercetin were synthesized by functionalization of C3, C3', and C5 hydroxyl groups. Antiviral activities of these synthesized compounds were tested against influenza virus (porcine H1N1 strain). Quercetin-3-gallate which is structurally similar to EGCG showed greater antiviral activity among the synthesized compounds. Its antiviral activity was comparable to that of EGCG with better *in vitro* therapeutic index.

Second chapter in the thesis involves the progress towards the synthesis of mini graphenes like hexa-peri-benzocorene cyclophane (HBCC). Bilayered graphenes are highly conducting materials with potential application in electronic devices and in lithium ion batteries. Despite great potential, bilayer graphenes with defined distance between the two layers have not been achieved through chemical synthesis. Chemical synthesis of HBCC from commercially available *p*-xylene was carried out. Final product, presumably compound **90** (the structure has not been completely characterized), is insoluble in all tested solvents including aqueous acids

and organic solvents such as DMSO, DMF, benzene, 1,2-dichlorobenzene, dichloromethane, THF, hexanes and diethyl ether. The insoluble nature of the final product **90** restricted the analysis to UV-visible spectroscopy. Synthesis of soluble analog incorporating the long chain ether groups is being investigated in Dr. Hua's laboratory.

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Major Professor
Dr. Duy H. Hua

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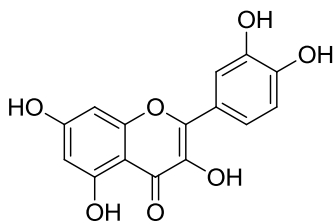
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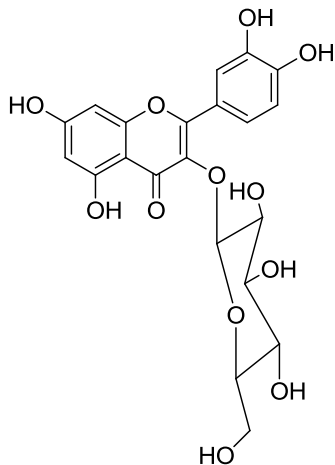
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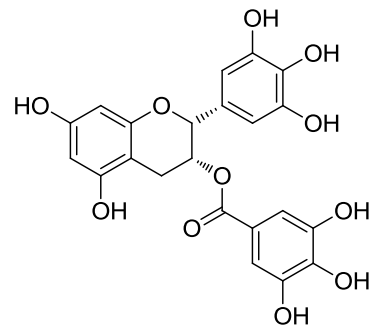
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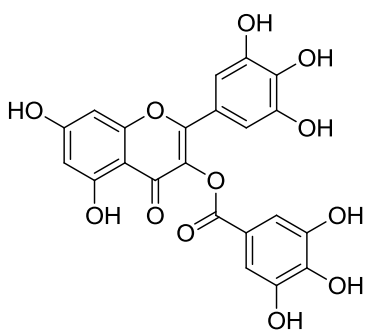
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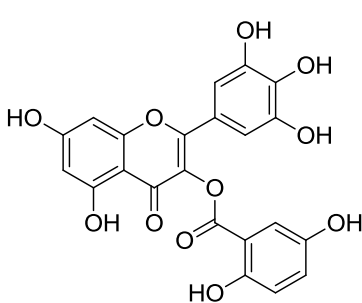
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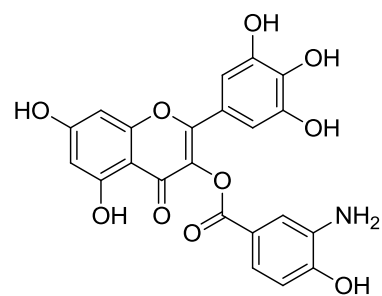
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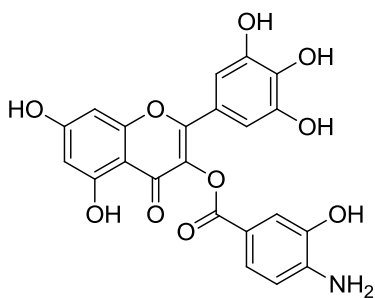
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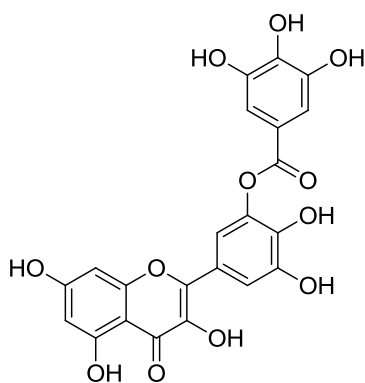
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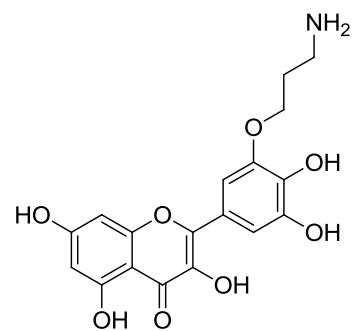
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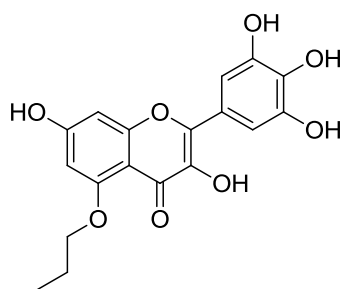
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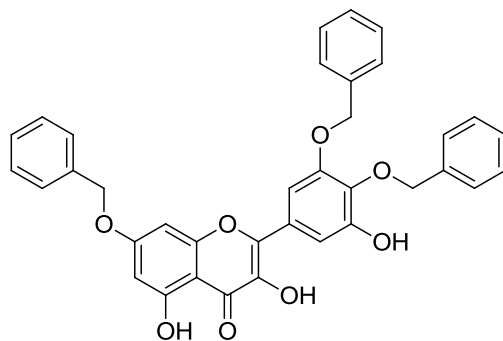
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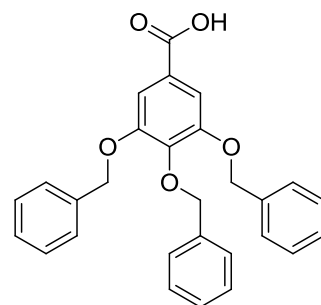
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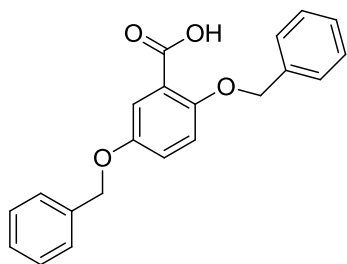
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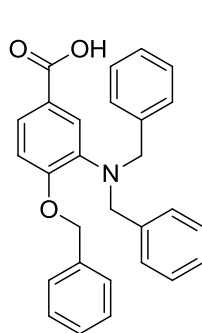
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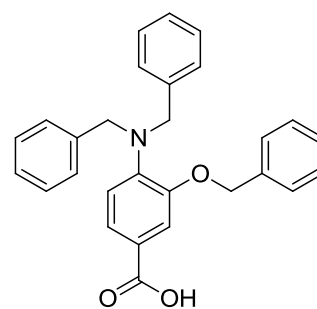
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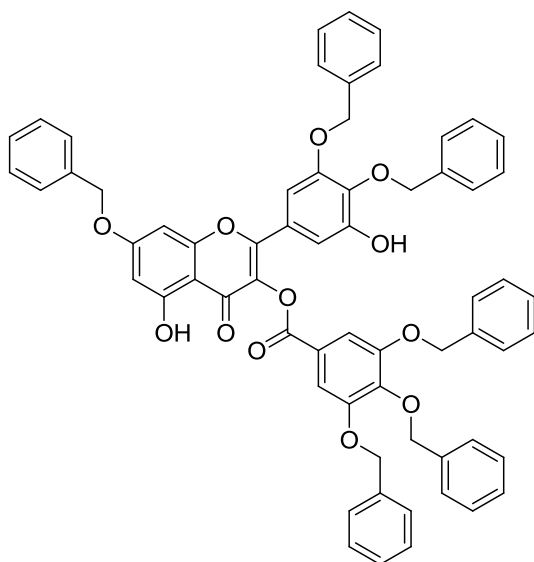
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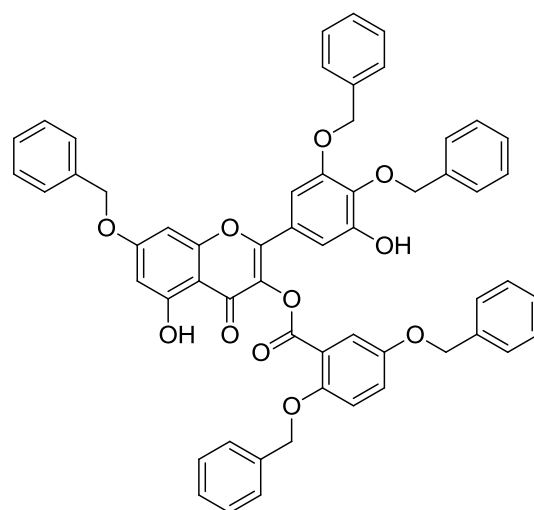
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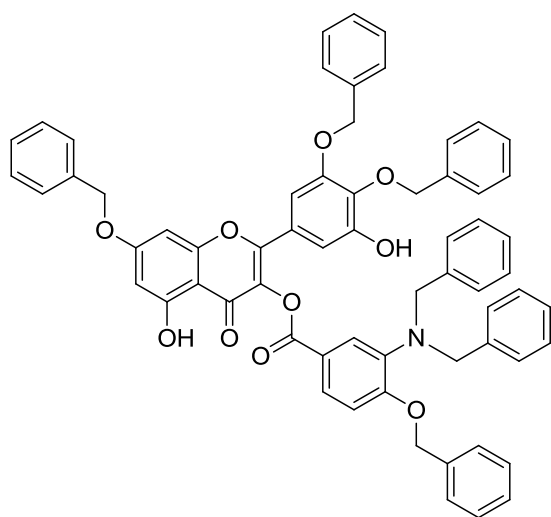
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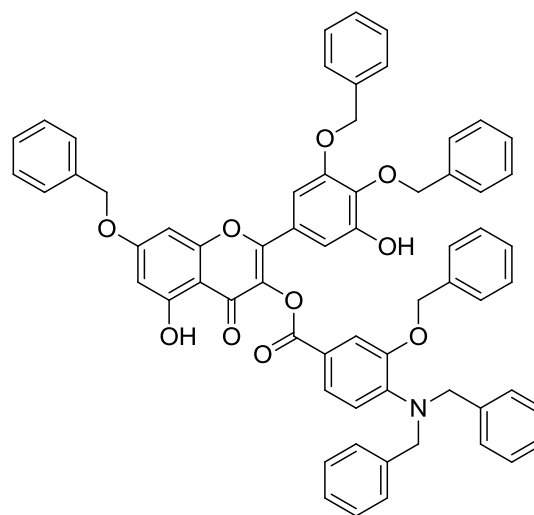
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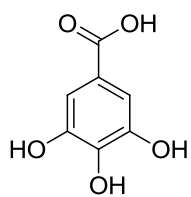
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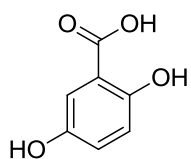
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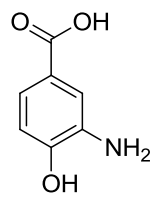
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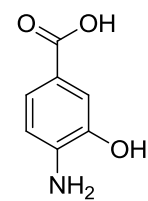
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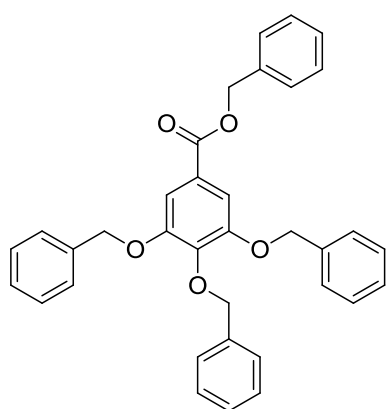
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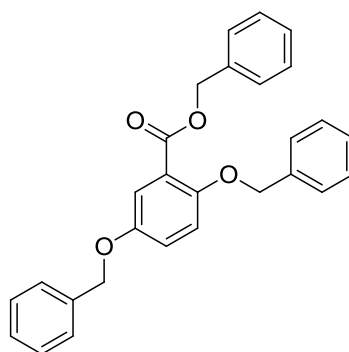
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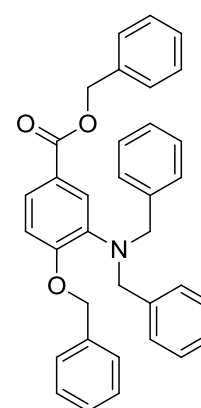
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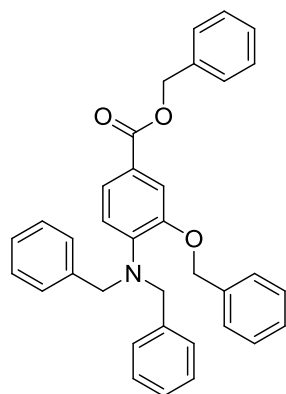
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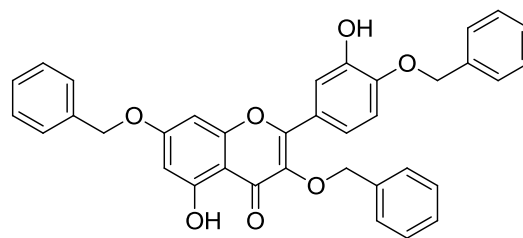
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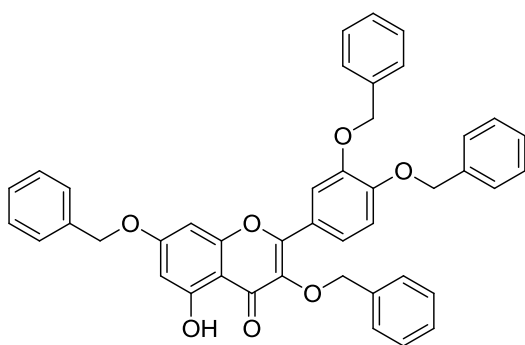
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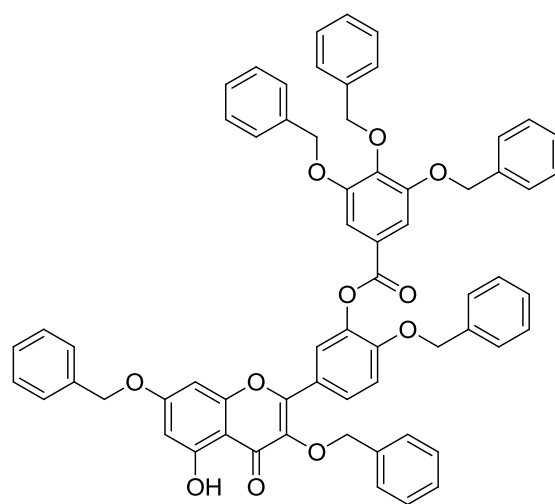
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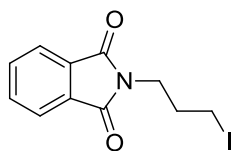
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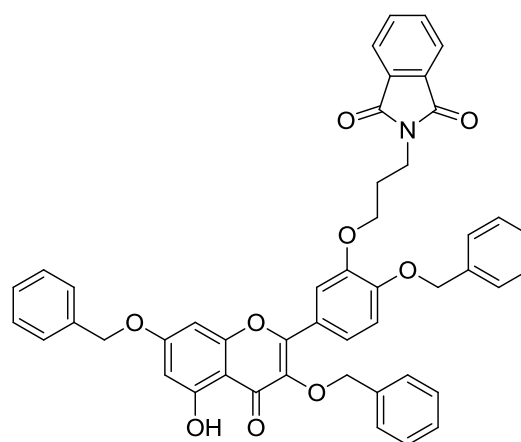
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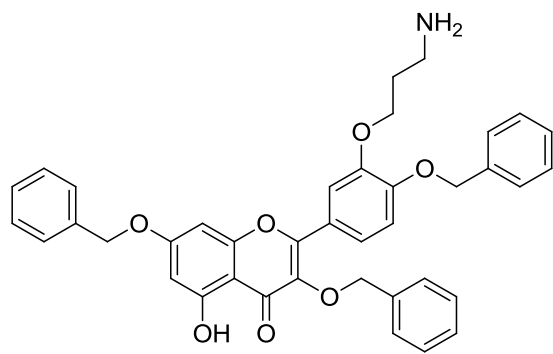
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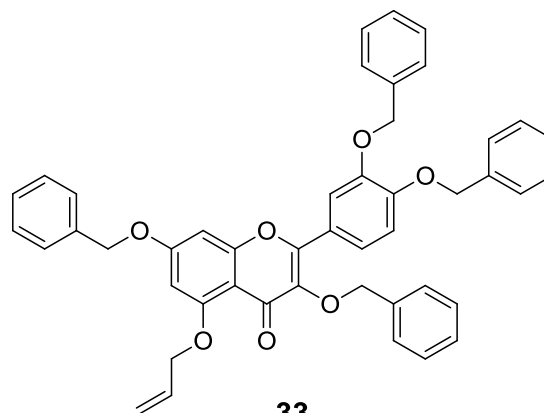
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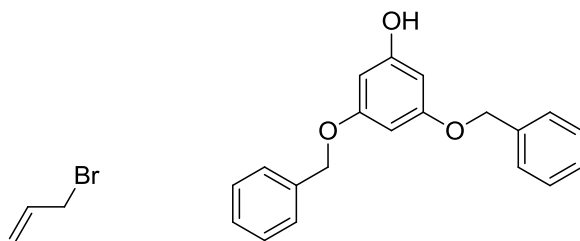
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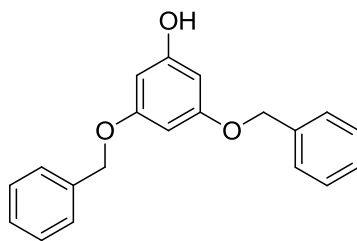
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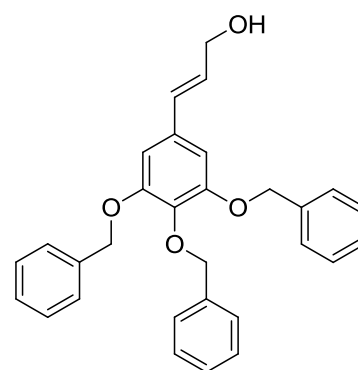
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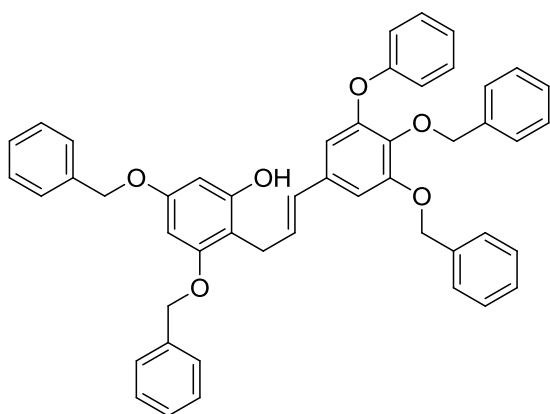
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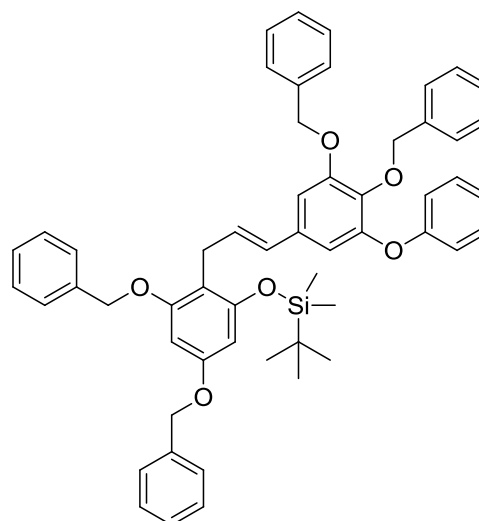
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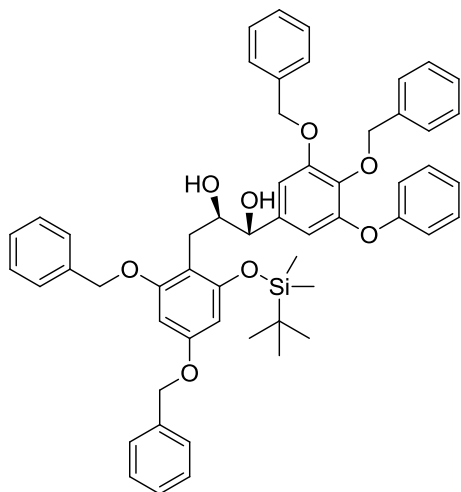
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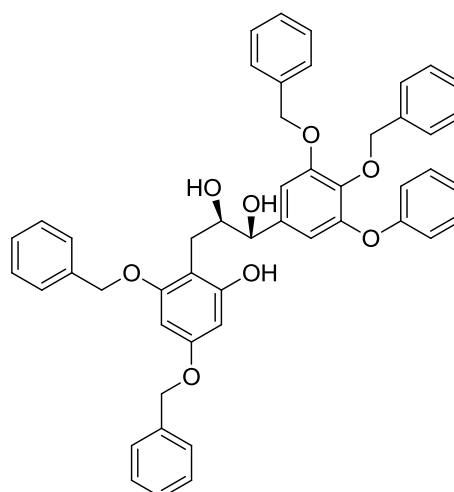
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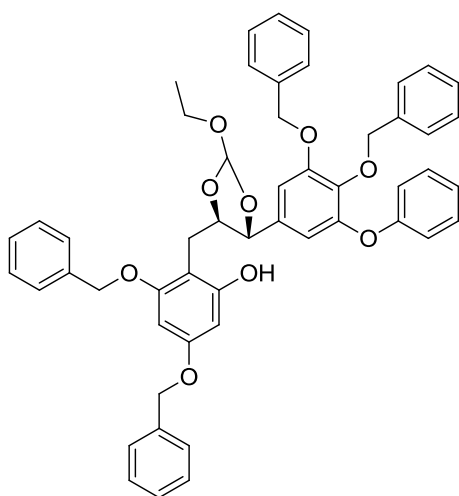
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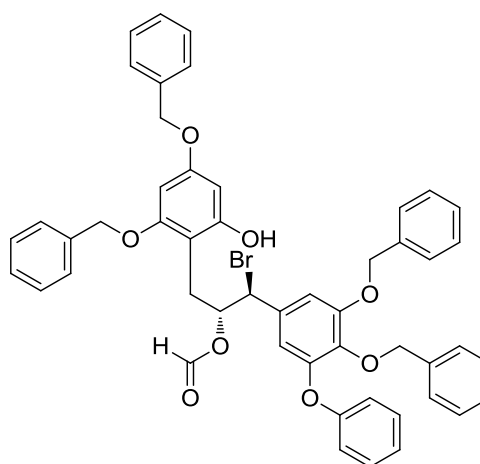
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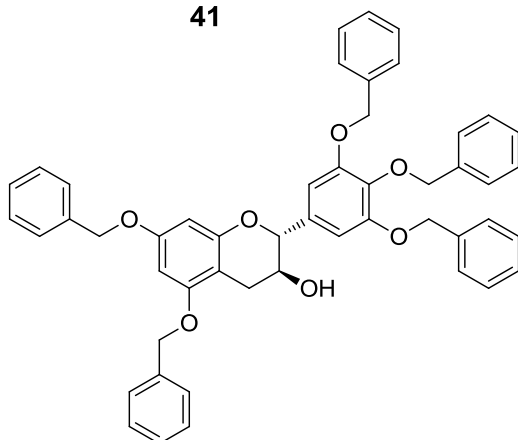
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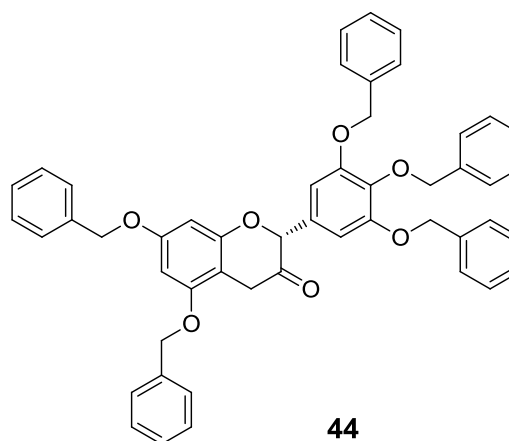
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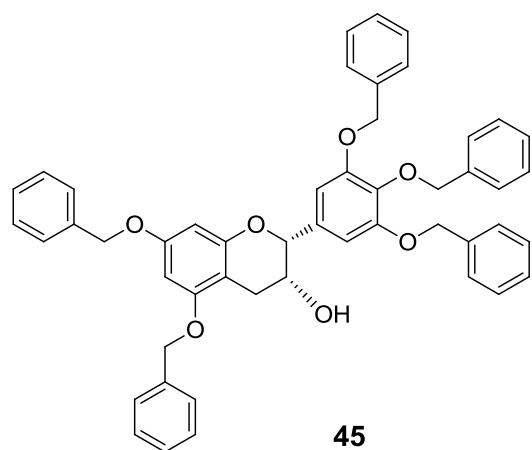
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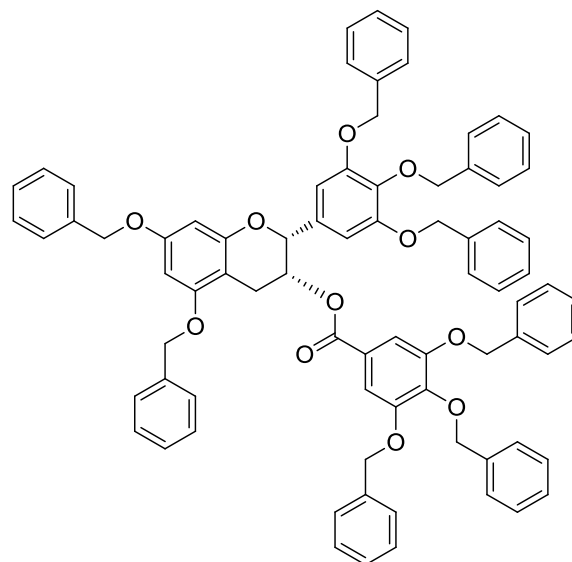
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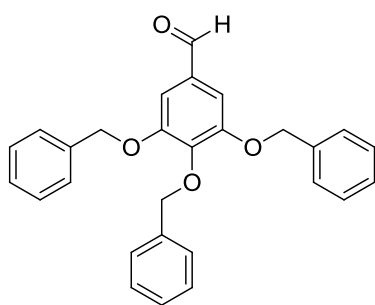
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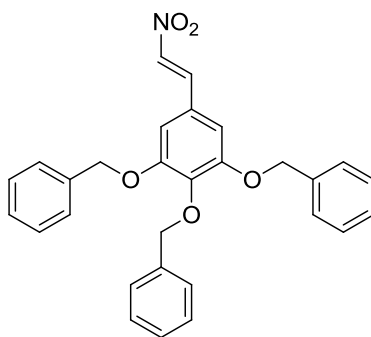
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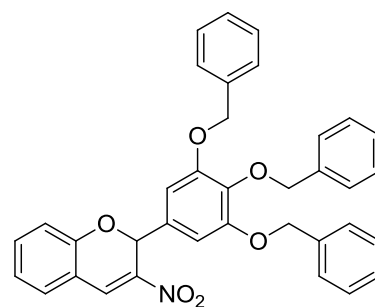
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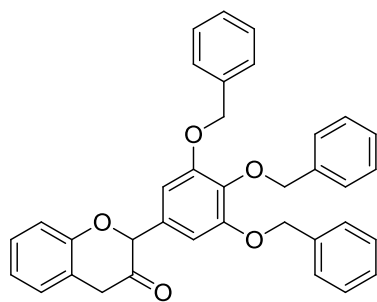
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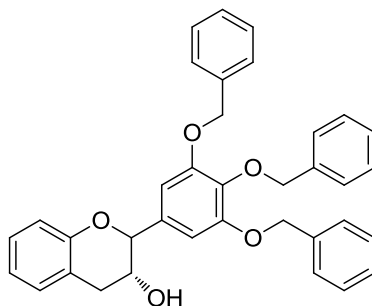
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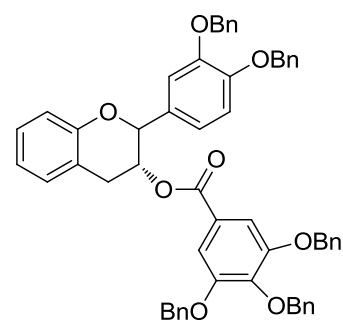
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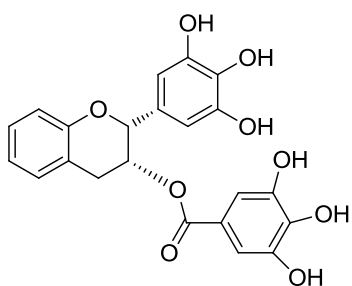
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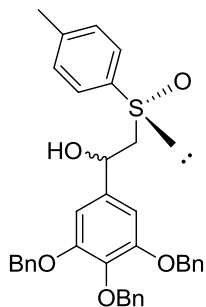
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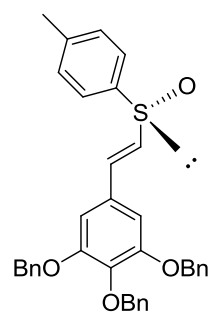
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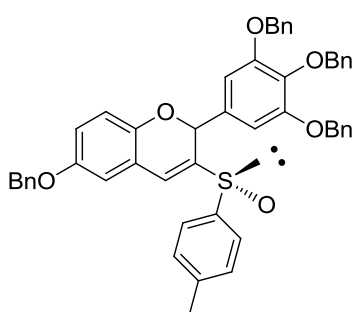
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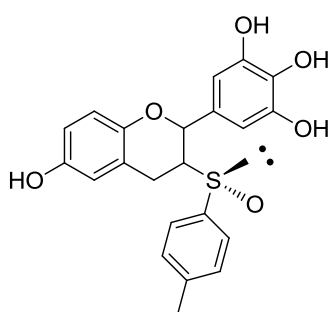
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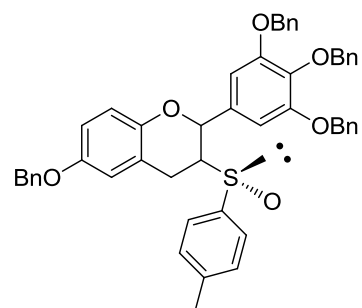
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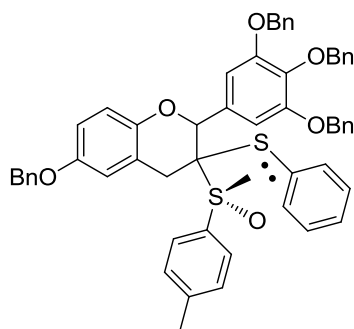
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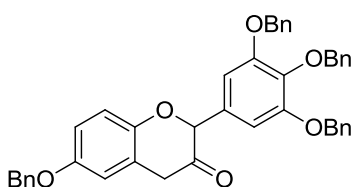
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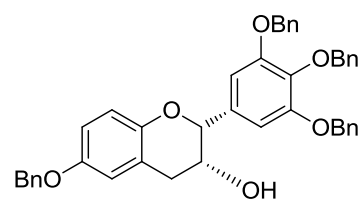
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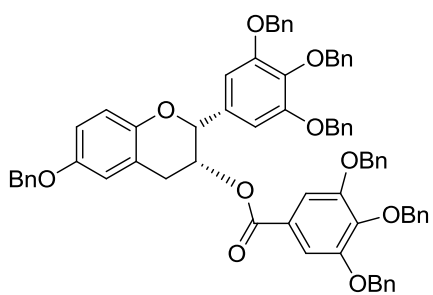
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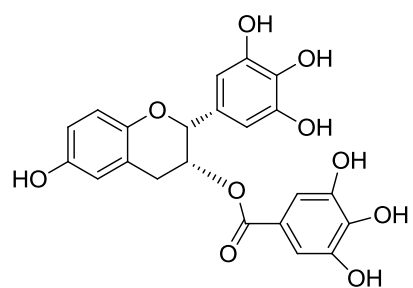
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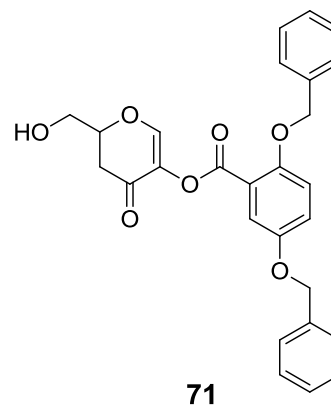
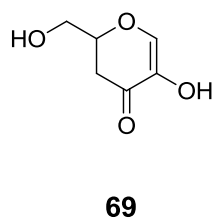
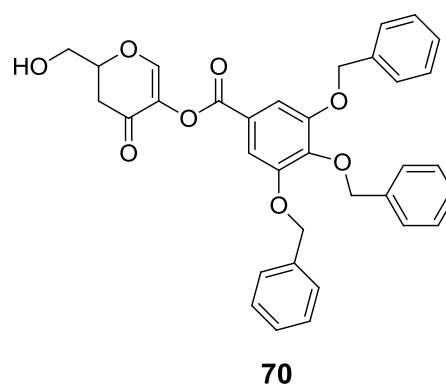
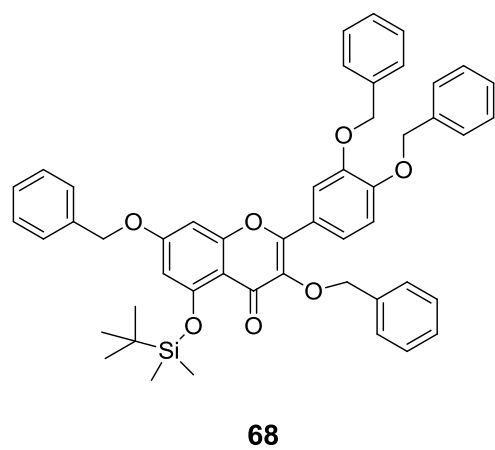
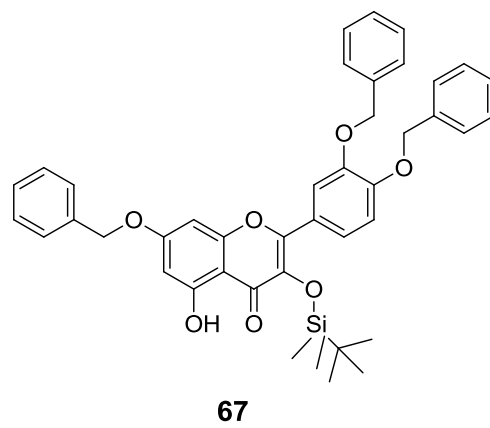
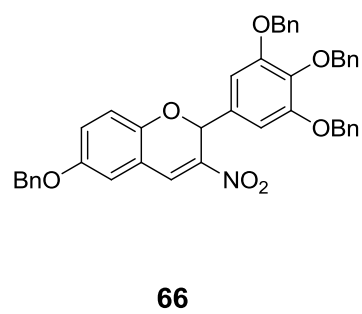
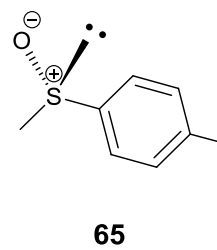
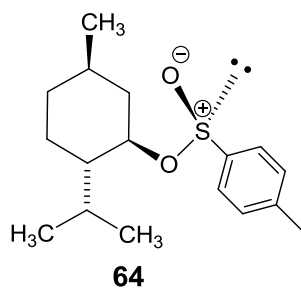
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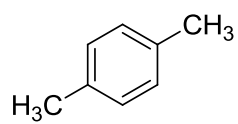


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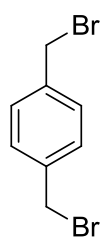


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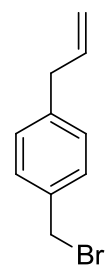




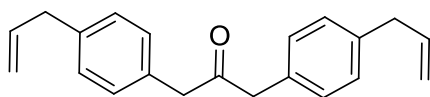
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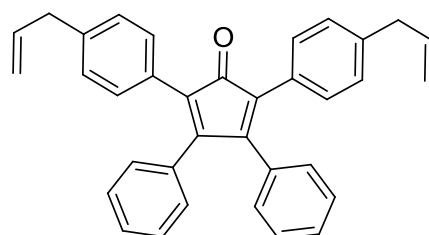
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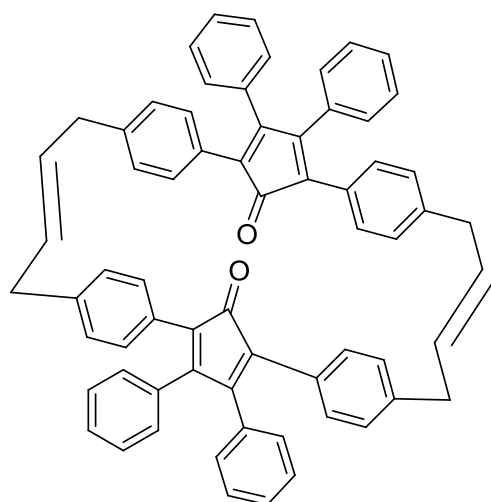
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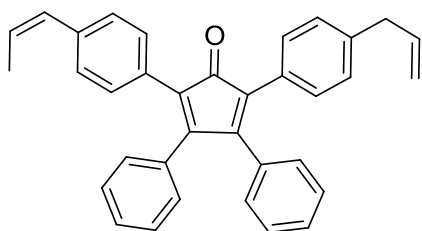
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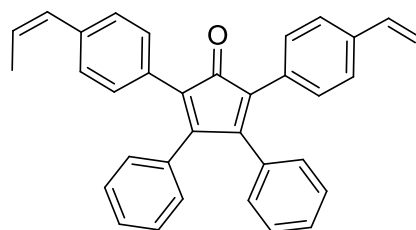
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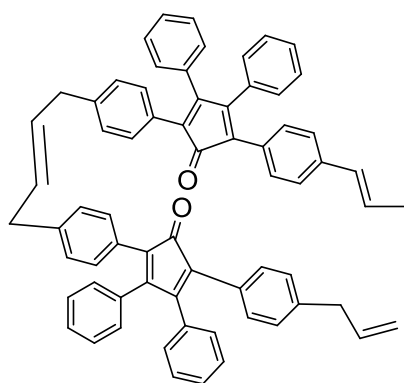
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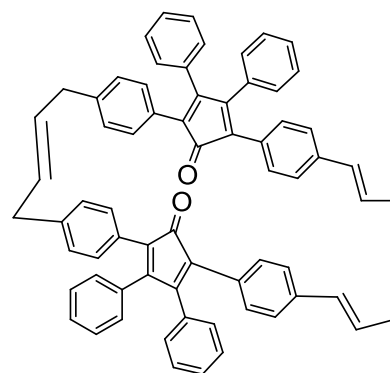
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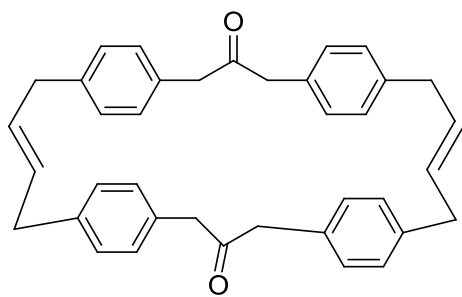
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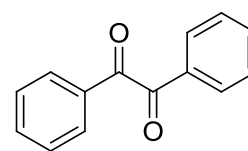
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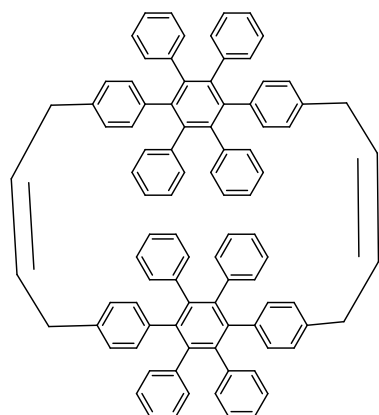
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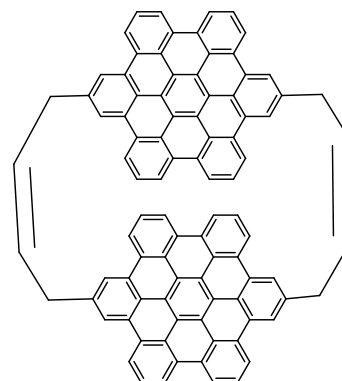
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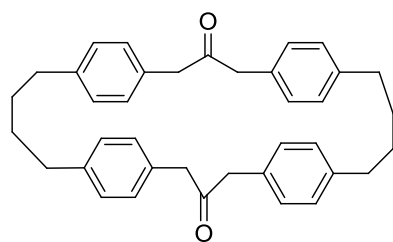
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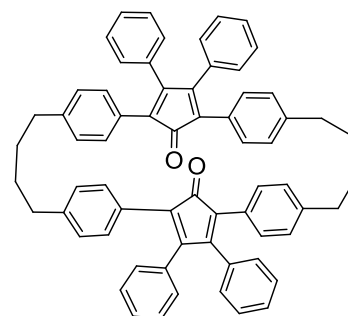
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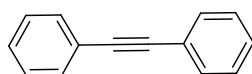
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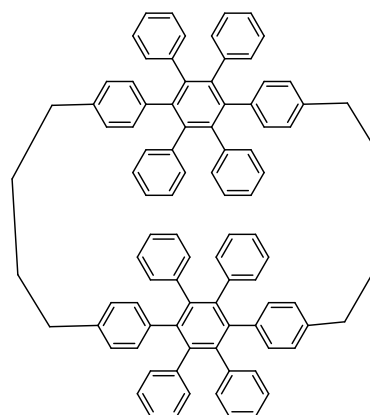
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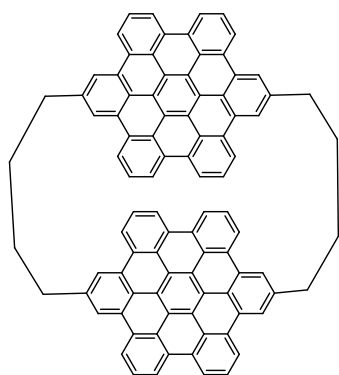
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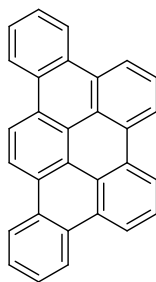


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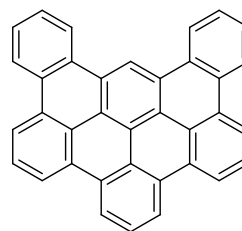


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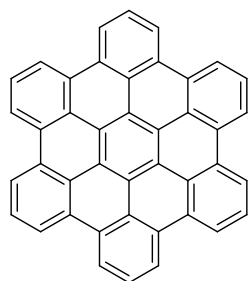
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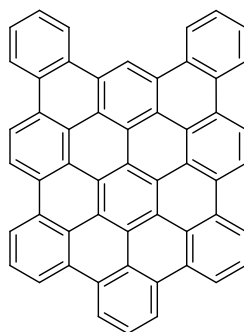
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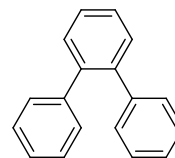
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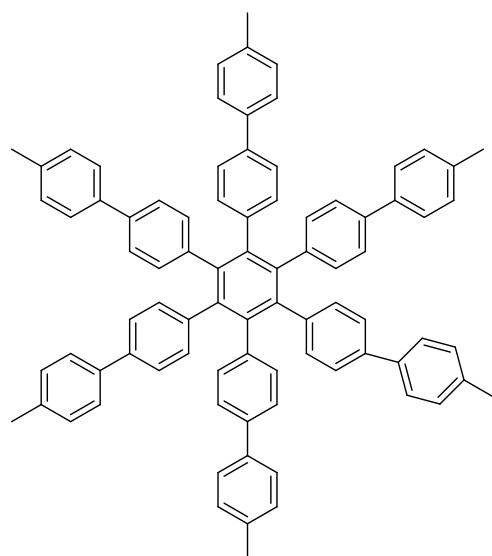
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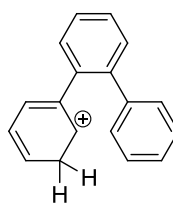
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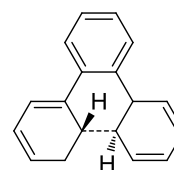
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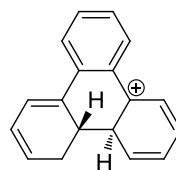
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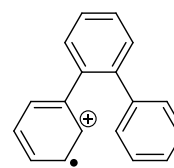
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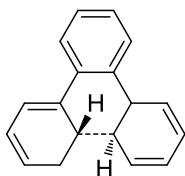
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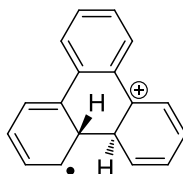
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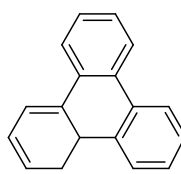
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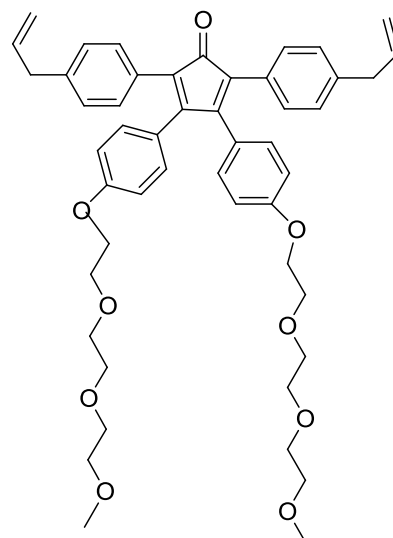
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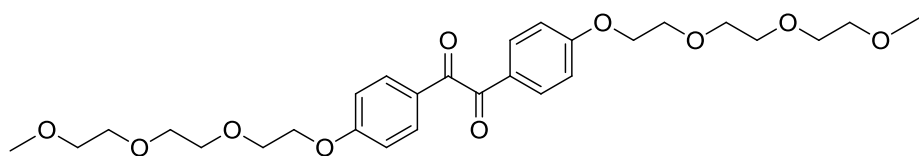
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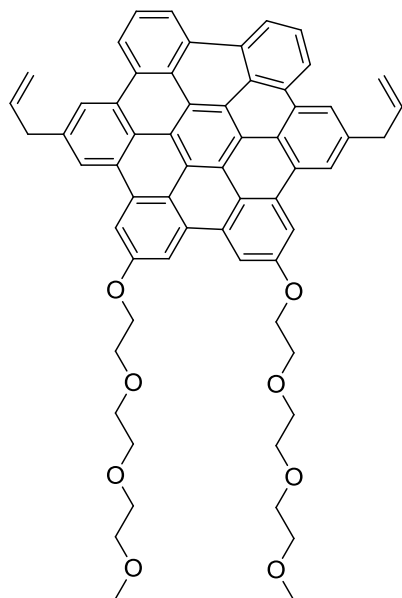
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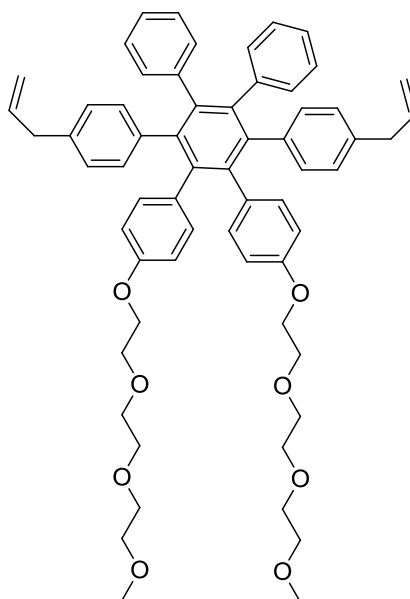
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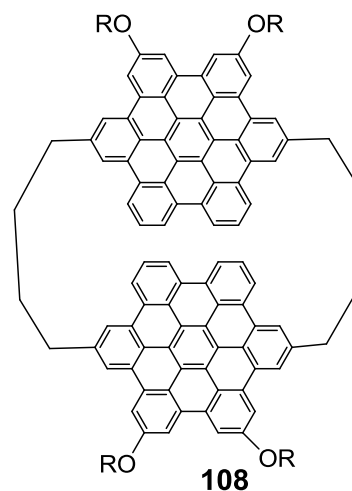
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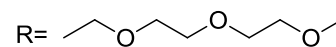
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Acknowledgements

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I would like to express my deepest gratitude to my parents and wife for all the love, care and moral support they provided. Their love and care have always helped me overcome various obstacles and move on with life.

Finally, thank you god for all opportunities and blessings I have.

List of abbreviations

AcOH	acetic acid
AFM	atomic force microscopy
Bn	benzyl
^{13}C NMR	carbon nuclear magnetic resonance
CNT	carbon nanotube
CPE	cytopathic effect
CVD	chemical vapor deposition
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(N,N-dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide)
ED ₅₀	median effective dose
EGCG	Epigallocatechin gallate
EtOAc	ethyl acetate
EtOH	ethanol
FET	field effect transistor
HBC	hexa-peri-hexabenzocoronene
^1H NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectrometry

ITO	indium tin oxide
LCD	liquid crystal display
LDA	lithium diisopropylamine
MALDI	matrix assisted laser desorption/ionization
MDCK	madin-darby canine kidney
MOI	multiplicity of infection
MP	melting point
NBS	<i>N</i> -bromosuccinimide
OLED	organic light emitting diode
OTf	triflate
PAH	poly aromatic hydrocarbon
Ph	phenyl
PPTS	Pyridinium <i>p</i> -toluenesulfonate
Psi	pound per square inch
rt	room temperature
TBDMS	<i>tert</i> -butyldimethylsilyl
TD ₅₀	median toxic dose
THF	tetrahydrofuran
TI	therapeutic index
TLC	thin layer chromatography
UV	ultra violet

Dedication

To

Tilak Thapa and Rama Devi Thapa

Chapter 1 - DESIGN, SYNTHESIS, AND ANTI-VIRAL ACTIVITY OF QUERCETIN DERIVATIVES.

1.1. Introduction.

Influenza, commonly referred as flu is an infectious disease caused by RNA virus that belongs to family of *orthomyxoviridae*.¹ Influenza affects the respiratory tract mainly nose, throat, bronchi and, occasionally, lungs.¹ Infection usually lasts for about a week, and is characterized by sudden onset of high fever, headache, aching muscles, non-productive cough and sore throat.² Young children, elderly people, pregnant women and people with weak immune system are referred as high risk group to influenza infection.² People get infected when they come in direct contact with the mature viral particle produced by infected people when sneezing or coughing.

In general, influenza lasts for a week² and does not pose any serious threat to the human health however; sometimes it can be serious and results in death. There have been various pandemic outbreaks of influenza resulting to the death of millions of people worldwide.³ Seasonal influenza is the seventh leading cause of death in the United States and the leading cause of death in children ages 1 to 4 years.⁴ Ninety percent of deaths in people 65 and older are the result of influenza with associated pneumonia.⁴ Every year in the United States approximately 36,000 people die, 114,000 are hospitalized, \$600 million are spent in direct costs to the health care system, and the country incurs \$1 billion in economic losses.⁴ Thus influenza poses a significant health threat to human beings.

Despite intensified research on influenza virus and its infection, there is no known drug that can cure influenza. Vaccines are regarded as the best method for preventing influenza infection and transmission. Every year the center for disease control and prevention collects data on most prevalent influenza virus strains circulating around the world and prepares a vaccine against it.³ Vaccines have been effective and have significantly decreased the rate of hospitalization in high risk group⁵ people for normal seasonal flu, however there are various drawback associated to vaccine. The virus that is used in vaccine is grown in egg. This egg grown vaccine requires almost six months to be prepared.⁵ In the case of an epidemic, which is caused by mutated virus, there is a need of large supply of vaccine in short time, thus immediate supply of vaccine would not be possible which may result in uncontrolled spread of virus worldwide. Furthermore, the prevalent virus circulating worldwide each year differs from that of the previous year so, vaccine formulation needs to be changed every year.³ Vaccine does not provide immediate protection against influenza instead, requires about two weeks after being administered to become effective³, thus these vaccine should be provided long before the onset of flu season. Furthermore, these vaccines are specific to particular strain of virus thus may not be effective to other viral strains.³ Hence, our goal is to design and synthesize anti-viral agents against influenza viruses.

1.2. Anti-viral drugs

Vaccines alone are not effective and sufficient to prevent influenza outburst. Medication that can be provided instantly and be effective in short period of time over wide range of influenza viral strains is always in need.

Influenza virus is spherical in shape consisting of outer cover made up of lipid membrane.⁶ Embedded in this membrane are two very important glycoproteins called

hemagglutinin (HA) and neuraminidase (NA).⁶ Hemagglutinin plays two important roles in viral replication and transmission. Firstly, it maintains the contact between the viral particle and host cell by binding itself to the sialic acid residue present in the host cell.⁶ Secondly, hemagglutinin facilitates the fusion of viral and host membranes and helps the entry of viral genome into the host cell.⁶ Neuraminidase is another important glycoprotein present on the surface of influenza virus. This enzyme removes residues called *N*-Acetyl-neuraminic acid from chains of sugars and from other glycoproteins.⁶ Change in neuraminic acid residues caused by neuraminidase allows the detachment of matured viral particle from the host cell and also prevents aggregation of detached virus particle with each other. Neuraminidase, thus, helps in spreading of mature virus easily through the respiratory tract.⁶

Another important component in influenza virus is the M2 ion channel.⁷ It is present in the lipid membrane of influenza virus. These channels are pH-activated proton channels that mediate acidification of the interior of viral particles entrapped in endosomes.⁷ The low pH of endosome activates the M2 ion channel before hemagglutinin-mediated fusion.⁸ Conductance of protons through this channel facilitates dissociation of the matrix protein from the viral nucleoproteins, a required process for unpacking of the viral genome.⁸ In addition to its role in release of viral nucleoproteins, the M2 ion channel also helps in preventing premature conformational rearrangement of newly synthesized hemagglutinin.⁹

Various antiviral drugs are synthesized to inhibit the action of glycoprotein and M2 ion channel. There are currently four FDA approved antiviral drugs namely amantadine, rimantadine, oseltamivir, and zanamivir.¹⁰ Amantadine and rimantadine are M2 ion channel inhibitors,¹⁰ that help resist the pH change and prevent influx of the viral genetic material into

the cytoplasm of the host cell. Oseltamivir and zanamivir are hemagglutinin inhibitors¹⁰ which prevent attachment of viral particle to the host cell.

Influenza virus are RNA virus which contain segmented genetic material highly prone to antigenic shift, genetic drift and reassortment causing frequent change in the genetic composition of the viral particle.¹¹ This genetic mutation causes change in the structure of the surface glycoprotein and renders existing antiviral drugs and vaccine ineffective.¹¹ Recent research shows that there are number of cases that shows new viral strains that are highly resistant to both classes of inhibitors.^{10,11,12} Generation of these highly resistant strains of virus against existing antivirals always poses a possible threat of epidemic that could potentially kill millions of people around the world, thus there is always a need of new antiviral drugs to prevent and cure influenza.

Recent studies have revealed that the cause of severe influenza-associated complications involves not only the virus replication-mediated apoptotic cell death in the infected cells but also non-infected cell injury by toxicity of reactive oxygen species derived from macrophages engulfing apoptotic cells.² These findings provide a possibility that compounds having both antiviral and antioxidant activities may be a drug of choice for the treatment of patients with severe influenza-associated complications. Quercetin and its derivatives are well known antioxidants,¹³ which are used as dietary supplements. In the past few years, antiviral activities of quercetin and its analogs^{14,15, 16} quercetin-3- β -galactoside, quercetin 3-rhamnoside, and quercetin 3- β -glucoside¹⁷ or isoquercetin¹⁸ have been reported. Quercetin is a cheap natural product that possesses both moderate anti-influenza and anti-oxidation activity thus, provided a good starting point from which we synthesized various analogs as potential antiviral drugs against influenza virus. We designed our antiviral compounds based on quercetin, and EGCG.

1.3. Synthesis of quercetin derivatives

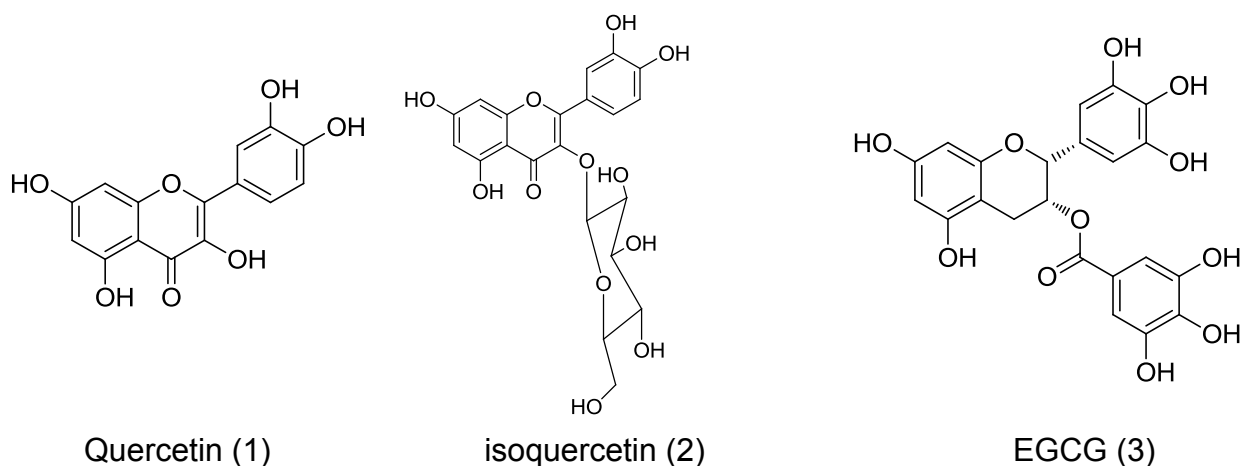
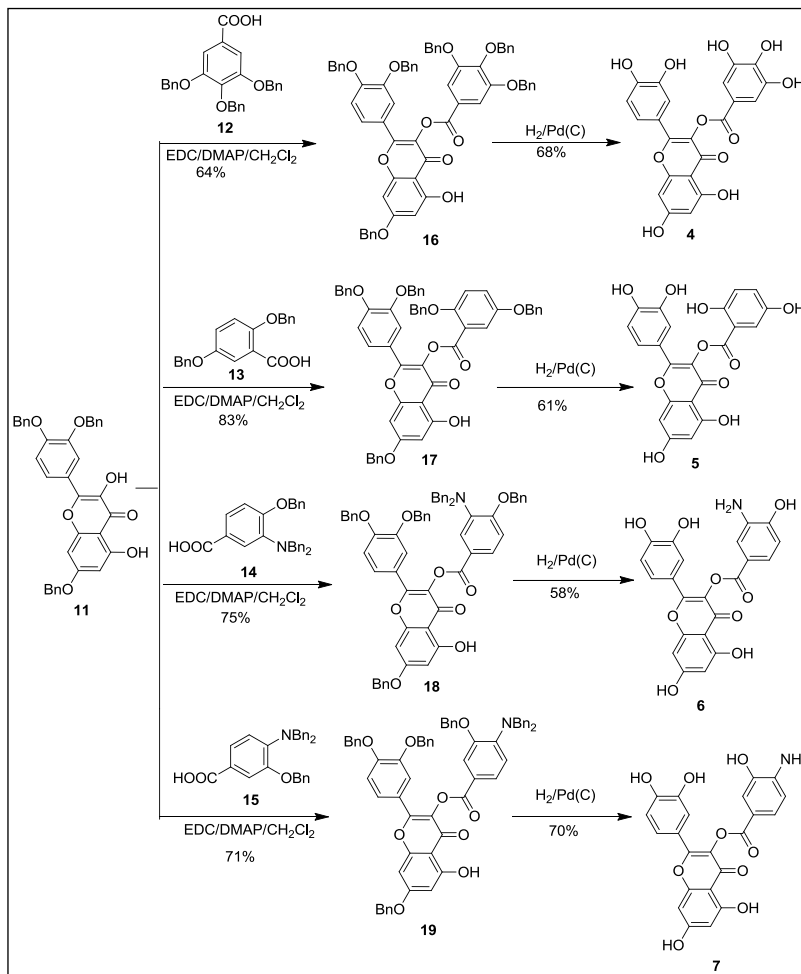


Figure 1-1. Structures of polyphenols in green tea

EGCG, a major component in green tea is known to have strong antioxidant activity and in numerous cases has been shown to have anti-influenza activity.^{19,20} However, EGCG has not been used as an antiviral compound because of its poor lipid membrane permeability and low chemical stability.¹⁹ It was previously reported that the introduction of long alkyl chain to EGCG improved its lipid membrane permeability²¹, while protection of its hydroxyl groups with acetyl groups increased its chemical stability under physiological conditions.²¹ Research has shown that the galloyl group present in C3-position of EGCG plays vital role in anti-influenza activity.²² Kim et al.¹⁸ have recently shown that isoquercetin, a plant derived natural product is capable of inhibiting the replication of influenza A virus. We thus decided to take quercetin, which has a core structure similar to that of isoquercetin and modify C3, C3' and C5 hydroxyl groups with various substituents like galloyl, alkyl and amino alkyl groups to determine the effect of substituents on influenza activity.

1.3.1. Synthesis of C3-*O*-ester analogs of quercetin

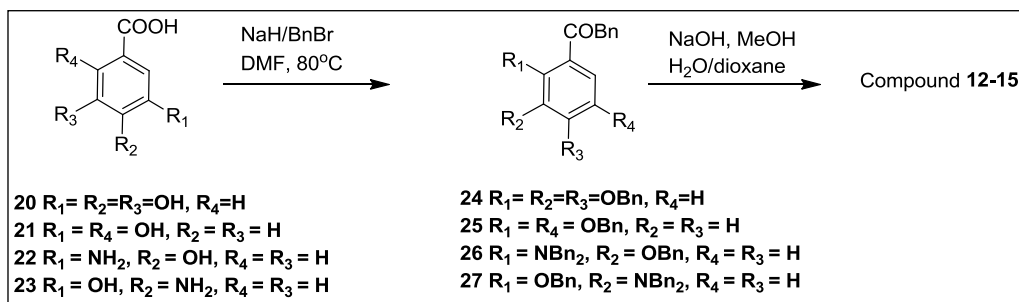
Scheme 1-1. Synthesis of quercetin C3-*O* ester analogs 4 - 7



For the synthesis of C3-*O*-ester analogs of quercetin, a reported selective protection of the three most reactive hydroxyl functions at C7, C3', and C4' was adapted.²³ Hence, 3',4',7-tri-*O*-benzylquercetin, derived from tribenylation of rutin with potassium carbonate and benzyl bromide in DMF followed by removal of the C3-rutinoside with hydrochloric acid and ethanol, was condensed with 3,4,5-tribenzylgallic acid,²⁴ *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC), and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane to give ester **16** in 64% yield (Scheme 1-1). Removal of the benzyl

ether protecting groups of **16** with hydrogen (15 atmospheres) and 5% palladium/carbon afforded quercetin gallate **4** (68% yield).

Scheme 1-2. Synthesis of benzyl protected acids of compound 20 - 23



It should be noted that C5-hydroxyl function of quercetin is less reactive than C3-hydroxyl due to intramolecular hydrogen bonding and resonance conjugation with C4-keto function. Quercetin is pentahydroxyl compound with differing acidity thus these hydroxyl groups could be selectively functionalized. Reaction of tribenzyl quercetin **11**, with TBDMS-Cl or allyl bromide was conducted to determine if C-3-hydroxyl function could be selectively reacted without reacting C-5 hydroxyl group. It was found that TBDMS protection of both C-3 and C-5 hydroxyl groups took place in the presence of excess of TBDMS-Cl to give **67** and **68** where as with limited amount of TBDMS-Cl C-3 hydroxyl protected product **67** was formed selectively.

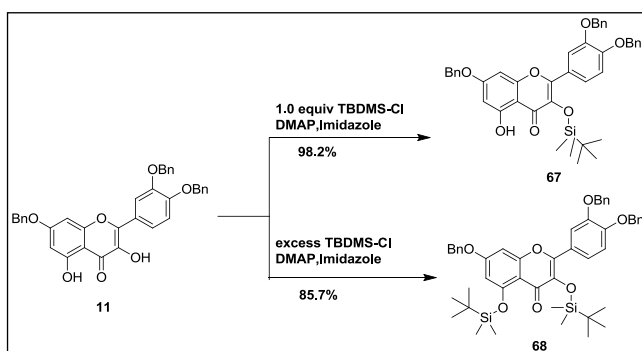


Figure 1-2. C3 and C5 silyl ethers of compound 11

Furthermore, reaction of **11** with allyl bromide in the presence of strong base NaH, resulted in alkylations in both C-3 and C-5 hydroxyl positions where as weak base K₂CO₃ gave only C-3 hydroxyl alkylation.

Direct esterification of C3-OH group of quercetin with various carboxylic acids would eliminate the requirement of forming moisture sensitive acid chlorides thus the reaction of bulky acid **12** and **13** separately with kojic acid (**69**) was carried out in the presence of EDC as a coupling agent to test the feasibility of the reaction. Kojic acid possesses a 4*H*-pyran-4-one moiety with hydroxyl group in the C-5 position similar to the benzopyran ring in quercetin thus; kojic acid was chosen as reference compound to study the EDC coupling of the hydroxyl group in the pyran ring with acids **12** and **13**. Ester formation readily took place to give the compound **70** and **71** respectively, thus eliminating the need for synthesizing acid chloride.

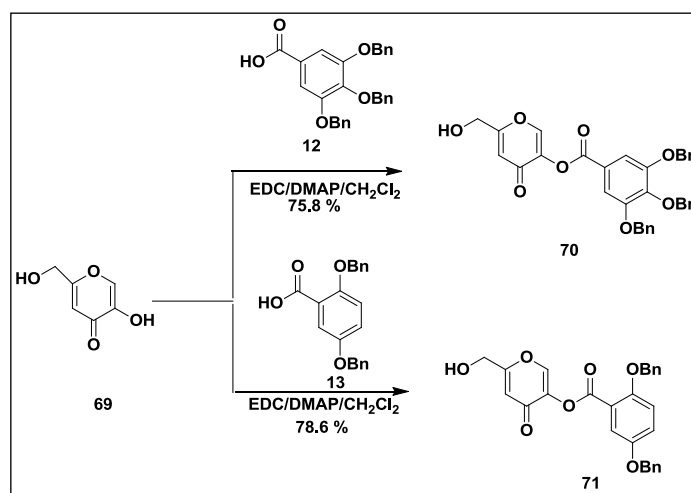


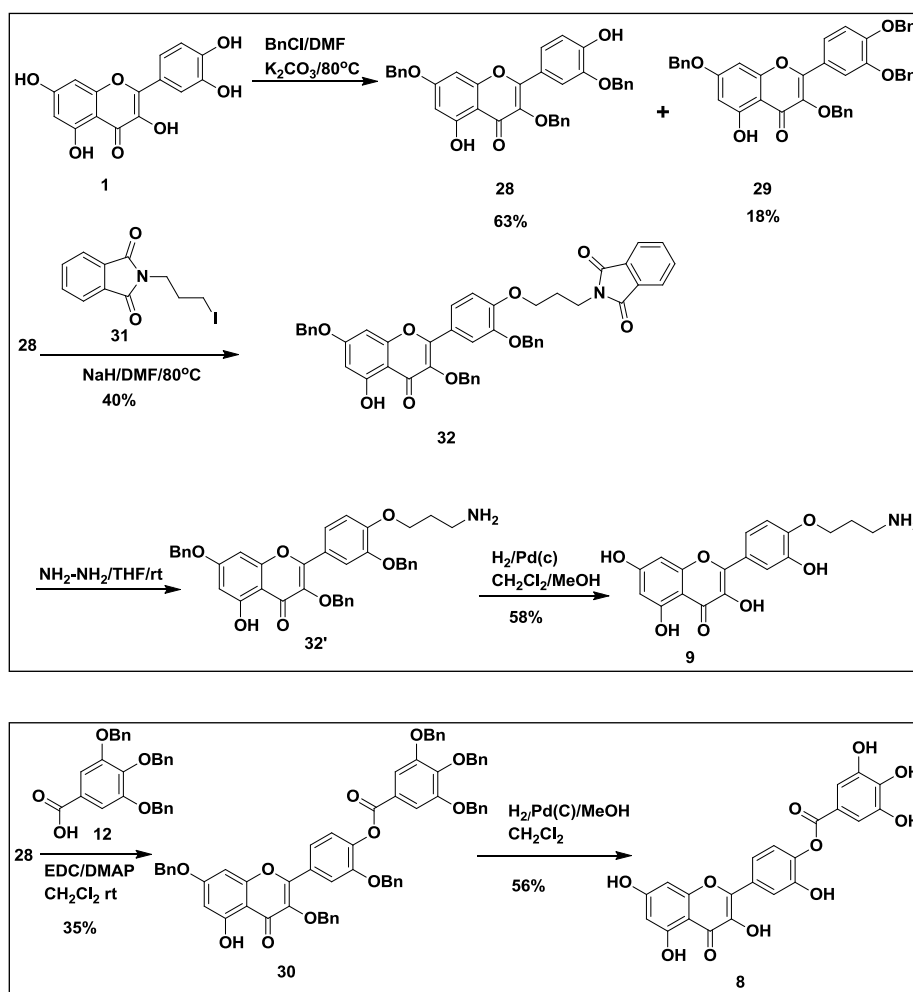
Figure 1-3. EDC coupling of kojic acid

Similarly, condensation of compound **11** with 2,5-dibenzyloxybenzoic acid (**13**),²⁵ 4-benzyloxy-3-(*N,N*-dibenzylamino)benzoic acid (**14**), and 3-benzyloxy-4-(*N,N*-dibenzylamino)benzoic acid (**15**) separately gave benzyl esters **17**, **18**, and **19** (83%, 75%, and 71% yield), respectively, which upon hydrogenation furnished respectively quercetin analogs **5**,

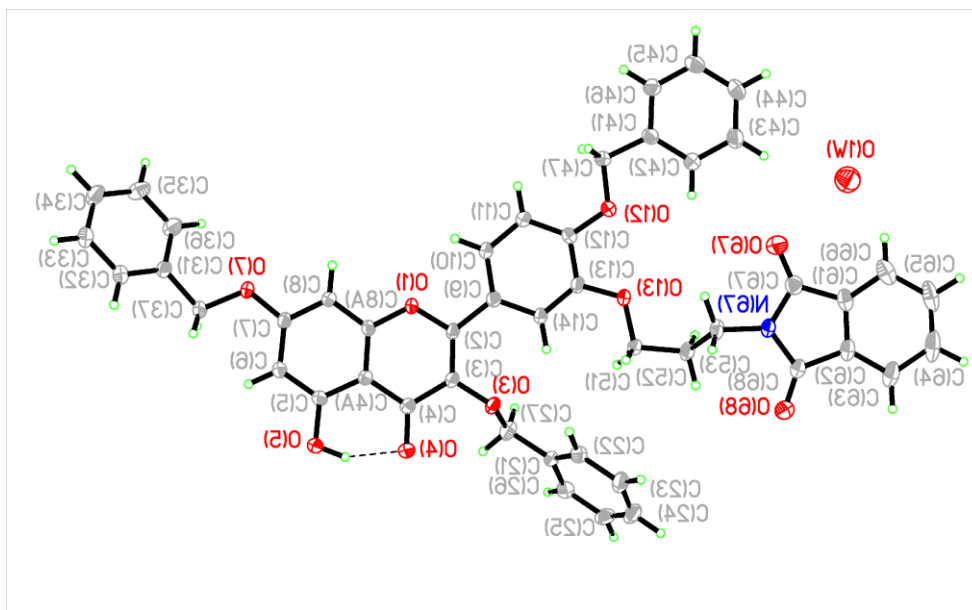
6, and **7** (61%, 58%, and 70% yield). Compounds **12** and **13** are known and were prepared by a modified procedure of the benzylation of gallic acid (**20**) and 2,5-dihydroxybenzoic acid (**21**), respectively, with sodium hydride (or sodium carbonate) and benzyl bromide in DMF^{24, 25} followed by basic hydrolysis with sodium hydroxide. Carboxylic acids **22** and **23** were similarly tetrabenzylated and hydrolyzed to give benzylated carboxylic acids **14** and **15** in 76% and 87% overall yield, respectively.

1.3.2. Synthesis of C3'-O-ester analogs of quercetin

Scheme 1-3. Synthesis of quercetin C3'- O-ester analogs of quercetin



To access quercetin analogs containing C3'-*O*-substituents, we prepared compounds **28** and **29** as described previously²⁶ from quercetin **1** and sodium carbonate and three equivalents of benzyl chloride in DMF (Scheme 1-3). A mixture of tribenzyl **28** (63% yield) and tetrabenzyl **29** (18% yield) were isolated after column chromatographic separation. C3'-Alkylation of **28** with sodium hydride and *N*-(3-iodopropyl)phthalimide (**31**) gave compound **32** (40% yield).



Compound **32** when subjected to reduction with hydrazine in ethanol under refluxing condition gave very polar compound which was difficult to purify.

Figure 1-4. An ORTEP drawing of X-ray crystallographically determined structure of compound 32.

IR spectroscopy of this crude compound showed no peak corresponding to the product with carbonyl group. Mass Spectra analysis revealed the product with additional mass of fourteen, which corresponds to the hydrazone formed by the reaction of carbonyl group in the ring with excess of hydrazine in refluxing condition. Attempts to hydrolyze back the hydrozone to ketone were unsuccessful. In order to avoid this complication, two equivalents of hydrazine in THF was added drop wise to the solution of **32** in THF at room temperature. The reaction solution was maintained at room temperature and monitored by TLC. Crude product obtained was then subjected to reduction with hydrogen over palladium/Carbon to afford 3-aminopropyl quercetin **9**. The structure of compound **32** was unequivocally determined by a single-crystal x-ray analysis (Figure 1.4). The crystal was triclinic having a space group of P-1 and R factor of 0.051.

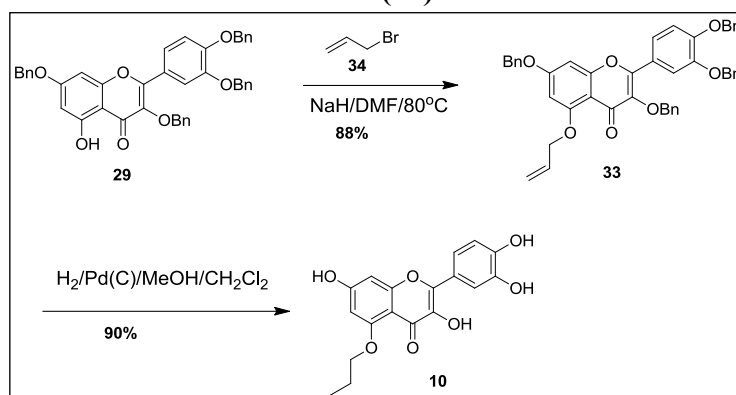
Similarly, EDC coupling of tribenzyl quercetin **28** with tribenzyl protected gallic acid **12**, in the presence of DMAP in dichloromethane gave a good yield of coupled compound **30** which upon reduction with hydrogen over palladium/Carbon furnished C3'-O-gallic derivative **8** (56% overall yield).

1.3.3. Synthesis of 3,7-(dihydroxy)-2-(3,4-dihydroxyphenyl)-5-propyloxy-4-oxo-4H-chromene, C5-O-ester analog.

Similarly, alkylation of tetrabenzyl quercetin **29** with sodium hydride and allyl bromide in DMF at 80°C provided C5-O-allyl quercetin (**33**) (88% yield), which upon reduction with

hydrogen over palladium/carbon furnished C5-*O*-propyl derivative **10** (90% yield). Allyl bromide was chosen as the alkylating agent instead of propyl iodide because it gave a higher yield of the alkylation product.

Scheme 1-4. Synthesis of 3,7-(dihydroxy)-2-(3,4-dihydroxyphenyl)-5-propyloxy-4-oxo-4*H*-chromene (10).



1.4. Anti-influenza virus activity of synthesized quercetin analogs

Anti-influenza activity of various synthesized quercetin analogs were conducted by Professors Yunjeong Kim and Kyeong-Ok Chang in their laboratory at the Department of Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University. The experimental procedures related to the bio-evaluation of quercetin analogs will not be discussed in detail; instead a brief discussion of the procedure and outcome of the experiments is made.

Influenza virus Oh7 was inoculated to two-day-old monolayer of Madin-Darby canine kidney (MDCK) cells in 6-well plates at a multiplicity of infection (MOI) of 0.05 or 5. Amantadine or oseltamivir carboxylate was used as a positive control. Viral replication was assessed by various methods including virus titration with TCID₅₀, and real-time qRT-PCR.⁷

The inhibition of influenza A virus (A/swine/OH/511445/2007[H1N1], Oh7) by compounds **1** – **10** and **29** were evaluated following a procedure reported previously.¹⁸ In brief,

Madin-Darby canine kidney (MDCK) cells were infected with influenza virus Oh7. These infected cells were incubated with each compound at various concentrations from 0.1 – 150 μ M. Incubation was conducted in the presence of trypsin (10 μ g/mL) for up to 4 days. The effective doses for 50% virus reduction (ED_{50}) as well as toxic doses at 50% cell death (TD_{50}) for above compounds were determined and are summarized in Table 1-1. Immunofluorescence assay and Western blot analysis with antibodies to viral nucleoprotein were conducted to determine the viral replication. Synthesized compounds were tested against influenza with EGCG as reference standard. Quercetin-3-gallate and isoquercetin appear to have similar ED_{50} values against H1N1 virus. ED_{50} value of isoquercetin, EGCG and quercetin-3-gallate was determined to be 1.2 μ M, 8.3 μ M and 9.1 μ M, respectively. Therapeutic index (TI) is defined as the ratio of amount of compound that is required to kill 50% of the population to that of minimum amount of compound required to be effective against 50% of the population. Higher the TI, lesser is the dose required to obtain the therapeutic effect without lethal effect. Although ED_{50} values for quercetin-3-gallate were slightly lower than that of EGCG, its therapeutic index (TI) value of 9.9 is better than that of EGCG of 5.5 thus, quercetin-3-gallate is a preferred compound in term of anti-viral drug. C3-Dihydroxyl and hydroxylaminobenzoate analogs, compounds **5** – **7**, have ED_{50} values of 20 – 24 μ M and similar TD_{50} values as that of EGCG indicating modification of the gallate moiety (of EGCG and quercetin-3-gallate) retains the anti-influenza activity. Quercetin (**1**), without gallate function, is less effective with ED_{50} and TD_{50} values of 48.2 and 83.4 μ M, respectively.

Table 1-1: ED_{50} , and TD_{50} values of various natural and synthetic compounds against H1N1, Oh7 strain.

Compound	ED_{50} value in μ M	TD_{50} value in μ M	Therapeutic index (TI)
Isoquercetin (2)	1.2	45.1	37.6
EGCG (3)	8.3	45.5	5.5

Quercetin-3-gallate (4)	9.1	90.2	9.9
5	19.4	45.2	2.3
6	22.6	60.1	2.7
7	24.1	54.8	2.3
8	>50	ND	-
9	>50	ND	-
28	>50	ND	-

Compound **8**, **9**, and **10**, synthesized by functionalization of C3' and C5 hydroxyl groups with gallate, aminopropoxy and propoxy groups are found to be less effective with ED₅₀ values higher than 50 μ M. Benzylated analogs like compound **29** were not effective either. Therefore the TD₅₀ values of compounds **8** – **10** and **29** were not determined. It appears that hydroxyl and aminohydroxybenzoate groups in C3 position retain or enhance the anti-viral activity whereas, derivatization of C3' and C5 led to lower antiviral activity.

1.5. Attempted synthesis of EGCG analog (2*R*,3*R*)-6-hydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4,5-trihydroxybenzoate.

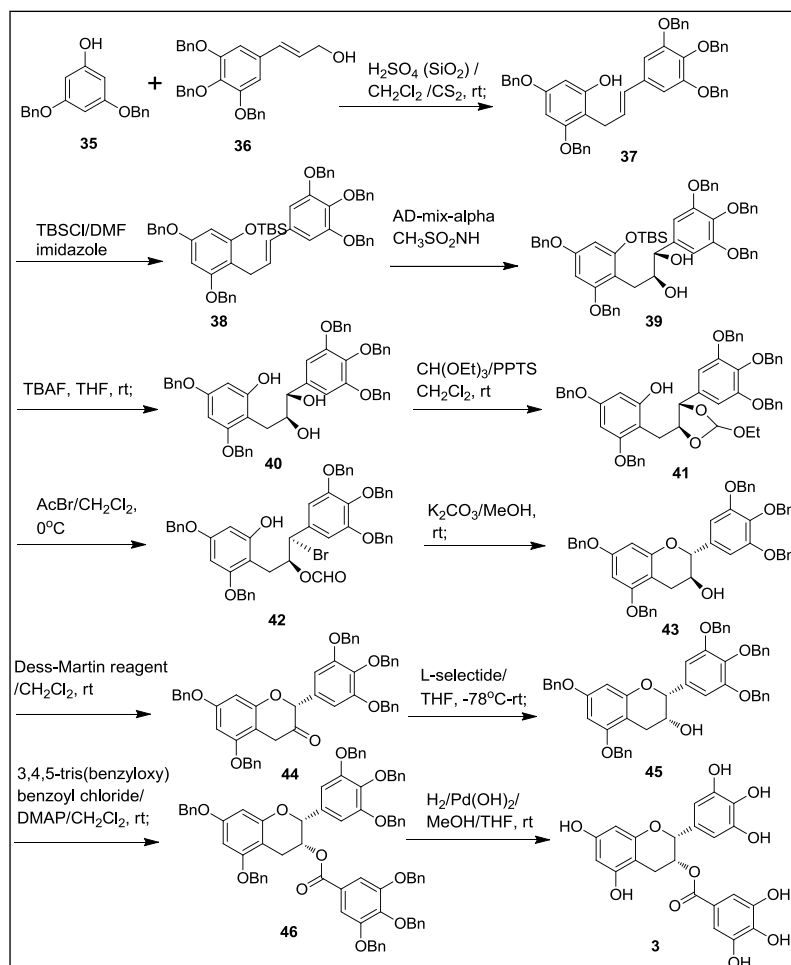
1.5.1. Literature background

There are various successful synthetic routes for the total synthesis of EGCG and its analogs.^{27,28,29,30} Based on the formation of benzopyran ring, the synthetic strategy towards EGCG and its analogs can be categorized into two types: intramolecular cyclization of the chalcone, and intermolecular Oxa-Michael followed by aldol condensation reaction. Two representative examples are discussed here.

The total synthesis of EGCG was first reported by Li and Chang in 2001. Their synthetic route to EGCG is shown in Scheme 1-4.²⁷ The synthetic route made use of Friedel-Craft reaction between cinnamic alcohol **36** and 3,5-dibenzoxy phenol **35** to generate the chalcone **37**, followed

by intramolecular cyclization to give the desired cyclic compound. Asymmetric dihydroxylation using AD-mix with subsequent cyclization in the presence of K_2CO_3 and acetone afforded cyclic benzopyran **43**.

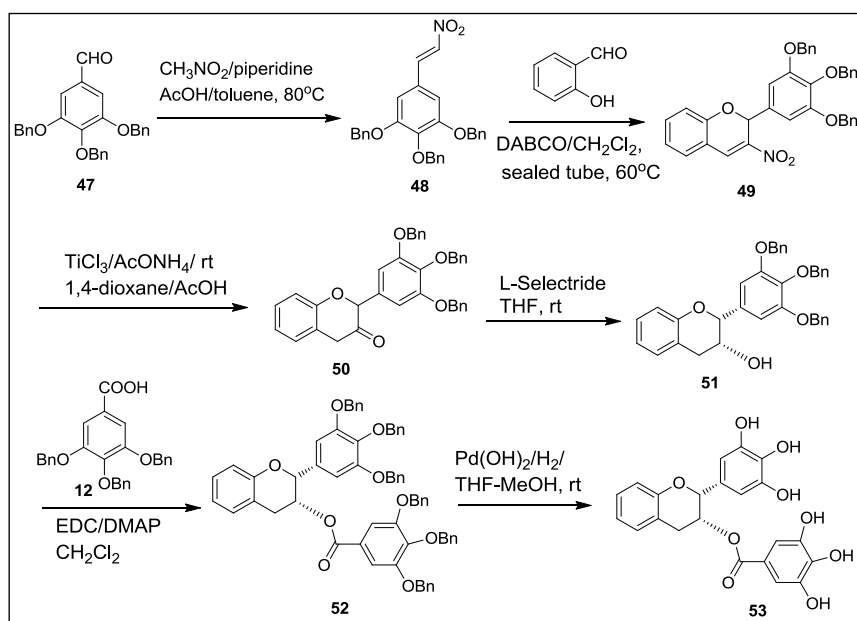
Scheme 1-5. Synthesis of EGCG via chalcone intramolecular cyclization



The challenge of formation of thermodynamically less stable *cis* disubstituted compound **45** was solved by enantioselective reduction of ketone using L-Selectride in THF at -78°C. Coupling of **45** with tribenzyl protected gallic acid chloride in dichloromethane followed by removal of benzyl groups by hydrogenation gave product **3** with spectral property similar to that of the natural EGCG.²⁷

Synthesis of dideoxy-epigallocatechin gallate (**53**), which is a derivative of EGCG was reported by Furuta et al. in 2007.³⁰ The synthetic Scheme adopted is shown in Scheme 1-6. This Scheme makes use of intermolecular Oxa-Michael reaction followed by aldol condensation reaction to obtain the desired benzopyran ring.

Scheme 1-6. Synthesis of EGCG via intermolecular Oxa-Michael reaction



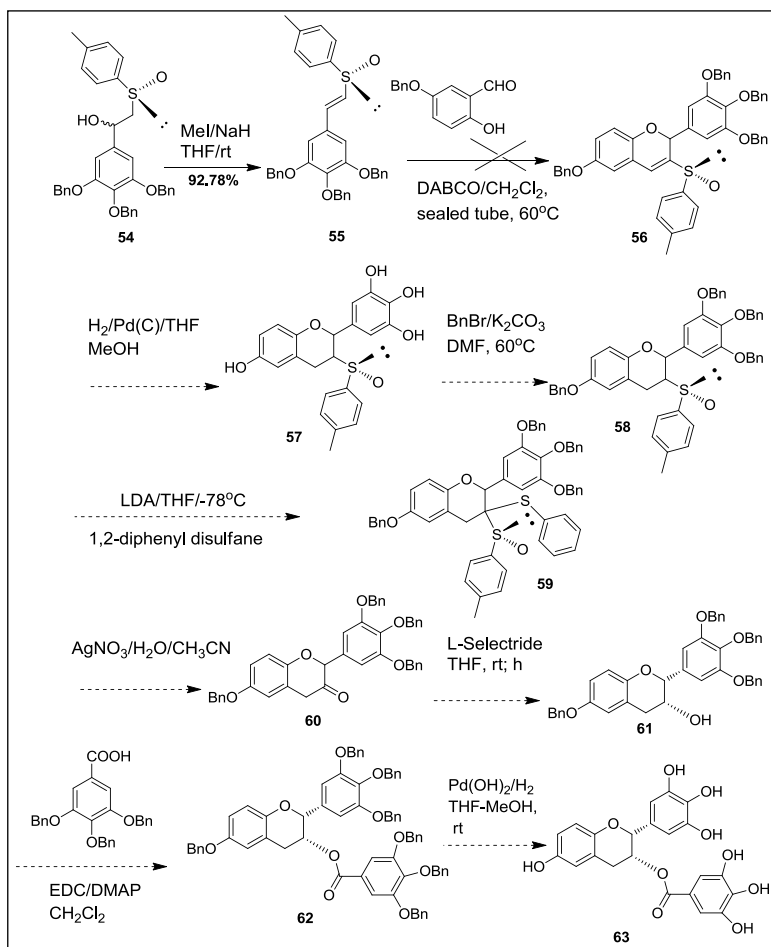
Nitro-aldol reaction followed by dehydration of compound **47** with nitromethane gave compound **48**.³⁰ Coupling of **48** with *o*-hydroxybenzaldehyde in the presence of DABCO give the compound **49**. Conversion of the nitro-alkene **49** to ketone **50** under reductive Neff reaction

was obtained using titanium trichloride.³⁰ Required *cis* stereo-chemistry in the benzopyran ring of compound **51** was established by reduction of compound **50** using L-Selectride. EDC coupling with gallic acid followed by hydrogenation gave the desired product **53**.³⁰

1.5.2. Synthesis of EGCG analog **63**

Synthetic Scheme 1-7, similar to that of Furuta's was proposed towards the synthesis of compound **63**.

Scheme 1-7. Synthesis of EGCG analog **63 by chiral sulfoxide method**

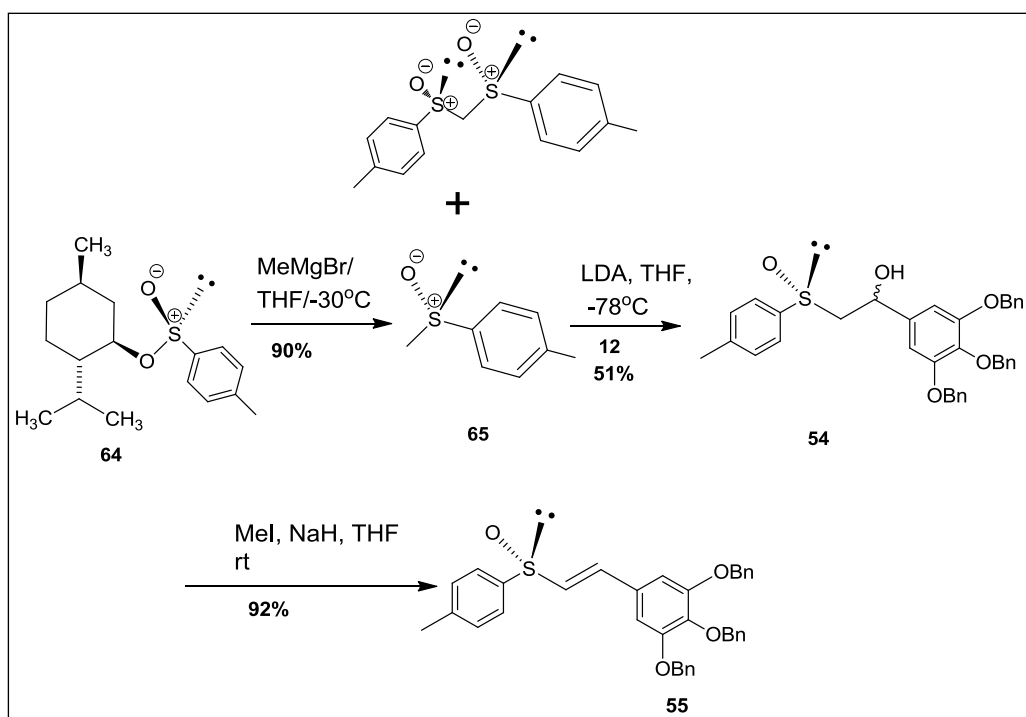


Chiral sulfoxide may be used such that the acidic hydrogen alpha to the sulfoxide group could be easily abstracted to afford the substitution reaction with 1,2-diphenyl disulfane followed by elimination to give the required ketone (**60**). Once we have the ketone in hand we can follow the same reduction and coupling procedure in literature³⁰ to afford the desired product with correct stereo-chemistry.

1.5.3. Synthesis of sulfoxide **55**

L-Menthol ether of *p*-toluene sulfonic acid **64** was treated with methyl lithium in THF at -78°C and gradually brought to room temperature. The reaction was monitored by TLC.

Scheme 1-8. Synthesis of sulfoxide **55**



The reaction was monitored by TLC. Analysis of the reaction mixture by mass spectrometry and NMR showed the formation of desired substitution product **65** along with the formation of

adduct of two sulfoxide moieties as represented by Scheme 1-8. When the reaction was carried out using methyl magnesium bromide in THF at -30°C instead of methyl lithium product **65**, with no formation of adduct was obtained.

Reaction of tribenzoxo gallic aldehyde with methyl *p*-toluene sulfonic acid **65**, and LDA in THF at -78°C gave a racemic mixture of alcohol **54**. This was used directly to synthesize the required alkene **55** without further purification.

Compound **55** was obtained from **54** by elimination reaction mediated by methyl iodide and NaH in THF.³¹ To the racemic mixture of alcohol **54** in THF, NaH was added and stirred for 0.5 h. Methyl iodide was syringed into the reaction mixture at room temperature and left to stir overnight, quenched using NH₄Cl, purified to obtain the desired product **55** (93% yield).

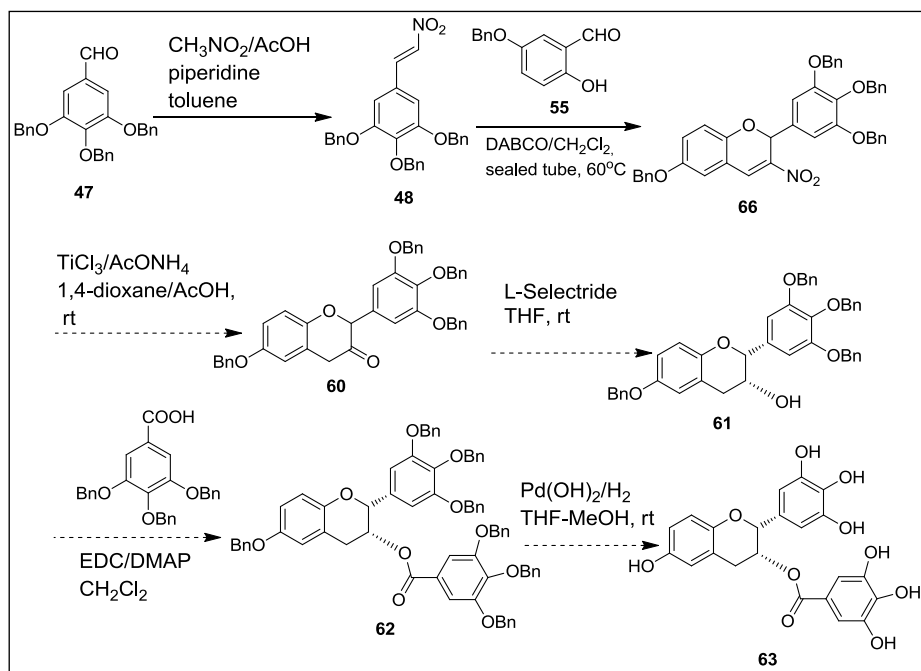
1.5.4. Attempted Synthesis of compound 56.

In order to synthesize compound **56**, compound **55** was reacted with 4-(benzyloxy)-2-hydroxybenzaldehyde at various temperature and different bases like DABCO and K₂CO₃ in solvents like dichloromethane and dioxane. A reaction mixture containing compound **55**, 4-(benzyloxy)-2-hydroxybenzaldehyde and DABCO in dichloromethane was gradually heated at 100°C in a sealed tube for 24 h however, no product was detected. Conducting the reaction in dioxane and K₂CO₃ under reflux did not produce the product either. Starting materials were recovered in these reaction conditions.

Oxa-Michael reactions are very sensitive to the steric bulkiness around the double bond of enone or its analogs^{32,33}. One possible reason for not obtaining the cyclic product may be due to the steric hindrance caused by the bulky *p*-toluene sulfonic group present adjacent to the double bond.

Despite several attempts and varying conditions, no cyclization was achieved. An alternative approach that would eliminate the problem caused by the steric hindrance was then proposed as shown in Scheme 1-9. Replacement of *p*-toluenesulfonic group by nitro group not only makes the double bond more accessible but also more electrophilic to the attack by a nucleophile. Literature evidence^{32,34} shows that compound with alkoxy or benzyl group *para* to the hydroxyl group in Michael donor enhances the Michael addition due to electronic effect. Compound **55** with *p*-benzoxy group was chosen for the same reason.

Scheme 1-9. Proposed Alternative approach to the synthesis of EGCG analog 63



1.5.5. Synthesis of (E)-[*l*]{(5-(2-nitrovinyl)benzene-1,2,3-triyl)tris(oxy)}tris(methylene)]tribenzene (48)

Tribenzyl gallic aldehyde synthesized by known literature procedure³⁵ was dissolved in toluene. 3.0 equivalents each of nitromethane, piperidine and acetic acid were added under argon

and heated to 80°C for 24 h,³⁰ however very small amount of product was detected. Further addition of nitromethane did not alter the reaction outcome. Test reaction conducted using acetic acid rather than toluene as solvent showed an increase in the product conversion and decreased in reaction time. Three equivalents each of nitromethane and piperidine were added into the hot solution (80°C) of **47** and left to stir at that temperature for 10 h. Reaction was monitored by TLC. When a very small amount of aldehyde was remaining, reaction was cooled to room temperature, diluted with ether and washed with water. Organic layer was concentrated and purified using silica gel column chromatography to give pure product **48** (72% yield).

1.5.6. Synthesis of 6-(benzyloxy)-3-nitro-2-{3,4,5-tris(benzyloxy)phenyl}-2H-chromene. (66)

Nitroalkene **48** was reacted with aldehyde **55** according to the literature procedure.³⁰ Briefly, nitroalkene **48**, aldehyde **55** and K₂CO₃ in a sealed tube was diluted with dichloromethane and gradually heated to 90°C for 16 h. Mass spectra showed a significant amount of starting material with small peak of the desired product, thus the reaction was repeated using 1,2-dichloroethane as solvent, however no significant amount of product was detected. Changing solvent to dioxane and heating the reaction mixture to 150°C for 16 h did not change the reaction outcome either.

Change in solvent, temperature and prolonged reaction time did not produce much product thus reaction was carried out using DABCO as base. Starting materials along with catalytic amount of (0.2 equiv) of DABCO in a round bottom flask were heated to reflux for 36 h. TLC was used to monitor the reaction. When most of the nitroalkene **48** disappeared, the reaction was cooled to room temperature, diluted with aqueous NH₄Cl, extracted with dichloromethane, concentrated and column chromatographed to obtain the crude product **66**.

This product was crystallized in ether to give pure product **66** (40% yield). Reaction to convert the nitro compound **66** into the keto compound **60** using Neff reaction is being investigated in the Hua's laboratory.

1.6. Conclusions

Exploiting the difference in the acidity of various hydroxyl groups in quercetin, we were able to functionalize C3, C3' and C5 hydroxyl group to give various derivatives containing gallate ester, propyl ether and amino propyl ether groups. Synthesized derivatives were tested for their anti-influenza activity against influenza A (A/swine/OH/511445/2007 H1N1,Oh7) strain. The ED₅₀ of EGCG and quercetin-3-gallate was determined at 8.3 and 9.1 μ M, respectively, and therapeutic index (TI) value of quercetin-3-gallate of 9.9 is slightly better than that of EGCG of which is 5.5. C3-Dihydroxyl and hydroxylaminobenzoate analogs, compounds **5** – **7**, have ED₅₀ values of 20 – 24 μ M and similar TD₅₀ values as that of EGCG indicating modification of the gallate moiety (of EGCG and quercetin-3-gallate) retains the anti-influenza activity. Derivatization at C5 and C3' decreased the antiviral activity.

1.7. References

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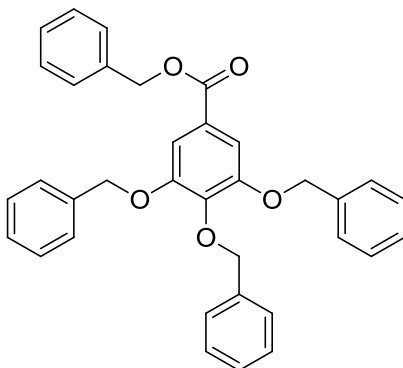
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1.8. Experimental Section.

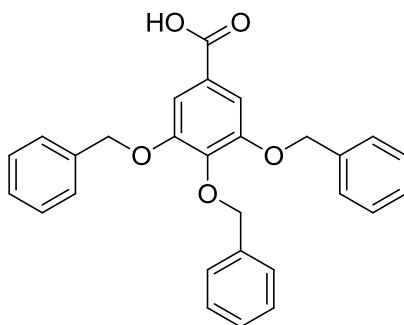
NMR spectra were obtained from a 400-MHz spectrometer (Varian Inc.), in CDCl₃, unless otherwise indicated, and reported in ppm. Infrared spectra were taken from a Nicolet 380 FT-IR instrument (Thermo Scientific) in solid forms and are reported in wave numbers (cm⁻¹). Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer (from Applied Biosystems). High-resolution Mass spectra were obtained from a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. The instrument was operated at 10,000 resolutions (W mode) with dynamic range enhancement that attenuates large intensity signals. The cone voltage was 60 eV. Spectra were acquired at 16666 Hz pusher frequency covering the mass range 100 to 1200 μ and accumulating data for 2 seconds per cycle. Mass correction for exact mass determinations was made automatically with the lock mass feature in the MassLynx data system. A reference compound in an auxiliary sprayer is sampled every third cycle by toggling a "shutter" between the analysis and reference needles. The reference mass is used for a linear mass correction of the analytical cycles. Chemicals such rutin, quercetin, and others were purchased from Fisher Scientific and Aldrich Chemical Co.

Synthesis of benzyl 3, 4, 5-tris(benzyloxy)benzoate (**24**)



A mixture of 5.0 g (29.00 mmol) of gallic acid, 15.0 g (0.15 mol) of sodium carbonate, 16.0 g (0.12 mol) of benzyl chloride in 50 mL of dried DMF was stirred under argon at 25°C for 14 h, diluted with 100 mL of water, and extracted with chloroform. The organic layer was washed three times with water, dried (MgSO₄), concentrated, crystallized from hexanes to give 9.1 g (58% yield) of pure colourless solid tetrabenzyl **24**: ¹H NMR δ 7.42 - 7.24 (22 H, m), 5.32 (2 H, s), 5.12 (6 H, s); ¹³C NMR δ 166.2, 152.7, 142.7, 137.6, 136.9, 136.3, 128.8, 128.7, 128.4, 128.4, 128.3, 128.2, 128.2, 127.7, 125.3, 109.5, 75.3, 71.5, 67.0.

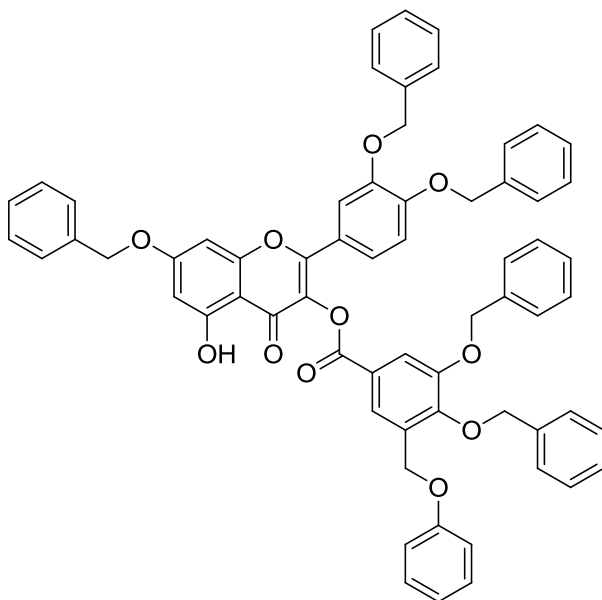
Synthesis of 3, 4, 5-tris(benzyloxy)benzoic acid (**12**)



A solution of 2.0 g (3.5 mmol) of compound **24**, 0.3 g (7.0 mmol) of sodium hydroxide in 45 mL of methanol, water, and diOxane (1:1:1) was stirred under reflux for 14 h, cooled to 25°C,

acidified with 1 N HCl, and extract with chloroform. The chloroform extract was washed with water and brine, dried (MgSO₄), concentrated, and crystallized from dichloromethane and diethyl ether to give 1.31 g (78% yield) of pure **12**¹² as a white solid, mp 190 – 195°C; ¹H NMR δ 7.43 – 7.27 (m, 17 H), 5.15 (s, 4 H, CH₂), 5.14 (s, 2 H, CH₂); ¹³C NMR δ 152.8, 137.6, 136.7, 128.8, 128.7, 128.4, 128.3, 128.2, 127.8, 109.8, 75.4, 71.4.

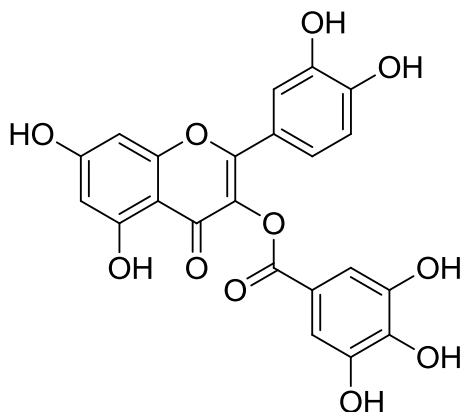
Synthesis of 7-(benzyloxy)-2-[3,4-bis(benzyloxy)phenyl]-5-hydroxy-4-oxo-4H-chromen-3-yl 3,4,5-tris(benzyloxy)benzoate (16).



A mixture of 0.10 g (0.17 mmol) of 3',4',7-tri-*O*-benzylquercetin **11**, 72.0 mg (0.16 mmol) of *O*-tribenzylgallic acid **12**, 27 mg (0.17 mmol) of EDC, and 4.0 mg of DMAP was dried under vacuum and maintained under argon. To it, 8 mL of CH₂Cl₂ was added, and the resulting solution was stirred at 25°C for 12 h. The reaction mixture was diluted with 20 mL of CH₂Cl₂, washed three times with water (30 mL each) and brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as

eluent to give 0.11 g (64% yield) of compound **16** as a white solid, mp 98 – 99°C. ^1H NMR δ 12.20 (s, 1 H, OH), 7.57 (s, 2 H), 7.48 – 7.27 (m, 32 H), 6.92 (d, J = 8.6 Hz, 1 H), 6.54 (d, J = 2.2 Hz, 1 H), 6.48 (d, J = 2.2 Hz, 1 H), 5.21 (s, 2 H), 5.16 (s, 2 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.12 (s, 2 H), 4.99 (s, 2 H); ^{13}C NMR δ 176.0, 165.11, 163.65, 162.20, 157.16, 156.35, 151.98, 148.76, 143.79, 137.51, 136.72, 136.66, 136.59, 135.86, 131.48, 128.99, 128.86, 128.77, 128.70, 128.65, 128.46, 128.31, 128.25, 128.06, 127.81, 127.73, 127.48, 127.31, 123.32, 122.81, 122.40, 114.62, 114.01, 110.20, 105.87, 99.24, 93.71, 75.43, 71.58, 71.02, 70.76. MS (electrospray) m/z 1017.7 ($\text{M}+\text{Na}^+$), 903.6, 518.5; HRMS calcd for $\text{C}_{64}\text{H}_{51}\text{O}_{11}^+$ ($\text{M}+\text{H}^+$) 995.3431, found 995.3445.

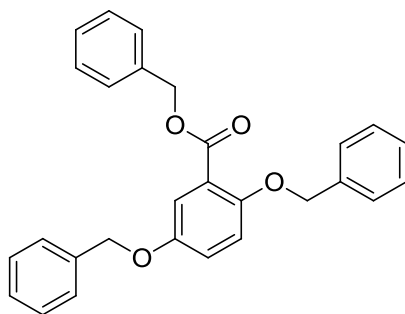
Synthesis of quercetin 3-gallate 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 3,4,5-trihydroxybenzoate (4).



A mixture of 0.11 g (0.11 mmol) of Compound **16**, 11.0 mg of 10% palladium/carbon in 5 mL each of methanol, dichloromethane, and ethyl acetate was stirred under hydrogen atmosphere at 25°C for 10 h. The mixture was filtered through Celite and concentrated to give 50.0 mg (68% yield) of compound **4** as a yellow solid, mp >270°C;¹⁰ ^1H NMR ($\text{DMSO}-d_6$) δ 12.20 (bs, 1 H, OH), 9.30 (bs, 6 H, OH), 7.36 (d, J = 2.0 Hz, 1 H), 7.26 (dd, J = 8.5, 2.0 Hz, 1 H), 6.28 (d, J = 1.8 Hz, 1 H), 7.12 (s, 1 H), 6.91 (s, 1 H), 6.87 (d, J = 8.5 Hz, 1 H), 6.54 (d, J =

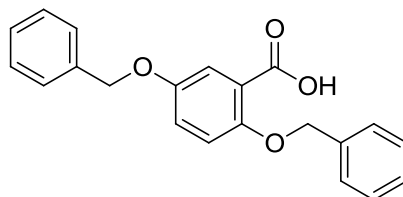
1.8 Hz, 1 H); ^{13}C NMR δ 175.77, 165.29, 164.00, 161.74, 157.28, 156.75, 149.89, 146.46, 146.35, 146.19, 146.16, 140.36, 130.61, 121.08, 120.44, 117.89, 116.43, 115.74, 110.05, 104.13, 99.71, 94.72; MS (electrospray) m/z 477.2 ($\text{M}+\text{Na}^+$; 100%), 413.4. HRMS calcd for $\text{C}_{22}\text{H}_{15}\text{O}_{11}^+$ ($\text{M}+\text{H}^+$) 455.0614, found 455.0589.

Synthesis of benzyl 2,5-dibenzyloxybenzoate (**25**).



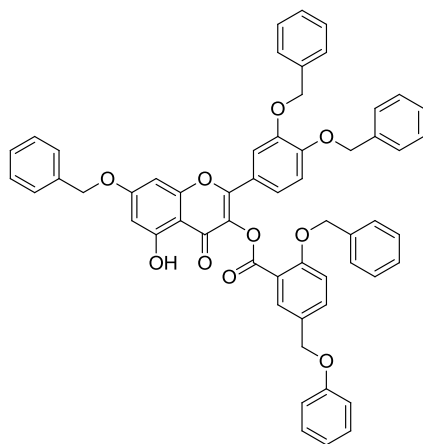
To a solution of 1.0 g (6.4 mmol) of 2,5-dihydroxybenzoic acid, 3.6 g (26 mmol) of potassium carbonate in 25 mL of DMF under argon at 25°C, was added 3.6 g (21 mmol) of benzyl bromide via syringe. The solution was stirred at 60°C for 12 h, cooled to 25°C, diluted with aqueous ammonium chloride, and extracted with dichloromethane. The organic layer was washed with water three times, and brine, dried (MgSO_4), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 2.8 g (87% yield) of compound **25** as white solid.¹⁴ ^1H NMR δ 7.48 (d, J = 3.2 Hz, 1 H), 7.42 - 7.25 (m, 15 H), 7.05 (dd, J = 8.8, 3.2 Hz, 1 H), 6.94 (d, J = 8.8 Hz, 1 H), 5.34 (s, 2 H), 5.09 (s, 2 H), 5.02 (s, 2 H); ^{13}C NMR δ 166.2, 152.9, 152.7, 137.1, 137.0, 128.8, 128.7, 128.7, 128.4, 128.3, 128.3, 128.0, 127.8, 127.4, 121.7, 120.6, 117.7, 72.0, 70.9, 67.1.

Synthesis of 2,5-dibenzoyloxybenzoic acid (**13**)



A solution of 1.0 g (2.4 mmol) of ester **25** and 0.19 g (4.7 mmol) of sodium hydroxide in 15 mL of methanol, diOxane, and water (1:1:1) was stirred under reflux for 14 h, cooled to 25°C, and most of the organic solvents were removed from a rotary evaporator. The residue was diluted with water, acidified with 1 N HCl, extracted twice with ethyl acetate (50 mL), and the ethyl acetate layers were combined, washed with water and brine, dried (MgSO₄), concentrated, and column chromatographed using a mixture of hexane and ethyl acetate (1:1) as eluent to give 0.72 g (91% yield) of compound **13** as white solid.¹⁴ ¹H NMR δ 11.06 (s, 1 H), 7.81 (d, *J* = 3.1 Hz, 1 H), 7.43 - 7.32 (m, 10 H), 7.17 (dd, *J* = 9.0, 3.1 Hz, 1 H), 7.07 (d, *J* = 9.0 Hz, 1 H), 5.26 (s, 2 H), 5.08 (s, 2 H); ¹³C NMR δ 165.3, 153.9, 151.9, 136.6, 134.6, 129.4, 129.4, 128.8, 128.4, 128.2, 127.8, 123.0, 119.0, 117.8, 115.1, 73.2, 70.9.

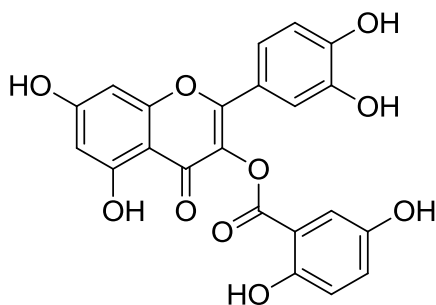
2-(3,4-dibenzyloxyphenyl)-7-benzyloxy-5-hydroxy-4-oxo-4H-chromen-3-yl 2,5-dibenzyloxybenzoate (17)



To a solution of 50.0 mg (0.15 mmol) of 2,5-dibenzyloxybenzoic acid **13**, 27.0 mg (0.15 mmol) of EDC, and 4.0 mg (3 μ mol) of DMAP in 3 mL of dichloromethane under argon at 25°C was added a solution of 50.0 mg (87 μ mol) of 3',4',7-tri-*O*-benzylquercetin **11** in 5 mL of dichloromethane via syringe. The reaction mixture was stirred at 25°C for 12 h, diluted with 50 mL of water, and extracted three times with 15 mL each of dichloromethane. The combined organic layer was washed with brine, dried (anhydrous MgSO_4), concentrated, and column chromatographed on silica gel using a mixture of 1:1 hexane and diethyl ether as eluant to give 65.0 mg (83% yield) of **17** as a white solid, mp 85 - 88°C. ^1H NMR δ 12.3 (s, 1 H, OH), 7.79 (d, J = 3.6 Hz, 1 H), 7.56 (d, J = 2.0 Hz, 1 H), 7.53 (dd, J = 8.6, 2 Hz, 1 H), 7.46 - 7.22 (m, 25 H), 7.15 (dd, J = 9.0, 3.6 Hz, 1 H), 7.00 (d, J = 9.0 Hz, 1 H), 6.88 (d, J = 8.2 Hz, 1 H), 6.54 (d, J = 2.0 Hz, 1 H), 6.48 (d, J = 2.0 Hz, 1 H), 5.16 (s, 2 H), 5.15 (2, 2 H), 5.12 (s, 2 H) 5.04 (s, 2 H), 4.97 (s, 2 H); ^{13}C NMR δ 176.1, 165.1, 162.8, 162.3, 157.2, 156.5, 154.1, 152.9, 151.9, 148.8, 136.9, 136.8, 136.7, 136.0, 131.5, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.25, 128.2, 128.0,

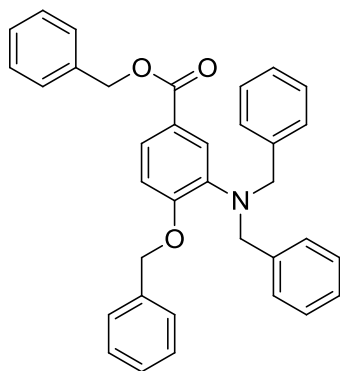
127.9, 127.8, 127.6, 127.4, 127.34, 127.32, 123.0, 122.6, 122.3, 119.2, 118.4, 116.8, 114.8, 114.0, 106.0, 99.2, 93.7, 72.1, 71.5, 71.03, 71.01, 70.8. MS (electrospray) m/z 889.5 ($M+H^+$; 100%), 413.2. HRMS calcd for $C_{57}H_{45}O_{10}$ ($M+H^+$) 889.3013, found 889.3035.

Synthesis of 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 2,5-dihydroxybenzoate (5).



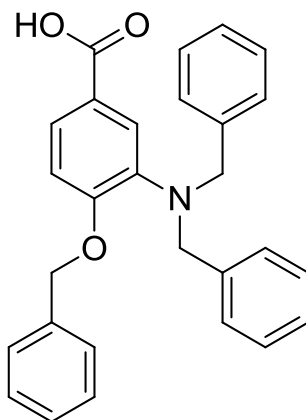
A mixture of 50.0 mg (56 mmol) of compound **17** and 5.0 mg of 10% palladium/carbon in 9 mL of ethyl acetate, methanol and dichloromethane (1:1:1) was shaken at 25°C under 25 psi hydrogen atmosphere for 10 h. The reaction mixture was diluted with 10 mL of methanol and filtered through Celite, and the filtrate was concentrated to give 15 mg (60% yield) of **5** as a solid, mp >270°C. ^1H NMR (DMSO- d_6) δ 12.14 (s, OH, 1 H), 11.08 (bs, OH, 1 H), 9.98 (bs, OH, 1 H), 9.59 (s, OH, 1 H), 9.48 (bs, OH, 1 H), 9.35 (s, OH, 1 H), 7.36 - 7.28 (m, 3 H), 7.06 (dd, J = 8.8, 2.8 Hz, 1 H), 6.89 (dd, J = 13.6, 8.4 Hz, 1 H), 6.51 (d, J = 1.2 Hz, 1 H), 6.27 (d, J = 1.6 Hz, 1 H); ^{13}C NMR (DMSO- d_6) δ 175.3, 165.4, 161.7, 157.3, 156.9, 154.1, 150.4, 150.1, 146.2, 130.1, 125.4, 121.2, 120.5, 120.1, 119.3, 116.5, 115.8, 115.7, 112.5, 104.0, 99.8, 94.8. MS (electrospray) m/z 461.1 ($M+Na^+$; 100%), 325.3. HRMS calcd for $C_{22}H_{15}O_{10}$ ($M+H^+$) 439.0665, found 439.0663.

Synthesis of benzyl 4-(benzyloxy)-3-(dibenzylamino)benzoate (26).



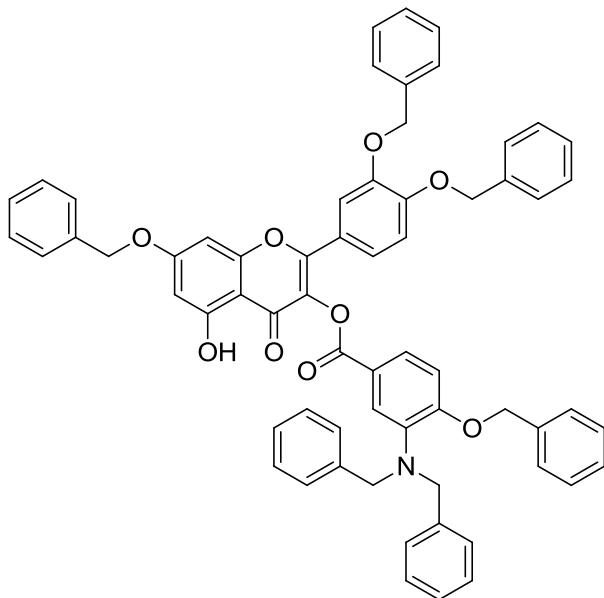
To a solution of 1.0 g (6.5 mmol) of 3-amino-4-hydroxybenzoic acid **22** and 0.71 g (29 mmol) of sodium hydride (50% oil, which was removed by washing with dried diethyl ether twice) in 20 mL of DMF under argon at 25°C was added 3.9 mL (33 mmol) of benzyl bromide. The reaction solution was stirred at 60°C for 14 h, cooled to 25°C, diluted with 50 mL of aqueous NH₄Cl, and extracted with dichloromethane. The organic layer was washed three times with water, and brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether to give 3.1 g (90% yield) of **26**: Mp 109 – 110°C; ¹H NMR δ 7.66 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.60 (d, *J* = 2.0 Hz, 1 H), 7.42 (dd, *J* = 8.0, 2.0 Hz, 2 H), 7.37 - 7.16 (m, 18 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 5.26 (s, CH₂O, 2 H), 5.19 (s, CH₂O, 2 H), 4.25 (s, CH₂N, 4 H); ¹³C NMR δ 166.5, 156.5, 140.0, 138.9, 136.7, 136.6, 128.8, 128.7, 128.3, 128.3, 128.2, 128.1, 127.7, 127.0, 125.2, 123.4, 122.8, 112.5, 70.8, 66.5, 55.9. MS (electrospray) *m/z* 514.3 (M+H⁺), 536.4 (M+Na⁺), 332.3. HRMS calcd for C₃₅H₃₂NO₃⁺ (M+H⁺) 514.2382, found 514.2362.

Synthesis of 4-(benzyloxy)-3-(dibenzylamino)benzoic acid (14**).**



A solution of 1.5 g (2.9 mmol) of benzoate **26** and 0.23 g (5.9 mmol) of sodium hydroxide in 15 mL of methanol, diOxane, and water (1:1:1) was stirred under reflux for 3 h, cooled to 25°C, and acidified with 5 mL of 1 N HCl. The solution was extracted with 50 mL of ethyl acetate, and the organic extract was washed three times with water (20 mL each), and brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (7:3) to give 0.70 g (84% yield) of acid **14** as white solid: Mp 177 – 180°C; ¹H NMR δ 4.26 (s, 4 H) 5.24 (s, 2 H) 6.97 (d, *J* = 8.4 Hz, 1 H) 7.14 - 7.49 (m, 15 H) 7.61 (s, 1 H) 7.70 (d, *J* = 8.4 Hz, 1 H); ¹³C NMR δ 172.0, 157.1, 140.1, 138.7, 136.6, 128.8, 128.7, 127.7, 127.1, 126.0, 123.9, 121.8, 112.5, 70.9, 55.8. MS (electrospray) *m/z* 424.4 (M+H⁺; 100%), 446.2 (M+Na⁺), 242.5. HRMS calcd for C₂₈H₂₆NO₃⁺ (M+H⁺) 424.1913, found 424.1899.

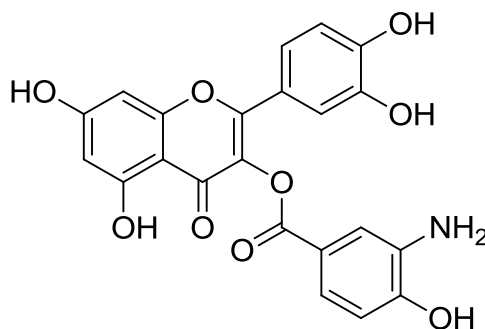
Synthesis of 7-(benzyloxy)-2-(3,4-dibenzyloxyphenyl)-5-hydroxy-4-oxo-4H-chromen-3-yl 4-(benzyloxy)-3-(dibenzylamino)benzoate (18**).**



To a solution of 0.15 g (0.35 mmol) of acid **14**, 55 mg (0.35 mmol) of EDC, 9 mg (7 μ mol) of DMAP in 3 mL of dichloromethane under argon at 25°C was added a solution of 0.14 g (0.24 mmol) of benzyl quercetin **11** in 5 mL of dichloromethane. The solution was stirred for 14 h, diluted with water and extracted with dichloromethane (30 mL). The organic extract was washed with water and brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 0.18 g (75% yield) of **18** as a white solid, mp 114 – 115°C. ¹H NMR δ 12.25 (s, 1 H, OH), 7.85 (dd, J = 8.6, 2.0 Hz, 1 H), 7.78 (d, J = 2.0 Hz, 1 H), 7.12 - 7.48 (m, 32 H), 7.00 (d, J = 8.6 Hz, 1 H), 6.90 (d, J = 9.4 Hz, 1 H), 6.53 (d, J = 1.6 Hz, 1 H), 6.47 (d, J = 2.0 Hz, 1 H), 5.20 (s, 2 H), 5.19 (s, 2 H), 5.15 (s, 2 H), 4.81 (s, 2 H), 4.27 (s, 4 H, CH₂N); ¹³C NMR δ 176.3, 165.0, 163.9, 162.3, 157.4, 157.2, 156.2, 151.8, 148.8, 140.6, 138.8, 136.9, 136.7, 136.4, 135.9, 131.5, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.37, 128.3, 128.1, 127.8, 127.7, 127.5, 127.3, 127.1, 126.2, 123.9, 122.7,

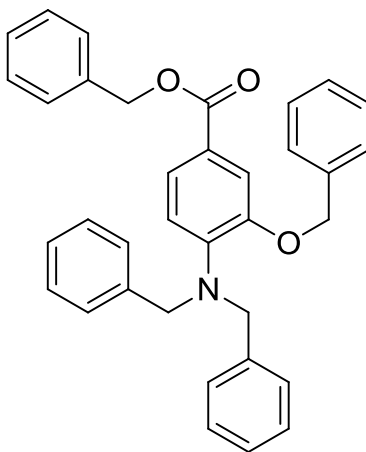
122.6, 120.8, 114.5, 114.1, 112.7, 106.0, 99.2, 93.6, 71.3, 71.1, 71.0, 70.8, 55.8 (2 C's). MS (electrospray) m/z 1000.6 ($M+Na^+$), 978.6 ($M+H^+$), 224.0 (100%). HRMS calcd for $C_{64}H_{52}NO_9^+$ ($M+H^+$) 978.3642, found 978.3681.

Synthesis of 5,7-dihydroxy-2-(3,4-dihydroxyphenyl)-4-oxo-4H-chromen-3-yl-4-hydroxy-3-aminobenzoate (6).



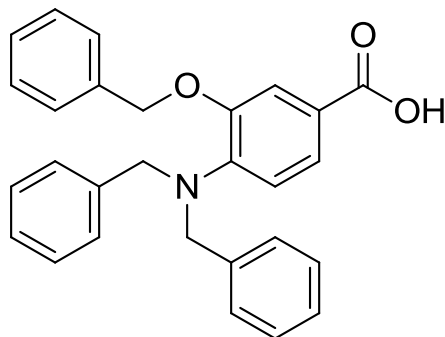
A mixture of 66.0 mg (0.07 mmol) of compound **18**, 20.0 mg of 10% palladium/carbon in 9 mL of ethyl acetate, methanol, and dichloromethane (1:1:1) was shaken in a hydrogenator under 36 psi of hydrogen at 25°C for 14 h. The mixture was diluted with 20 mL of methanol and filter through Celite, concentrated to dryness to give 17.0 mg (58% yield) of **6** as a yellow solid, mp >270°C. ^1H NMR (DMSO- d_6) δ 12.19 (s, 1 H, OH), 11.17 (bs, 1 H, OH), 9.93 (bs, 1 H), 9.47 (bs, 1 H), 7.93 (s, 1 H), 7.75 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 2.4 Hz, 1 H), 7.27 (dd, J = 8.4, 2.0 Hz, 1 H), 7.11 (d, J = 8.8 Hz, 1 H), 6.88 (d, J = 8.4 Hz, 1 H), 6.55 (d, J = 2.4 Hz, 1 H), 6.29 (d, J = 1.6 Hz, 1 H); ^{13}C NMR (DMSO- d_6) δ 176.0, 165.2, 164.0, 161.8, 157.3, 156.7, 149.8, 146.1, 143.8, 143.7, 130.7, 124.6, 121.1, 120.6, 116.4, 115.8, 115.7, 115.0, 113.6, 104.2, 99.6, 94.6. MS (electrospray) m/z 438.3 ($M+H^+$), 136.1 (100%). HRMS calcd for $C_{22}H_{16}NO_9^+$ ($M+H^+$) 438.0825, found 438.0810.

Synthesis of phenyl 3-(benzyloxy)-4-(dibenzylamino)benzoate (**27**).



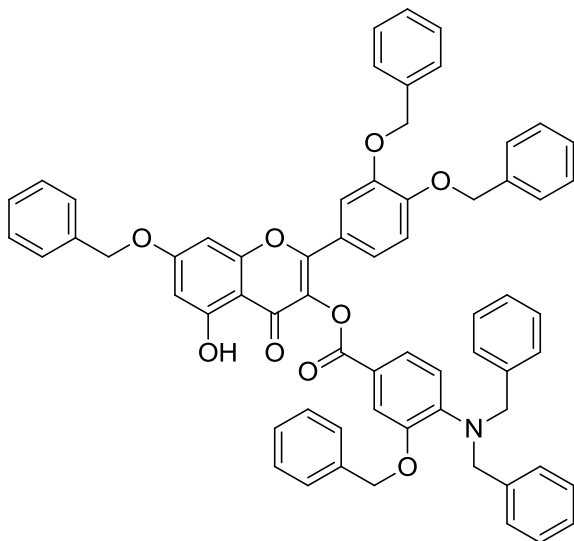
A mixture of 1.0 g (6.5 mmol) of 4-amino-3-hydroxybenzoic acid **23** and 0.7 g (27 mmol) of sodium hydride was dried under vacuum and maintained under argon. To it 5 mL of dried DMF was added and the solution was stirred at 25°C for 0.5 h. To the reaction solution, 3.1 mL (26 mmol) of benzyl bromide was added, and the resulting solution was stirred at 80°C for 16 h, cooled to 25°C, and 20 mL of saturated aqueous NH₄Cl was added. The mixture was extracted with 100 mL of ethyl acetate, and the organic layer was washed with 50 mL of water three times and brine, dried (anhydrous MgSO₄), concentrated, and column chromatographed on silica gel using a mixture of 5:1 hexane and ethyl acetate as eluent to give 3.0 g (90% yield) of **27** as white solid, mp 105 – 107°C. ¹H NMR δ 7.67 (d, *J* = 2.0 Hz, 1 H), 7.55 (dd, *J* = 6.4, 2.0 Hz, 1 H), 7.42 - 7.16 (m, 20 H), 6.76 (d, *J* = 8.8 Hz, 1 H), 5.31 (s, CH₂O, 2 H), 5.18 (s, CH₂O, 2 H), 4.40 (s, CH₂N, 4 H). ¹³C NMR δ 166.5, 156.4, 139.9, 138.8, 136.6, 129.4, 128.8, 128.7, 128.7, 128.3, 128.23, 128.20, 128.1, 127.7, 127.0, 125.1, 123.3, 122.6, 112.4, 70.7, 66.4, 55.8; MS (electrospray) *m/z* 514.3 (M+H⁺; 100%), 536.4 (M+Na⁺), 332.1. HRMS calcd for C₃₅H₃₂NO₃⁺ (M+H⁺) 514.2382, found 514.2394.

Synthesis of 3-(benzyloxy)-4-(dibenzylamino)benzoic acid (15).



A mixture of 1.0 g (2.0 mmol) of **27** and 0.16 g (4.0 mmol) of sodium hydroxide in 15 mL of methanol, diOxane, and water (1:1:1) was stirred under reflux for 3 h, cooled to 25°C, acidified with 5 mL of 1 N HCl, and extracted with 50 mL of ethyl acetate. The organic layer was washed three times with 20 mL of water, and brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give 0.8 g (97% yield) of acid **15** as white solid, mp 185 – 187°C. ¹H NMR δ 7.70 (s, 1 H), 7.59 (d, *J* = 8.2 Hz, 1 H), 7.14 - 7.44 (m, 15 H), 6.80 (d, *J* = 8.2 Hz, 1 H), 5.19 (s, 2 H, CH₂O), 4.44 (s, 4 H, CH₂N); ¹³C NMR δ 172.2, 150.5, 145.8, 138.4, 136.7, 128.7, 128.5, 128.2, 128.17, 128.0, 127.1, 124.6, 121.5, 119.5, 114.7, 71.1, 55.3; MS (electrospray) *m/z* 424.4 (M+H⁺, 100%). HRMS calcd for C₂₈H₂₆NO₃⁺ (M+H⁺) 424.1913, found 424.1914.

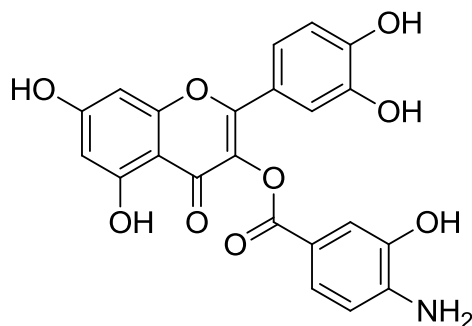
Synthesis of 7-(benzyloxy)-2-(3,4-dibenzyloxyphenyl)-5-hydroxy-4-oxo-4H-chromen-2-yl 3-(benzyloxy)-4-(dibenzylamino)benzoate (19).



To a solution of 48.0 mg (0.11 mmol) of **15**, 18.0 mg (0.11 mmol) of EDC, and 2.0 mg (18 μ mol) of DMAP in 3 mL of dichloromethane under argon at 25°C was added a solution of 50.0 mg (87 μ mol) tribenzyl quercetin **11** in 5 mL of dichloromethane. The reaction solution was stirred for 12 h, diluted with 50 mL of water, and extracted three times with dichloromethane (15 mL each). The combined organic layer was washed with brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (1:1) as eluent to give 60.0 mg (71% yield) of compound **19** as white solid, mp. 110 – 112°C; ¹H NMR δ 12.22 (s, 1 H, OH), 7.79 (d, J = 1.6 Hz, 1 H), 7.73 (dd, J = 8.4, 1.8 Hz, 1 H), 7.47 - 7.54 (m, 2 H), 7.14 - 7.45 (m, 30 H), 6.92 (d, J = 8.6 Hz, 1 H), 6.82 (d, J = 8.6 Hz, 1 H), 6.51 (d, J = 2.0 Hz, 1 H), 6.43 (d, J = 2.0 Hz, 1 H), 5.16 (s, 2 H), 5.13 (s, 2 H), 5.10 (s, 2 H), 4.93 (s, 2 H), 4.44 (s, 4 H, CH₂N); ¹³C NMR δ 176.7, 164.9, 163.86, 162.1, 157.1, 156.1, 151.7, 150.5, 148.5, 146.1,

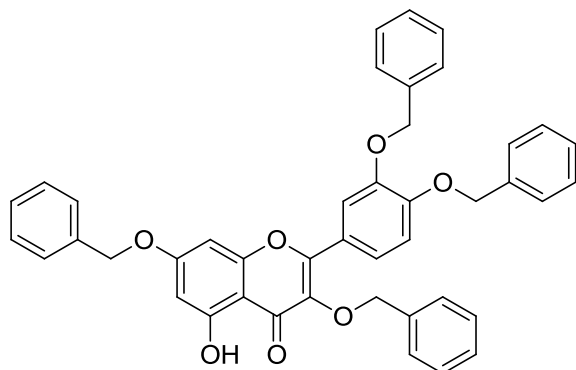
138.2, 136.7, 136.6, 136.4, 135.8, 131.5, 128.9, 128.7, 128.6, 128.5, 128.2, 128.17, 128.14, 128.1, 128.0, 127.9, 127.7, 127.4, 127.2, 127.1, 125.0, 122.6, 122.5, 119.9, 119.3, 114.9, 114.4, 113.8, 105.8, 99.1, 93.5, 71.3, 71.1, 70.9, 70.6, 55.2. MS (electrospray) m/z 1000.6 ($M+Na^+$), 978 ($M+H^+$), 224.0 (100%). HRMS calcd for $C_{64}H_{52}NO_9^+$ ($M+H^+$) 978.3642, found 978.3681.

Synthesis of 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl 4-amino-3-hydroxybenzoate (7).



A mixture of 0.1 g (0.1 mmol) of **19** and 40.0 mg of 10% palladium/carbon in 9 mL of ethyl acetate, methanol, and dichloromethane (1:1:1) was shaken at 25°C under 36 psi hydrogen atmosphere for 10 h. After removal from the hydrogenator, the mixture was diluted with 10 mL of methanol, filtered through Celite, concentrated to give a solid. This solid was washed with dichloromethane and vacuum dried to obtain 31.0 mg (70% yield) of **7** as a light yellow solid, mp >270°C (dec.). ^1H NMR (DMSO- d_6) δ 7.44 (dd, J = 8.3, 1.9 Hz, 1 H), 7.35 (dd, J = 8.3, 2.0 Hz, 2 H), 7.27 (dd, J = 8.3, 2.0 Hz, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 6.49 (d, J = 2.0 Hz, 1 H), 6.25 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (DMSO- d_6) δ 176.0, 165.2, 164.0, 161.8, 157.3, 156.7, 149.8, 146.1, 143.8, 143.7, 130.7, 124.6, 121.1, 120.6, 116.4, 115.8, 115.7, 115.0, 113.6, 104.2, 99.6, 94.6. MS (electrospray; negative mode) m/z 436.4 ($M-H^+$), 255.4. HRMS calcd for $C_{22}H_{16}NO_9^+$ ($M+H^+$) 438.0825, found 438.0816.

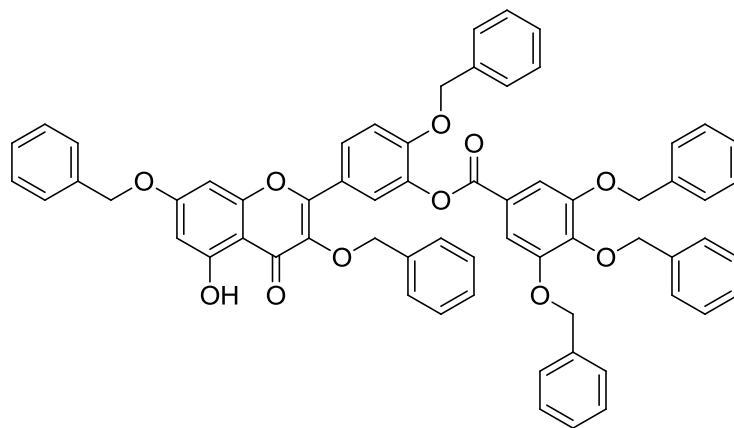
Synthesis of 3,7-(dibenzyloxy)-2-(4-benzyloxy-3-hydroxyphenyl)-5-hydroxy-4-oxo-4*H*-chromene (28) and 3,7-(dibenzyloxy)-2-(3,4-dibenzyloxyphenyl)-5-hydroxy-4-oxo-4*H*-chromene (29).



To a solution of 1.0 g (3.3 mmol) of quercetin **1** and 1.0 g (9.9 mmol) of sodium carbonate in 30 mL of DMF under argon at 80°C was added 1.3 g (9.9 mmol) of benzyl chloride via syringe. The solution was stirred at 80°C for 20 h and most of the DMF solvent was removed via vacuum distillation at 50 – 60°C/5 mm Hg. The remaining mixture was diluted with dichloromethane, washed with 2 N HCl, water, and brine, dried (anhydrous Na₂SO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 1.2 g (63% yield) of compound **28** and 0.4 g (18% yield) of compound **29** as yellow solid. Compound **28**:¹⁵ Mp 146 – 149°C; ¹H NMR δ 12.71 (s, 1 H, OH), 7.65 (d, *J* = 2 Hz, 1 H), 7.63 (s, 1 H), 7.46 – 7.22 (m, 15 H), 6.97 (d, *J* = 9 Hz, 1 H), 6.51 (d, *J* = 2 Hz, 1 H), 6.45 (d, *J* = 2 Hz, 1 H), 5.72 (s, 1 H, OH), 5.21 (s, 2 H), 5.14 (s, 2 H), 5.08 (s, 2 H); ¹³C NMR □ 179.0, 164.7, 162.2, 157.0, 156.5, 148.0, 145.8, 137.8, 136.0, 135.9, 129.0, 128.5, 127.7, 124.2, 122.1, 115.1, 111.8, 98.9, 93.2, 74.5, 71.4, 70.6. Compound **29**:¹⁵ Mp 110 – 114°C; ¹H NMR □ 12.70 (s, 1 H, OH), 7.72 (d, *J* = 2 Hz, 1 H), 7.56 (dd, *J* = 9, 2 Hz, 1 H), 7.50 – 7.20 (m, 20 H), 6.98 (d, *J* = 9 Hz, 1 H), 6.48 (d, *J* = 2 Hz, 1 H), 6.45 (d, *J* = 2 Hz, 1 H), 5.26 (s, 2 H), 5.15 (s, 2 H), 5.06 (s, 2 H), 5.01 (s, 2 H); ¹³C NMR δ 179.0, 164.7, 162.3, 156.9, 156.5,

151.3, 148.4, 137.7, 136.9, 136.7, 136.0, 129.0, 128.7, 128.5, 127.7, 127.4, 123.7, 122.8, 115.5, 113.9, 106.4, 98.8, 93.3, 74.6, 71.3, 71.1, 70.7.

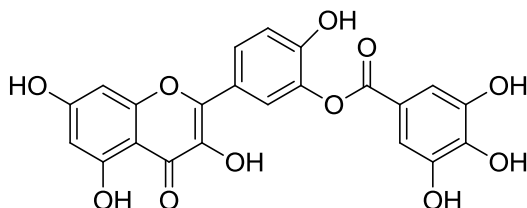
Synthesis of 5-(3,7-bis(benzyloxy)-5-hydroxy-4-oxo-4H-chromen-2-yl)-2-(benzyloxy)phenyl 3,4,5-tris(benzyloxy)benzoate (30).



To a solution of 0.12 g (0.26 mmol) of acid **12**, 40.0 mg (26 mmol) of EDC and 4.0 mg (35 μ mol) of DMAP in 2 mL of dichloromethane under argon was added a solution of 0.10 g (0.17 mmol) of compound **28**. The reaction solution was stirred at 25°C for 12 h, diluted with 50 mL of dichloromethane, washed three times with water, and brine, dried (anhydrous Na_2SO_4), concentrated and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluant to give 60.0 mg (35% yield) of compound **30** as white solid. ^1H NMR δ 12.7 (s, 1 H, OH), 7.94 (d, J = 2.0 Hz, 1 H), 7.92 (s, 1 H), 7.56 (s, 2 H), 7.46 - 7.18 (m, 30 H), 7.04 (d, J = 9.2 Hz, 1 H), 6.50 (d, J = 2.0 Hz, 1 H), 6.44 (d, J = 2.0 Hz, 1 H), 5.19 (s, 2 H), 5.17 (s, 2 H), 5.15 (s, 4 H), 5.12 (s, 2 H), 5.11 (s, 2 H); ^{13}C NMR δ 179.0, 164.8, 164.4, 162.3, 156.9, 155.6, 151.9, 151.6, 143.3, 140.4, 137.9, 137.6, 136.8, 136.4, 136.3, 136.0, 129.2, 129.0, 128.8, 128.77, 128.6, 128.54, 128.51, 128.45, 128.32, 128.26, 128.24, 128.0, 127.8, 127.7, 127.6, 127.4, 127.1, 124.4, 123.9, 123.7, 113.8, 110.0, 106.4, 98.9, 93.3, 75.4, 74.7, 71.6, 70.8, 70.7. MS

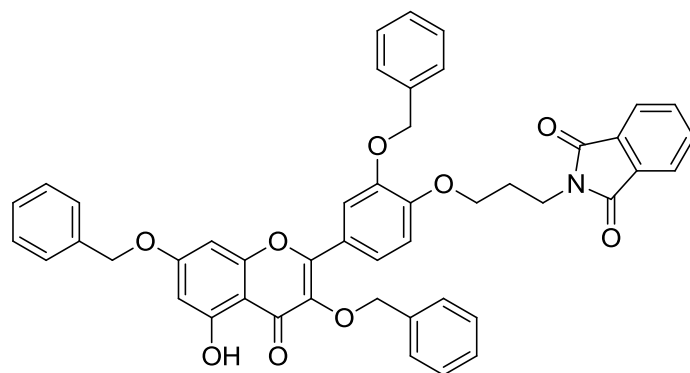
(electrospray) m/z 995.9 ($M+H^+$). HRMS calcd for $C_{64}H_{51}O_{11}^+$ ($M+H^+$) 995.3431, found 995.3475.

Synthesis of 2-hydroxy-5-(3,5,7-trihydroxy-4-oxo-4H-chromen-2-yl)phenyl 3,4,5-trihydroxybenzoate (8).



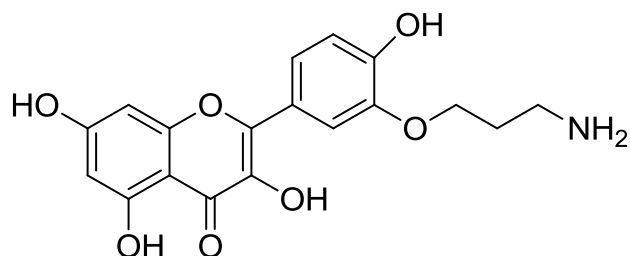
A mixture of 55.0 mg (55 μ mol) of compound **30** and 11.0 mg of 5% palladium/carbon in 11 mL of ethyl acetate, methanol, and dichloromethane (5:3:3) was shaken in a hydrogenator under 36 psi pressure of hydrogen at 25°C for 16 h. The reaction mixture was diluted with ethanol and filtered through Celite, concentrated to dryness to give a solid. The solid was washed with 5 mL of water and 15 mL of diethyl ether, and dried under vacuum to give 14.0 mg (56% yield) of C3'-gallate **8** as yellow solid. ^1H NMR (DMSO- d_6) δ 12.40 (s, 1 H, OH), 9.10 - 9.90 (bs, 5 H, OH), 7.96 (dd, J = 8.6, 2.2 Hz, 1 H), 7.91 (d, J = 2.4 Hz, 1 H), 7.10 (s, 3 H), 6.47 (d, J = 1.6 Hz, 1 H), 6.19 (d, J = 2.0 Hz, 1 H); ^{13}C NMR δ 176.6, 164.9, 164.8, 164.7, 161.3, 156.8, 151.8, 149.7, 146.4, 146.3, 139.8, 139.2, 137.7, 136.7, 123.5, 122.7, 118.9, 117.5, 109.9, 109.9, 103.7, 99.0. MS (electrospray) m/z 477.1 ($M+Na^+$), 455.2 ($M+H^+$). HRMS calcd for $C_{22}H_{15}O_{11}^+$ ($M+H^+$) 455.0614, found 455.0609.

Synthesis of 3,7-(dibenzoyloxy)-2-[4-benzoyloxy-3-(3-phthaloylpropyloxy)phenyl]-5-hydroxy-4-oxo-4*H*-chromene (32).



A solution of 1.1 g (1.9 mmol) of compound **28**, 0.73 g (2.3 mmol) of 3-iodopropylphthalimide **31**,^{16,17} and 92.0 mg (3.9 mmol) of sodium hydride (50% oil) in 20 mL of DMF was stirred under argon at 80°C for 48 h. The reaction solution was cooled to 25°C, diluted with aqueous NH₄Cl, and extracted three times with ethyl acetate. The organic layer was washed with water and brine, dried (MgSO₄), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 0.58 g (40% yield) of compound **32** as yellow solid. Mp 168 – 174°C; ¹H NMR δ 12.70 (s, 1 H, OH), 7.81 (dd, *J* = 8, 2 Hz, 2 H), 7.67 (dd, *J* = 8, 2 Hz, 1 H), 7.63 (d, *J* = 2 Hz, 1 H), 7.57 (dd, *J* = 8, 2 Hz, 1 H), 7.45 – 7.23 (m, 15 H), 6.91 (d, *J* = 8 Hz, 1 H), 6.55 (d, *J* = 2 Hz, 1 H), 6.44 (d, *J* = 2 Hz, 1 H), 5.14 (s, 2 H, CH₂OPh), 5.13 (s, 2 H, CH₂OPh), 5.07 (s, 2 H, CH₂OPh), 3.88 (m, 4 H, CH₂O & CH₂N), 2.15 (quin, *J* = 7 Hz, 2 H); ¹³C NMR δ 179.0, 168.5, 164.7, 162.3, 156.9, 156.5, 151.1, 148.6, 137.8, 136.9, 134.1, 132.4, 129.0, 128.5, 127.7, 127.2, 123.7, 123.4, 122.7, 114.6, 113.9, 106.4, 98.8, 93.3, 74.6, 70.9, 70.7, 67.0, 35.64, 28.64. MS (electrospray) *m/z* 782.3 (M+Na⁺), 760.6 (M+H⁺), 413.1 (100%). HRMS calcd for C₄₇H₃₈NO₉⁺ (M+H⁺) 760.2547, found 760.2571.

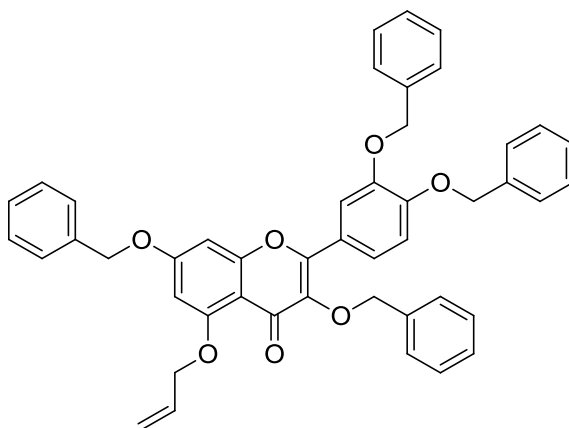
Synthesis of 3,5,7-(trihydroxy)-2-[4-hydroxy-3-(3-aminopropoxy)phenyl]-4-oxo-4*H*-chromene (9).



A solution of 100.0 mg (0.13 mmol) of phthalimide **32** and 99.0 mg (2.0 mmol) of hydrazine in 3 mL of THF was stirred under argon at 25°C for 11 h. The solution was diluted with 50 mL of dichloromethane, precipitated white solids was removed by filtration, and the filtrate was washed twice with water and brine, dried (anhydrous Na₂SO₄), concentrated to give 70.0 mg (85% yield) of 3,7-(dibenzyloxy)-5-hydroxy-2-[4-benzyloxy-3-(3-aminopropoxy)phenyl]-4-oxo-4*H*-chromene as yellow solid. ¹H NMR δ 7.50 – 7.10 (m, 17 H), 6.82 (d, *J* = 2 Hz, 2 H), 6.67 (d, *J* = 2 Hz, 1 H), 6.40 (bs, 2 H), 6.22 (s, 1 H), 4.99, (s, 2 H, CH₂O), 4.97 (s, 2 H, CH₂O), 4.69 (s, 2 H, CH₂O), 3.89 (t, *J* = 7 Hz, 2 H, CH₂O), 2.78 (t, *J* = 7 Hz, 2 H, CH₂N), 1.80 (quin, *J* = 7 Hz, 2 H). This material was used in next step without purification. A mixture of 50.0 mg (79 μmol) of the above benzyl quercetin, 15.0 mg of 5% palladium/carbon in 2 mL each of THF and methanol along with 5 drops of 2 N HCl, was shaken in a hydrogenator under 36 psi hydrogen for 16 h at 25°C. The mixture was diluted with 10 mL of methanol, filter through Celite, concentrated to give 17 mg (58% yield) of compound **9** as yellow solid. ¹H NMR (DMSO-*d*₆) δ 12.45 (s, 1 H, OH), 10.81 (s, 1 H, OH), 9.74 (s, 1 H, OH), 9.46 (s, 1H, OH), 7.75 (d, *J* = 2.0 Hz, 1 H), 7.71 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.47 (d, *J* = 2.0 Hz, 1 H), 6.21 (d, *J* = 2.0 Hz, 1 H), 4.13 (t, *J* = 6.0 Hz, 2 H), 3.05 (bs, 2 H),

2.07 - 2.03 (m, 2 H); ^{13}C NMR δ 176.5, 164.7, 161.3, 156.8, 149.6, 147.1, 147.0, 136.5, 122.7, 122.67, 116.4, 113.8, 103.7, 98.9, 94.3, 66.6, 37.2, 27.6. HRMS calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_7^+$ ($\text{M}+\text{H}^+$) 360.1083, found 360.1100.

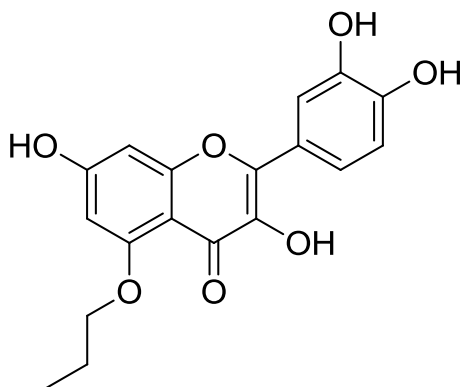
Synthesis of 3,7-(dibenzyloxy)-2-(3,4-dibenzyloxyphenyl)-5-allyloxy-4-oxo-4H-chromene (33).



To a solution of 54.0 mg (82 μmol) of compound **29** and 3.0 mg (0.12 mmol) of sodium hydride in 1 mL of DMF under argon at 25°C was added 12.0 mg (98 μmol) of allyl bromide via syringe. The reaction solution was stirred for 10 h, diluted with dichloromethane, neutralized with 1 N HCl, washed three times with water, and brine, dried (MgSO_4), concentrated, and column chromatographed on silica gel using 20% ethyl acetate in hexane as eluent to give 50.0 mg (88% yield) of compound **33** as a white solid, mp 107 – 110°C. ^1H NMR δ 7.72 (d, J = 2.0 Hz, 1 H), 7.54 (dd, J = 8.5, 2.0 Hz, 1 H), 7.46 - 7.21 (m, 20 H), 6.95 (d, J = 8.5 Hz, 1 H), 6.53 (d, J = 2.4 Hz, 1 H), 6.42 (d, J = 2.4 Hz, 1 H), 6.13 - 6.08 (ddt, J = 17.6, 10.4, 6.4 Hz, 1 H, =CH), 5.64 (dd, J = 17.6, 1.6 Hz, 1 H, =CH₂), 5.35 (dd, J = 10.4, 1.6 Hz, 1 H, =CH₂), 5.23 (s, 2 H, CH₂OPh), 5.12 (s, 2 H, CH₂OPh), 5.08 (s, 2 H, CH₂OPh), 4.94 (s, 2 H, CH₂OPh), 4.69 (d, J = 6.4 Hz, 2 H, CH₂O); ^{13}C NMR δ 174.1, 162.9, 160.1, 158.9, 153.2, 150.6, 148.4, 141.5, 140.0,

137.3, 137.2, 137.0, 135.9, 132.5, 129.1, 129.0, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.4, 124.1, 122.2, 118.3, 115.3, 113.9, 110.1, 97.9, 93.8, 74.2, 71.2, 71.0, 70.7, 70.1. MS (electrospray) m/z 725.5 ($M+Na^+$, 100%), 703.4 ($M+H^+$), 396.3. HRMS calcd for $C_{46}H_{39}O_7^+$ ($M+H^+$) 703.2696, found 703.2687.

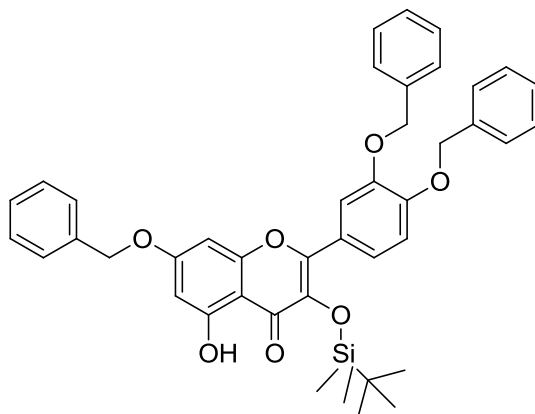
Synthesis of 3,7-(dihydroxy)-2-(3,4-dihydroxyphenyl)-5-propyloxy-4-oxo-4H-chromene (10).



A mixture of 80.0 mg (0.11 mmol) of compound **33** and 30.0 mg of 10% palladium/carbon in 6 mL of ethyl acetate, acetone, and ethanol (1:1:1) was shaken in a hydrogenator under 36 psi of hydrogen at 25°C for 18 h. The reaction mixture was diluted with ethanol and filtered through celite; the filtrate was concentrated to dryness giving 35.0 mg (90% yield) of compound **10** as yellow solid, mp 269 – 272°C. ^1H NMR (DMSO- d_6) δ 10.60 (bs, 1 H, OH), 9.40 (bs, 1 H, OH), 9.30 (bs, 1 H, OH), 8.70 (s, 1 H, OH), 7.62 (d, J = 2.0 Hz, 1 H), 7.47 (dd, J = 9.0, 2.0 Hz, 1 H), 6.86 (d, J = 9.0 Hz, 1 H), 6.42 (d, J = 2.0 Hz, 1 H), 6.31 (d, J = 2.0 Hz, 1 H), 3.98 (t, J = 7.0 Hz, 2 H), 1.77 (sextet, J = 7.0 Hz, 2 H), 1.08 (t, J = 7.0 Hz, 3 H). ^{13}C NMR δ 171.0, 162.4, 160.0, 157.9, 146.9, 145.1, 141.7, 137.2, 122.3, 119.1, 115.6, 114.5, 105.2, 104.3,

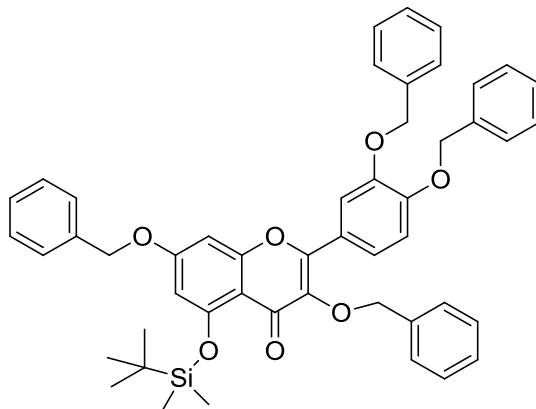
96.4, 94.4, 69.8, 22.0, 10.5. MS (electrospray) m/z 345.5 ($M+H^+$; 100%), 303.1. HRMS calcd for $C_{18}H_{17}O_7^+$ ($M+H^+$) 345.0969, found 345.0972.

7-(benzyloxy)-2-{3,4-bis(benzyloxy)phenyl}-3-(tert-butyldimethylsilyl)oxy-5-hydroxy-4*H*-chromen-4-one (66)



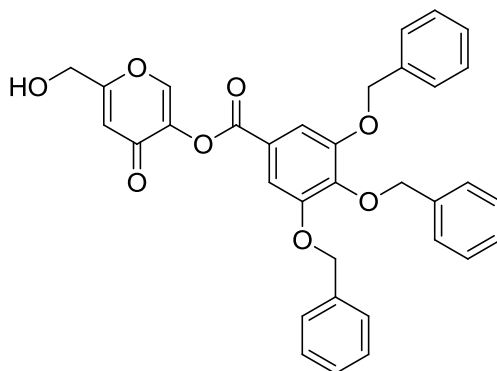
Solution of 54.0 mg (0.09 mmol) of **27** and 3.5 mg (0.03 mmol) of DMAP in 0.5 mL of dichloromethane was cooled to 0°C using ice-water bath. 24 μ l (0.18 mmol) of dry triethylamine and 28.3 mg (0.18 mmol) of TBDMS-Cl were syringed into the reaction. Reaction was stirred at 25°C for 2 h, diluted with 10 mL of dichloromethane, washed with water (5 mL x 3 times), dried ($MgSO_4$), concentrated and column chromatographed on silica gel using 20% ethyl acetate in hexane as eluent to give 55.0 mg (98% yield) of yellow solid product. ^1H NMR δ 12.72 (s, 1 H), 7.62 - 7.60 (m, 2 H), 7.47 - 7.33 (m, 12 H), 7.26 (t, J = 3.2 Hz, 3 H), 6.95 (d, J = 9.2 Hz, 1 H), 6.48 (d, J = 2.3 Hz, 1 H), 6.44 (d, J = 2.0 Hz, 1 H), 5.13 (s, 4 H), 5.07 (s, 2 H), 0.95 (s, 9 H), 0.3 (s, 6 H); ^{13}C NMR δ 179.02, 164.60, 162.31, 156.90, 156.72, 152.78, 145.15, 137.56, 136.62, 136.50, 136.03, 128.97, 128.75, 128.59, 128.48, 128.40, 128.38, 128.04, 127.73, 123.56, 123.24, 121.60, 113.14, 106.38, 98.64, 93.40, 74.35, 70.88, 70.69, 25.87, 18.58, -4.39.

3, 7-bis(benzyloxy)-2-{3,4-bis(benzyloxy)phenyl}-5-(tert-butyldimethylsilyl)oxy-4*H*-chromen-4-one (67)



Solution of 50.0 mg (0.08 mmol) of compound **28** and 2.8 mg (0.02 mmol) of DMAP in 0.5 mL of dichloromethane was cooled to 0°C using ice-water bath. 10 µl (0.15 mmol) of dry triethylamine and 22.6 mg (0.15 mmol) of TBDMS-Cl were added into the reaction. Reaction was stirred for 2 h at 25°C, diluted with 10 mL of dichloromethane, washed with water (5 mL x 3 times), dried (MgSO₄), concentrated, and column chromatographed on silica gel using 20% ethyl acetate in hexane as eluent to give 48.0 mg (86% yield) of yellow solid product. ¹H NMR δ 7.7 (d, *J* = 2.0 Hz, 1 H), 7.49 - 7.37 (m, 18 H), 7.21 - 7.19 (m, 3 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 6.58 (d, *J* = 2.4 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 5.25 (s, 2 H), 5.12 (s, 2 H), 5.04 (s, 2 H), 4.98 (s, 2 H), 1.08 (s, 9 H), 0.3 (s, 6 H); ¹³C NMR δ 185.22, 173.88, 162.36, 158.39, 157.13, 153.38, 151.65, 150.57, 148.26, 139.50, 137.21, 136.99, 136.03, 129.16, 128.95, 128.76, 128.57, 128.25, 128.13, 126.01, 127.72, 127.54, 127.36, 124.26, 123.09, 122.25, 120.00, 115.31, 113.83, 112.25, 105.70, 95.41, 74.25, 71.21, 71.03, 70.05, 26.23, -4.17.

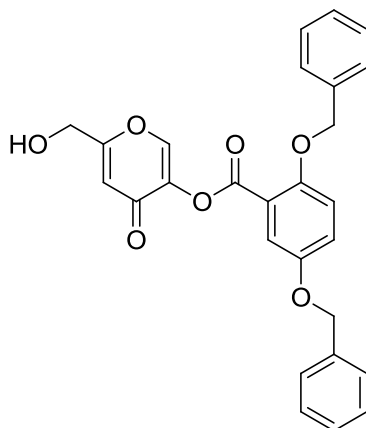
6-(hydroxymethyl)-4-oxo-4H-pyran-3-yl 3,4,5-tris(benzyloxy)benzoate (68)



Solution of 50.0 mg (0.35 mmol) of Kojic acid, 65.4 mg (0.42 mmol) EDC, 8.6 mg (0.07 mmol) DMAP and 184.8 mg (0.42 mmol) of tribenzyl protected gallic acid in 2 mL of DMF was stirred at 25°C for 8 h, diluted with 20 mL of dichloromethane, washed with water (20 mL x 3 times), dried (MgSO₄), concentrated and column chromatographed on silica gel using 40% ethyl acetate in hexane as eluent to give 150.0 mg (76% yield) of white solid product. ¹H NMR δ 7.7 (d, *J* = 2.0 Hz, 1 H), 7.49 - 7.43 (m, 18 H), 7.21 - 7.19 (m, 3 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 6.58 (d, *J* = 2.4 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 5.25 (s, 2 H), 5.12 (s, 2 H), 5.04 (s, 2 H), 4.98 (s, 2 H), 1.08 (s, 9 H), 0.3 (s, 6 H); ¹³C NMR δ 173.33, 168.48, 163.55, 152.86, 148.28, 143.42, 141.41, 137.40, 136.62, 128.78, 128.44, 128.31, 128.27, 127.83, 123.08, 113.40, 110.03, 75.39, 71.44, 60.90.

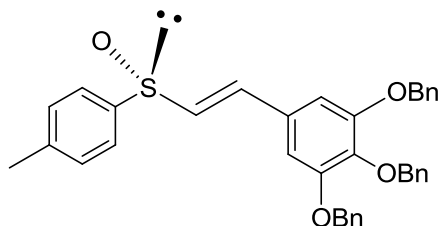
6-(hydroxymethyl)-4-oxo-4H-pyran-3-yl 2,5-bis(benzyloxy)-2-phenethylbenzoate

(69)



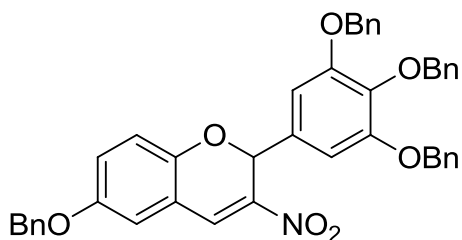
Solution of 38.3 mg (0.35 mmol) of Kojic acid, 41.8 mg (0.42 mmol) EDC, 5.5 mg (0.07 mmol) DMAP and 75.0 mg (0.23 mmol) of 2,5 dibenzyl protected benzoic acid in 2 mL of DMF was stirred at 25°C for 8 h, diluted with 20 mL of dichloromethane, washed with water (20 mL x 3 times), dried (MgSO₄), concentrated and column chromatographed on silica gel using 40% ethyl acetate in hexane as eluent to give 80.2 mg (79% yield) of solid product. ¹H NMR δ 7.91 (s, 1 H), 7.71 (d, *J* = 3.1 Hz, 1 H), 7.49 - 7.28 (m, 10 H), 7.15 (dd, *J* = 9.2, 3.3 Hz, 1 H), 6.99 (d, *J* = 4.8 Hz, 1 H), 6.61 (s, 1 H), 5.16 (s, 2 H), 5.06 (s, 2 H), 4.51 (dd, *J* = 6.6, 0.8 Hz, 2 H), 2.67 (t, *J* = 6.6 Hz, 1 H). ¹³C NMR δ 173.56, 169.17, 162.51, 153.91, 152.60, 148.35, 141.20, 136.86, 136.73, 128.77, 128.68, 128.27, 127.82, 127.32, 122.37, 118.59, 117.99, 116.19, 113.15, 71.77, 70.87, 60.68.

Synthesis of Compound 55



To a slurry of 50.0 mg (0.87 mmol) of compound **54** and 13.84 mg (0.35 mmol) of NaH in 1 mL of dry THF, 36.83 mg (0.26 mmol) of methyl iodide was added after 0.5 h and stirred at 25°C for additional 16 h. Reaction was diluted with 50 mL of ethyl acetate, neutralized with 15 mL of NH₄Cl solution, washed with water (50 mL x 5 times), dried (MgSO₄), concentrated and column chromatographed on silica gel using 20% ether in hexane as eluent to give 45.0 mg (93% yield) of product as white solid. ¹H NMR δ 7.58 (d, *J* = 8.2 Hz, 2 H), 7.43 - 7.32 (m, 15 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 12.0 Hz, 1 H), 6.76 (s, 2 H), 6.68 (d, *J* = 16 Hz, 1 H), 5.10 (s, 4 H), 5.09 (s, 2 H), 2.43 (s, 3 H); ¹³C NMR δ 153.25, 141.95, 140.94, 140.17, 137.68, 136.87, 136.26, 132.44, 130.34, 129.52, 128.73, 128.37, 128.19, 128.10, 127.59, 125.11, 107.77, 75.44, 71.50, 21.64.

Synthesis of 6-(benzyloxy)-3-nitro-2-{3,4,5-tris(benzyloxy)phenyl}-2*H*-chromene (66)



Solution of 30.0 mg (0.064 mmol) of nitroalkene **48**, 17.5 mg (0.077 mmol) o-hydroxy aldehyde and 0.7 mg (0.0064 mmol) of DABCO in 1 mL of dichloroethane was heated to 80°C for 48 h. Reaction was cooled to room temperature, diluted with 30 mL of ether, washed with aq NH₄Cl, brine, dried (MgSO₄) concentrated and column chromatographed on silica gel using 40% ethyl acetate in hexane as eluent to give 17.33 mg (40% yield) of yellow solid as product. ¹H NMR δ 7.89 (s, 1 H), 7.43 - 7.18 (m, 20 H), 6.94 (d, *J* = 9.0 Hz), 6.70 (d, *J* = 9.0 Hz, 1 H), 6.59 (s, 1 H), 6.40 (s, 1 H), 5.03 (s, 2 H), 5.01 (s, 2 H), 5.00 (s, 2 H); ¹³C NMR δ 154.06, 153.04,

147.81, 144.77, 139.56, 137.89, 137.00, 136.68, 132.25, 129.49, 128.97, 128.74, 128.69, 128.49,
128.40, 128.15, 128.07, 127.71, 127.65, 121.77, 118.50, 118.34, 115.14, 107.12, 75.38, 74.01,
71.45

Chapter 2 - Progress towards the synthesis of mini graphene like hexa-peri-hexabenzocoronene cyclophane

Introduction

2.1. Graphenes

Graphene is a flat monolayer of sp^2 hybridized carbon atoms tightly packed into a two-dimensional honeycomb lattice.³⁶ Creating individual graphene layers was believed to be impossible³⁶ until its first successful isolation, characterization, and property study by A. K. Geim and K. S. Novoselov in 2004³⁶ at the university of Manchester, U.K. These researchers were awarded the 2010 Nobel Prize in physics for their work on graphene. Despite the development of various advanced scientific techniques, graphene remained elusive until 2004 because single layers of carbon are transparent.³⁶ Geim and Novoselov were able to observe graphene on silicon wafers with a carefully chosen SiO_2 thickness using an optical microscope.³⁷ There has been an enormous interest in graphene since their initial isolation. Many research scientists are working towards the controlled synthesis and practical application of graphene.³⁸ It is regarded as a wonder material with the potential to completely revolutionize various aspects of the world such as electronics and transistors.

2.2. Synthesis of Graphenes

Despite having only been discovered a few years ago, there has been an enormous interest in graphene within the scientific community, and many researchers are actively involved in graphene research. The primary problem associated with graphene, however, is its synthesis

and purification. Various methods have been developed to synthesize graphene and are summarized below.

Exfoliation and cleavage

Chemical vapor deposition

Thermal decomposition of silicon carbide (SiC)

Unzipping of carbon nanotubes

2.2.1. Exfoliation and Cleavage

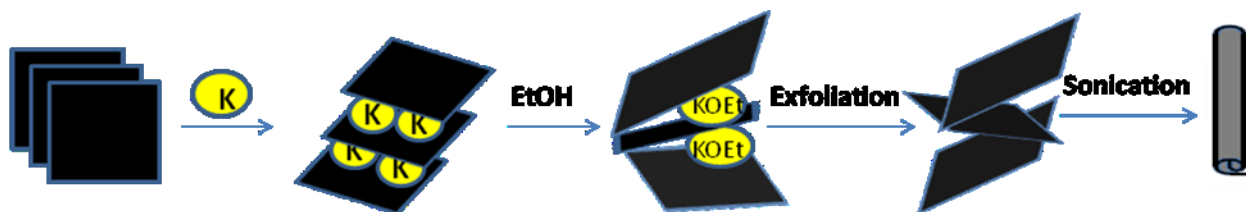


Figure 2-1. Schematic representation of the exfoliation technique.

Graphite consists of multiple graphene monolayer sheets stacked one atop another and held together by weak van der Waals forces.³⁶ Researchers have exploited the weak attractive forces between the layers to successfully exfoliate layers of graphene using chemical or mechanical energy. Viculus³⁹ was the first to use the exfoliation technique to obtain graphene layers. A schematic representation of the exfoliation technique is shown in Figure 2-1. The highly exothermic reaction between potassium and graphite allows for the insertion of potassium between the graphene layers, and subsequent treatment with ethanol (solvent) provides the energy required to break the π - π stacking between the layers. Viculus was able to obtain graphite 45 layers thick but was unable to produce pure, single-layered graphene. Using a modified technique, large and flat graphene sheets only a few layers thick were produced by Somani.⁴⁰ Novoselov et al. conducted the repeated exfoliation of highly oriented pyrolytic

graphite to produce both single and few-layer graphenes.³⁶ single and few-layered graphenes up to mm in size were produced from bulk graphite bonded to borosilicate glass via exfoliation.³⁷

2.2.2. Chemical Vapor Deposition Technique

Chemical vapor deposition (CVD) has been used to produce high-quality, large, flat graphene sheets ranging from multilayer to single layer.⁴¹ This technique has also been useful for the large-scale production of graphenes with relatively high purity. Ni, Cu and Si are commonly used surfaces for the deposition of graphenes.⁴¹ The first few-layered graphenes synthesized using chemical vaporization methods were prepared in 2006 on nickel foils from camphor.⁴¹ Both the electrical and mechanical properties of graphene degrade during isolation from the metal surface, which renders these graphenes less useful. CVD onto a copper substrate produced few-layered graphenes that were isolated without any degradation by annealing at 350°C and using argon gas to detach the copper substrate.⁴² In 2009, Kim showed that the thickness of the graphene layers formed depends on the thickness of Ni substrate and the rate of cooling of the surface. Thinner Ni surfaces and faster cooling (10°CS^{-1}) were critical for producing few-layered graphenes.⁴³ These single and few-layered graphenes were successfully transferred to a transparent substrate via the slow etching of the Ni layer using FeCl_3 . Using FeCl_3 instead of HNO_3 for etching prevented the degradation of the graphenes.⁴³

2.2.3. Unzipping of Carbon Nanotubes

Carbon nanotubes (CNT) are regarded as seamless tubes formed by the wrapping graphene sheets.⁴⁴ Researchers have used a variety of methods to unzip multi-walled carbon nanotubes to produce graphene.

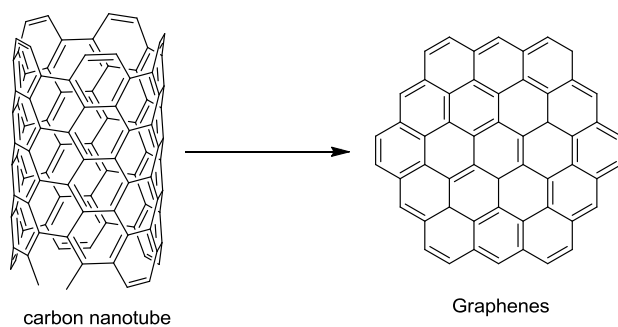


Figure 2-2. Schematic representation of unzipping of carbon nanotubes

The primary problem with unzipping these carbon nanotubes is developing a process to cleaving them along their longitudinal direction.⁴⁴ Argon plasma was used by Jiao⁴⁴ to unzip carbon nanotubes and produce nanographenes. Multi-walled carbon nanotubes were unzipped longitudinally to yield few-layer graphenes via stepwise chemical treatment, which includes exfoliation using H_2SO_4 , an excess of KMnO_4 and H_2O_2 followed by reduction in NH_4OH and hydrazine.⁴⁵ These methods are now being used for the large scale production of graphenes. The hydrogenation of carbon nanotubes at 50 atmospheres of H_2 and a temperature of 550°C unzipped the carbon nanotubes and produced graphenes;⁴⁶ however, this process hydrogenates the graphenes and degrades their quality.

2.2.4. Thermal decomposition of Silicon Carbide

When silicon carbide is annealed at high temperatures, silicon desorbs from the surface and leaves carbon behind.⁴⁷ These carbons form graphene layers of variable thicknesses. This technique for generating graphene is becoming popular because the number of graphene layers produced can be tuned and large flat graphene sheets can be synthesized at a low cost.⁴⁷ Graphene sheets formed at a lower temperature, 1400°C , when 6H-SiC was heated.⁴⁷

Advancements in this technique have led to the production of high-quality few-layered graphenes at low temperatures⁴⁸ with a predetermined number of layers using SiC.⁴⁹ Furthermore, wafer sized graphenes were produced using Ni doped SiC.⁴⁹

2.3. Types of Graphenes

Graphenes have distinctive optical, AFM and Raman spectra dependant on the number of layers present.⁴⁷ Differently layered graphenes also possess different physical properties. Graphenes that are ten or more layers thick do not exhibit the unusual properties of graphene and are of less interest to the scientific community.⁵⁰ Thus, graphene sheets that are less than ten layers thick can be broadly categorized into the following types:⁵⁰

Single-layered graphenes

Bilayer graphenes

Few-layered graphenes

Single-layered graphenes have a single layer of carbon atoms closely packed in a honeycomb structure, whereas bilayer graphenes consist of two graphene layers stacked on top of each other.⁵⁰ Graphene sheets containing three to ten layers stacked together are called few-layered graphenes.

2.4. Applications

2.4.1. Electrodes for Lithium Ion Battery

Modern electronics are powered by energy-dense lithium-ion batteries.⁵⁰ This battery uses graphite as an anode due to its reasonable specific capacity and reversibility⁵⁰; however, due to the ever increasing demand for high-density energy storage, people are looking for new electrode materials. The slow rate of lithium ion diffusion, poor electron transport in the

electrode and increased resistance at the electrode and electrolyte interface at high charge-discharge rates pose severe limitations on many materials for use as electrodes.⁵⁰ Graphene, another form of carbon, has high conductivity, good chemical tolerance, a surface area of over 2600 m²/g and can be of great value as a lithium ion battery electrode. It was found that tin oxide and graphene nanocomposite used as an electrode had a reversible capacity of 810 mAh/g, and both its cyclic performance and lithium ion storage increased relative to graphite electrodes,⁵¹ which demonstrates the potential for graphenes and their composites as electrodes in lithium ion batteries.

2.4.2. Transparent Electrodes

Graphenes have extraordinary chemical, thermal and mechanical stabilities as well as high conductivities and flexibility.⁴³ It has been shown that an atomic graphene thickness is highly transparent with an absorbance of only 2.3% of the incident light.⁴³ These properties make graphene an ideal candidate for transparent electrodes in solar cells and LCD displays. LCD displays currently use indium tin oxide (ITO),⁴³ which requires high vacuum treatment and contains the rare metal Indium. Furthermore, ITO is brittle and prevents the preparation of flexible and foldable screens. The maximum transparency obtained using ITO is 95% relative to 98% for graphenes, and at the 90% transparency used in LCD displays, ITO delivers approximately 10 Ω /square compared to 100 Ω /square for graphenes.⁵² Research has shown that the conductivity of graphene sheets changes little in the folded state relative to the flat (planar) state; therefore, it is an ideal material for foldable electronics.⁴³ Currently, the use of graphene in organic light emitting diode (OLED) is in the earliest phase and researchers believe it may be years before actual mass production.

2.4.3. Graphene based Biosensors

Graphene sensors are made based on the changes in the electrical conductivity of graphene due to foreign molecules adsorbed onto the surface.⁵³ When certain foreign molecules adsorb onto the surface of graphene, its conductivity either decreases or increases depending on the electron donating or withdrawing nature of the adsorbent. As a 2D sheet of carbon, graphene has a large surface area exposed to the adsorbents, which maximizes the chances of detection. Furthermore; graphene possesses metallic conductivity; thus, there is a notable change in conductivity upon the addition or removal of a few electrons in the graphene surface.⁵³ In fact Schedin⁵³ demonstrated that a device fabricated from graphene can sense an individual molecule of gases such as NH_3 , CO , NO_2 and H_2O adsorbed onto its surface. Vacuum annealing this device at 150°C removed any adsorbed gaseous molecules from the graphene surface, which was then able to sense new molecules proving the reusability of the sensor.⁵⁴ Fowler⁵⁵ designed a sensor using graphene synthesized from graphite via chemical exfoliation using anhydrous hydrazine that was able to detect NO_2 , NH_3 and 2,4-dinitrotoluene. Because Pd has a good affinity for H_2 , the electro-deposition of Pd onto graphene improved the response of the graphene sensors to H_2 .⁵⁶ Shan et al.⁵⁴ constructed a novel polyvinylpyrrolidone protected graphene/polyethylenimine-functionalized ionic liquid/glucose oxidase electrochemical biosensor capable of sensing glucose with a 14 mM concentration. Although still in the preliminary stages of development, graphene has great potential as a building material for biosensors.

2.4.4. Field Effect Transistors

Graphenes have good conductivity, mechanical strength and chemical stability⁵⁷ and are regarded as potential candidates to replace silicon-based field effect transistors; however, graphene behaves like a semi-metallic conductor with a very small or zero band gap, which leads to a low on/off current ratio and seriously reduces its applicability to field effect transistors (FET).⁵⁷ It is, however, possible to modify the band structure of graphene and create a band gap between graphene layers.⁵⁸ Creating a band gap between graphene layers can be achieved in three ways: constraining a large-area graphene in one dimension to form graphene nanoribbons, biasing bilayer graphene and applying strain to the graphene.⁵⁸

Theoretical investigations and optical measurements indicate a band gap of up to a few hundred millielectronvolts can be created in bilayer graphenes. In fact an, on/off current ratio of approximately 100 and 2000 was observed in dual-gate bilayer graphene FETs at room temperature and 20 K, respectively.⁵⁸ An electrical band gap of >130 and 80 meV with an average electric displacement of 2.2 and 1.3 Vnm⁻¹, respectively, was also observed.⁵⁸ This demonstration revealed the potential of bilayer graphenes for application to field effect transistors. As they possess a reasonable band width and can be used in further fabrication steps, the use of graphene nanoribbons in FET is more practical than flat and large 2D graphene sheets.⁵⁹ Before today, only prototype FETs have been made using graphene, and they are less effective than silicon oxide based FETs.

2.5. Results and Discussion

Poly-aromatic hydrocarbons (PAHs) are planar (flat) molecules composed of benzene rings connected to adjacent benzene rings via C-C bonds.⁶⁰ These molecules contain highly conjugated pi systems and are regarded as small graphene pieces. Hexa-peri-hexabenzocoronene,

a representative PAH, is the simplest member of the coronene family that displays graphene-related properties. Thus, these molecules are highly applicable to organic electronic devices such as solar cells, field effect transistors, and light emitting diodes. Research has shown that bilayer graphenes exhibit fascinating properties but are difficult to synthesize and isolate. Furthermore, the chemical synthesis of a bilayer hexa-peri-hexabenzocoronene with a known separation between the two layers has not yet been achieved. Thus, the synthesis of a bilayer PAH would not only allow a proper study of the physical and optoelectronic properties of graphene, but it would also assist in designing real life applications for graphenes and graphene-like materials. Because of these useful properties and application associated with PAHs, we chose hexa-peri-hexabenzocoronene as our target molecule for synthesis.

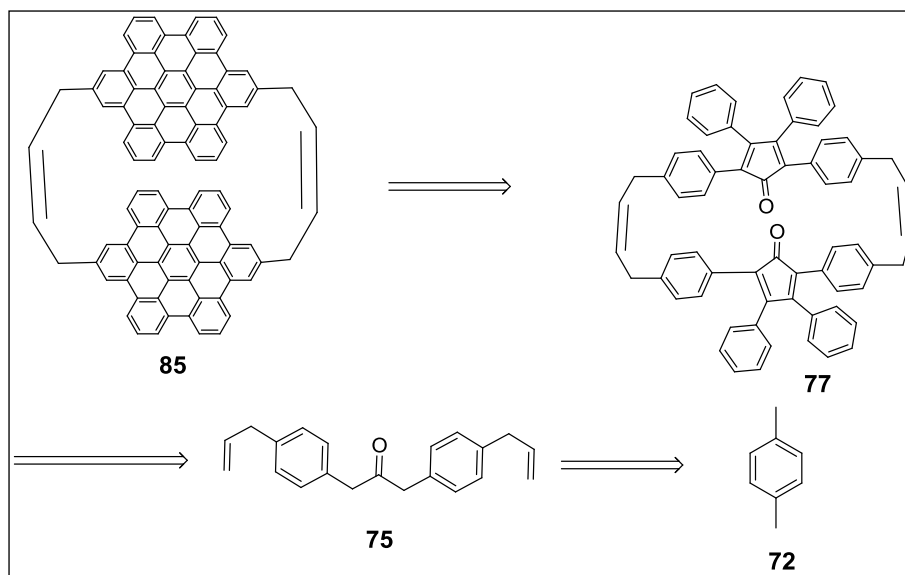
The ultimate goal of this project was to synthesize single-walled carbon nanotubes with a defined diameter via organic synthesis from simple, commercially available organic precursors. The synthesis of the macrocyclic polyaromatic hydrocarbon **77**, which is a critical intermediate in the synthesis of carbon nanotubes, using an unsaturated linker was accomplished by Dr. Bernard Wiredu (PhD 2009) in Dr. Hua's laboratory. The synthetic route reported in his thesis is shown in Scheme 2-4 and 2-6. The successful synthesis of macrocycles **82**, **77** and **84** was accomplished by Dr. Wiredu using Grubb's catalyst mediated alkene metathesis. These compounds were characterized by NMR, mass spectrometry and single crystal X-ray analysis.

The work described in this chapter is a continuation of that initially performed by Dr. Wiredu towards the synthesis of carbon nanotubes. In this chapter, I discuss the problems posed by the synthesis of macrocyclic compounds containing unsaturated linkers, the optimization of various conditions for previous reactions to improve their yields, and both the synthesis and attempted characterization of macrocyclic intermediate **90**.

2.5.1. Retro synthetic analysis

The synthesis of bilayer graphenes was envisioned as shown in the retro synthetic analysis in Scheme 2-1. Starting from a simple *p*-xylene (**72**), 1,3-bis(4-allylphenyl)propan-2-one (**75**) would be synthesized and used to obtain the desired macrocyclic cyclopentadienone, **77**. This macrocyclic dienone **77** would then undergo a Diels-Alder reaction to yield a hexaphenyl substituted benzene, which would give the required product **85**, upon oxidative dehydrogenation.

Scheme 2-1. Retro synthetic analysis of HBCC

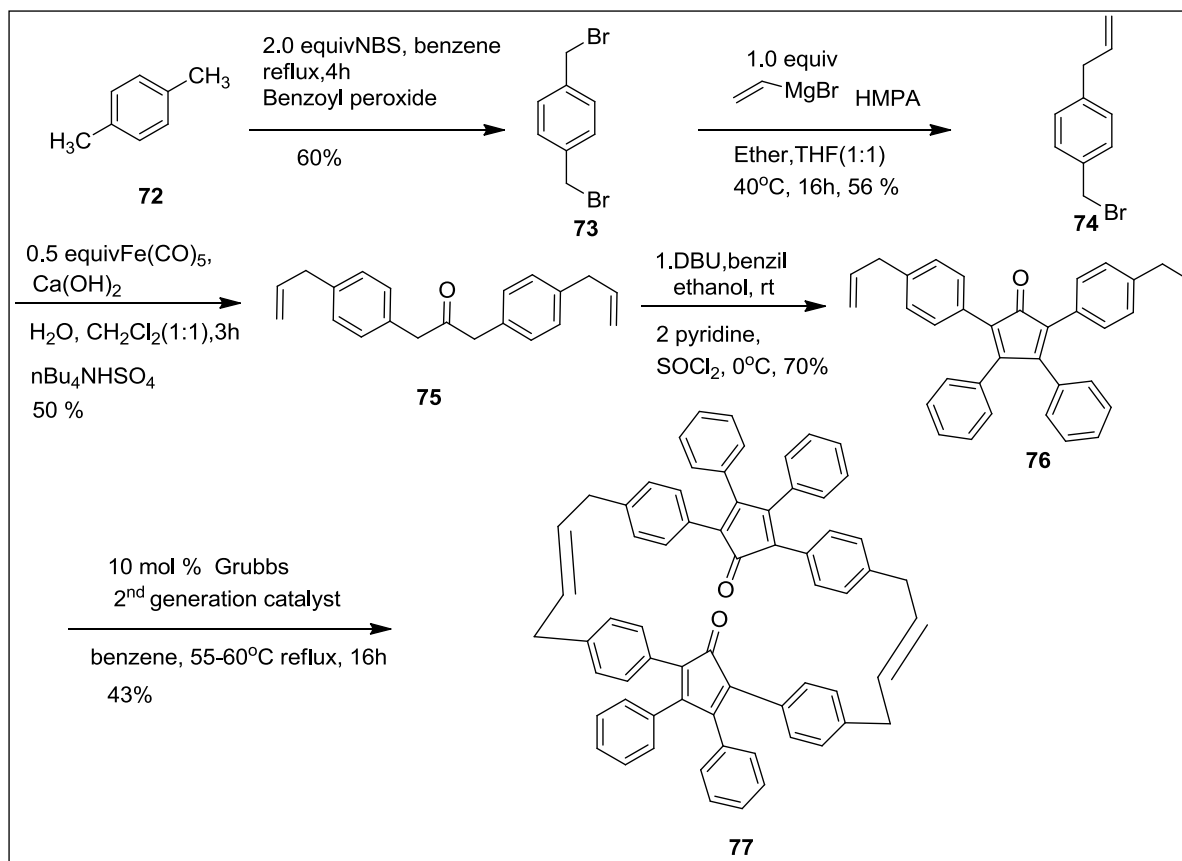


2.5.2. Synthesis of macrocyclic cyclopentanone **77**

As shown in Scheme 2-2, the macrocyclic cyclopentanone was to be made via the homodimerization of terminal alkene **75** using Grubb's second generation catalyst. *p*-Xylene was converted into 1,4-bis(bromomethyl)benzene (**73**) using NBS and benzoyl peroxide in refluxing benzene⁶¹ and further converted into 1-allyl-4-(bromomethyl)benzene (**74**) by reacting with vinylmagnesium bromide in THF and ether at 40°C for 16 h.⁶²

The carbonyl coupling of bromide **74** was mediated by $\text{Fe}(\text{CO})_5$ in degassed dichloromethane⁶⁰ and water at room temperature using phase transfer catalyst tetrabutylammonium hydrogensulfate to obtain compound **75**. Vigorous stirring of the reaction mixture was required to ensure the proper mixing of the reactants and obtain ketone **75**. The reactive reagent in this coupling reaction is believed to be the calcium salt of iron tetracarbonyl with iron in the -2 oxidation state.⁶² The double addition of bromide using reactive iron species occurs in two different steps. The second addition, the rate determining step, is believed to occur as shown in Scheme 2-3 and yields the coupled product, 1,3-bis(4-allylphenyl)propan-2-one (**75**).

Scheme 2-2. Synthesis of macrocyclic cyclopentadienone **77**



Scheme 2-3. Proposed mechanism of carbonylative coupling of benzyl bromide

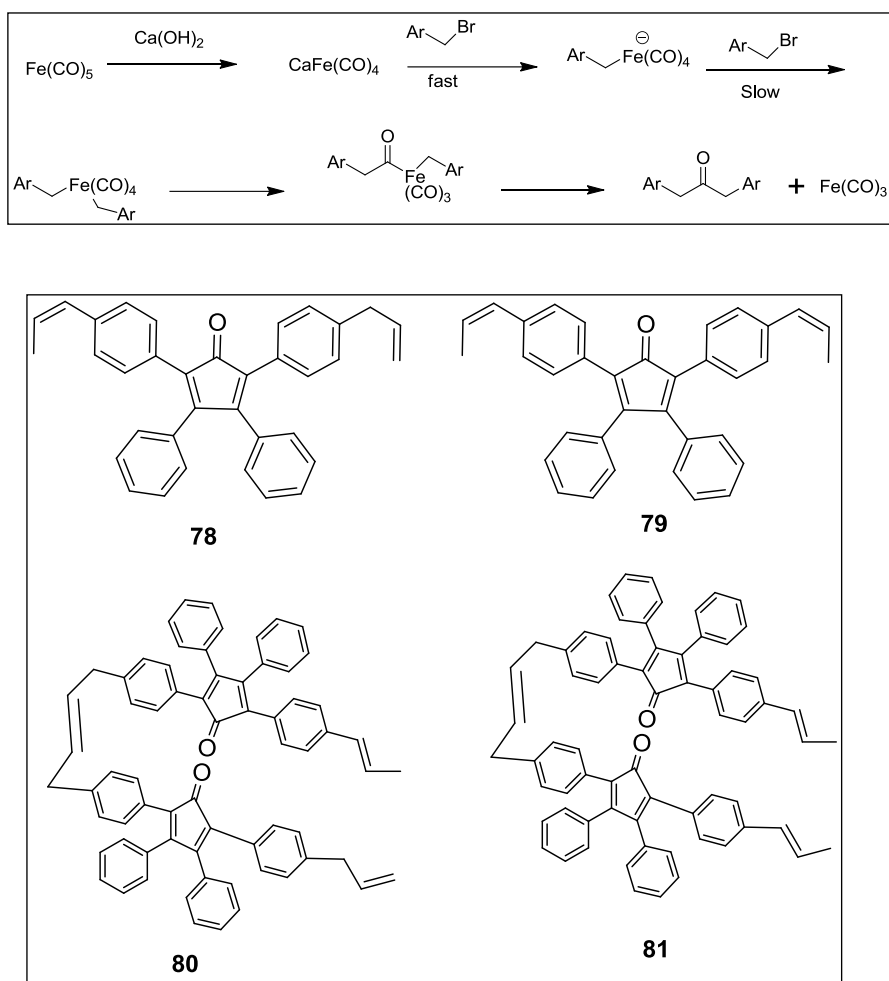
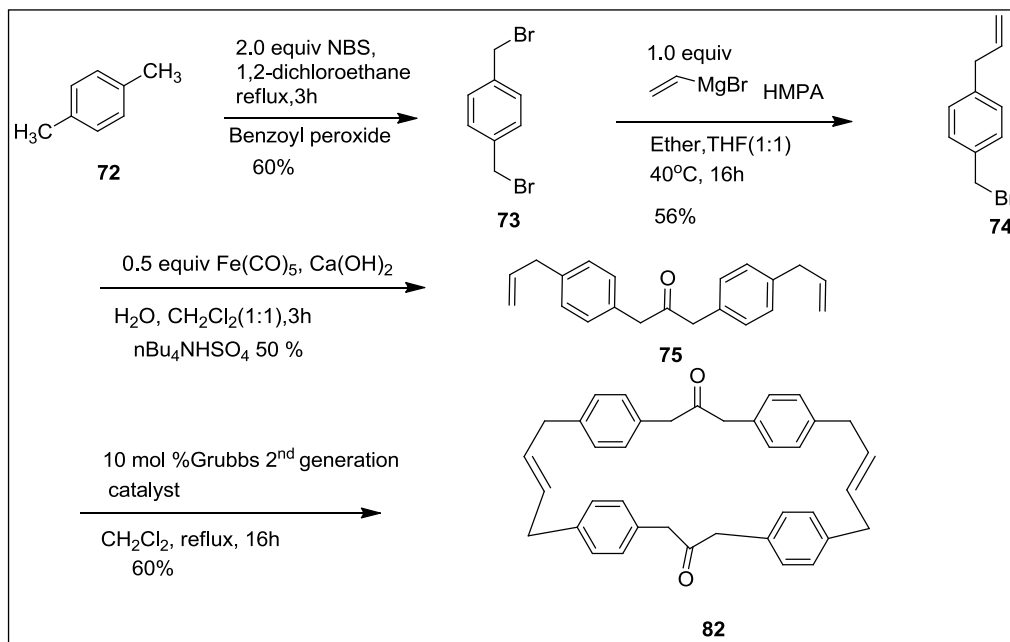


Figure 2-3. Several isomerized and incompletely cyclized products of metathesis reaction

The aldol addition of 1,3-bis(4-allylphenyl)propan-2-one (**75**) to benzil in ethanol using DBU as the base yields an aldol adduct that was subjected to elimination using pyridine and thionyl chloride to form cyclopentadienone **76**. The homodimerization of cyclopentadienone **76** was conducted using Grubb's second generation catalyst to yield the desired macrocyclic cyclopentadienone, **77**. High dilutions were used to prevent a polymerization reaction; however, significant isomerization of the terminal alkene into the internal alkene and the formation of incompletely cyclized products, shown in Figure 2-3, were both observed and reduced the yield of compound **77**. To optimize this protocol and minimize the isomerization of the terminal

double bonds, the reaction sequences were revised. As a result, the homodimerization of alkene **75** into the large macrocycle **82** was conducted prior to the formation of the cyclopentanone as shown in Scheme 2-4.

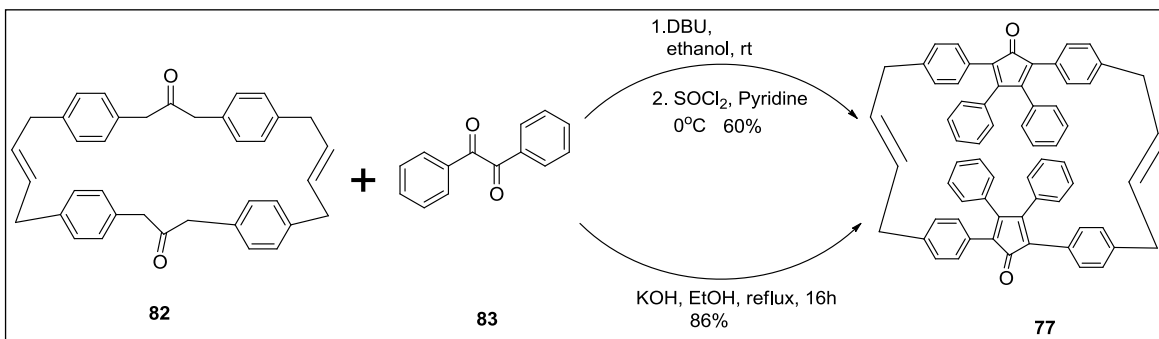
Scheme 2-4. Synthesis of macrocycle **82**



The treatment of alkene **75** with Grubb's second generation catalyst in benzene afforded the desired cyclized product, **82**; however, the yield was poor. Furthermore, the reaction time was long and required a large volume of benzene, (300 mL for 100 mg of **75**), which posed significant problems when conducting the reaction. The use of dichloromethane not only eliminated the toxic benzene but also reduced the reaction time to 16 h relative to the 72 h required for benzene. The reaction yield improved to 60% when Grubb's second generation catalyst in dichloromethane was added drop wise to a solution of alkene **75** in dichloromethane under reflux. It was also observed that the formation of the isomerized side products and incomplete cyclization was reduced relative to using benzene. The structure of the macrocyclic

diketone **82** was established via single crystal X-ray analysis and found to have a trans double bond in the macrocycle.

Scheme 2-5. Synthesis of large macrocyclic cyclopentadienone **77**

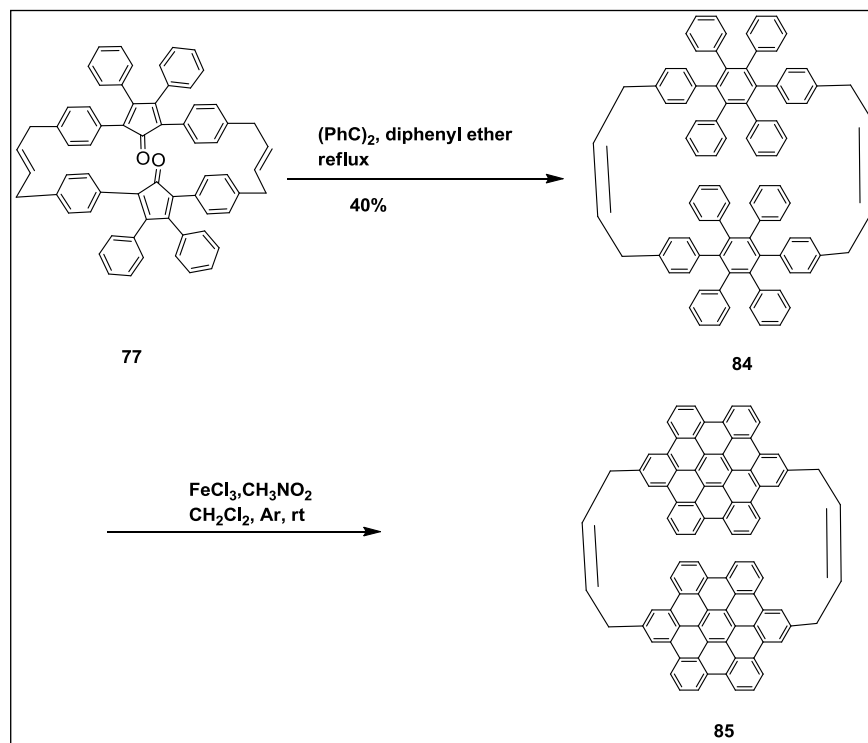


The reaction of macrocyclic diketone **82** with benzil was performed in ethanol at room temperature in the presence of DBU followed by a thionyl chloride mediated elimination⁶³ in pyridine to yield the desired cyclopentadienone, **77**, as shown in Scheme 2-5. The use of KOH instead of DBU in refluxing ethanol produced the desired product in a single step with an 86% yield and thus avoiding the use of the toxic thionyl chloride reagent while improving the yield.

2.5.3. Attempted synthesis of hexa-peri-hexabenzocorenene cyclophane (HBCC) bilayer superbenzene **85**

The synthesis of HBCC bilayer superbenzene **85** was attempted as shown in Scheme 2-6. A Diels-Alder^{62, 64} reaction with macrocyclic cyclopentadienone **82** was performed using diphenylacetylene in diphenyl ether under reflux to yield the hexabenzene substituted product **84** in 40% yield. The structure of this product was confirmed by a single crystal X-ray analysis. Compound **84** was found to be a *trans* isomer.

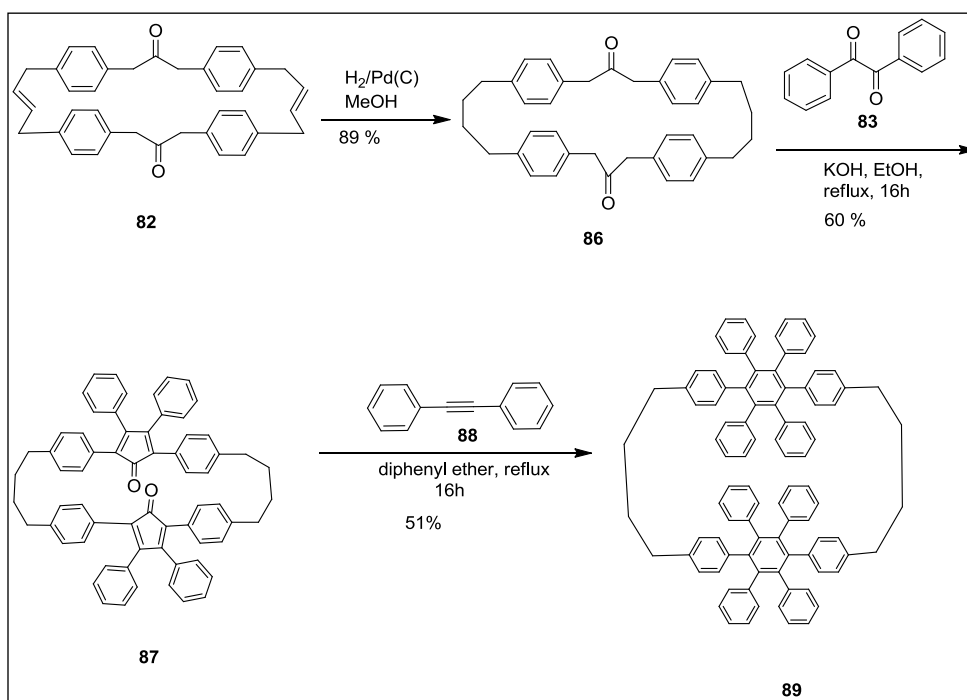
Scheme 2-6. Synthesis of hexa-peri-hexabenzocorenene cyclophane (HBCC) bilayer superbenzene **85**



Hexaphenyl benzene **84** was treated with iron trichloride in nitromethane and dichloromethane to perform the dehydrogenation reaction; however, because of the low yield, the reaction product could not be completely isolated and characterized.

The presence of an unsaturated linker in cyclopentadienone **77** was thought to be responsible for the seemingly low yield of the Diels-Alder reaction. Refluxing the unsaturated cyclopentadienone **77** in diphenyl ether above 256°C seems too harsh for the double bond linkers. Furthermore, the presence of an unsaturated linker makes the macrocyclic cyclopentadienone **77** rigid, which might affect the Diels-Alder reaction outcome. Thus, it was thought that the saturation of the unsaturated linker would provide flexibility in the macrocyclic cyclopentadienone and possibly increase the reaction yield.

Scheme 2-7. Synthesis of bilayer hexaphenyl macrocycle **89**



Reduction of the unsaturated macrocyclic cyclopentadienone, **77**, was thought to easily form the saturated analog **87**; however, when **77** was reduced with 10% Pd/C in ethanol under 1 atmosphere of hydrogen, the reduction of both the cyclopentadienone ring and the double bond in the linker of **77** was observed. This observation prompted us to follow Scheme 2-7 to obtain the saturated analog **87**.

Compound **82** was treated with 10% Pd/C in methanol under 1 atmosphere of hydrogen to yield saturated compound **86**. The condensation of compound **86** with benzil in the presence of KOH in ethanol under reflux produced the saturated macrocyclic cyclopentadione **87**. Compound **87** was purple in color and had a decreased solubility in ether and dichloromethane, which assisted in its easy purification via washing with these solvents. The Diels-Alder reaction of cyclopentadione **87** with diphenyl acetylene in refluxing diphenyl ether yielded hexaphenyl

benzene compound **89** with an improved yield of 51%. The structure of compound **89** was confirmed by a single crystal X-ray analysis as shown in Figure 2-4.

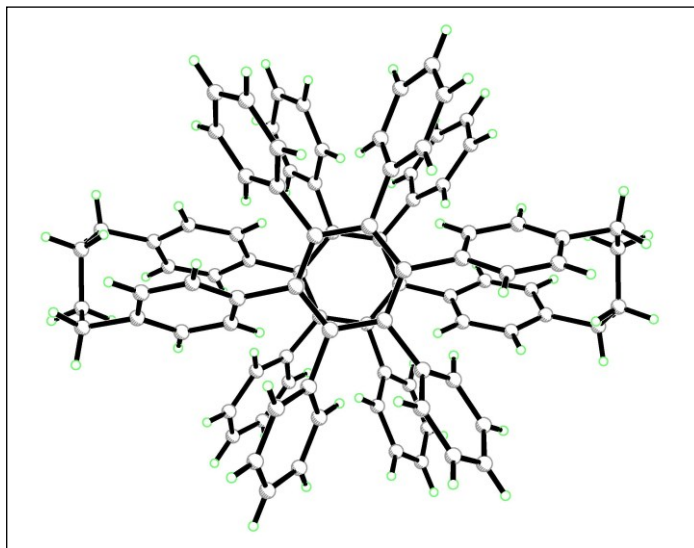
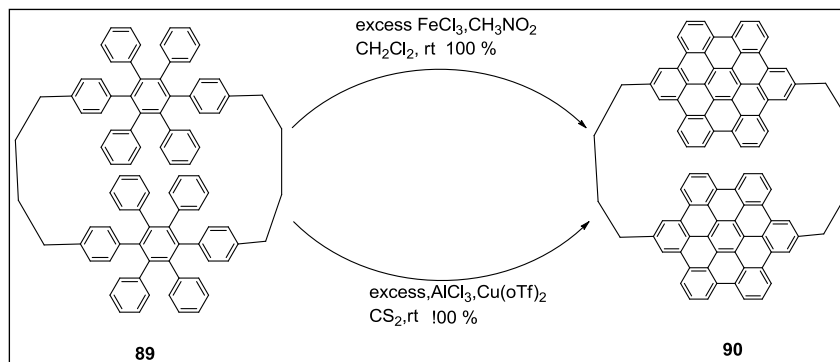


Figure 2-4. Single crystal X-ray analysis of compound 89

The final step involves the oxidative dehydrogenation of hexaphenyl benzene to form the completely planar bilayer structure and is of great importance because it would provide the first bilayered, graphene-like material separated by a saturated linker of known bond length. The synthesis of this bilayered graphene-like material would open up the possibility of studying the various properties and potential applications of graphene.

Scheme 2-8. Oxidative dehydrogenation of compound 89



The oxidative dehydrogenation of compound **89** to obtain compound **90** was performed via two well-known procedures as shown in Scheme 2-8. Hexaphenyl benzene **89** in distilled dichloromethane was added drop wise to a slurry containing excess anhydrous iron trichloride^{64,65} in dry nitromethane under a constant flow of argon into the reaction mixture. Similarly, the starting material in the AlCl_3 ⁶⁵ mediated reaction, hexaphenyl benzene **89**, was left in dry carbon disulfide to stir at room temperature in an excess of anhydrous AlCl_3 and coppertriflate until the starting material disappeared according to TLC.

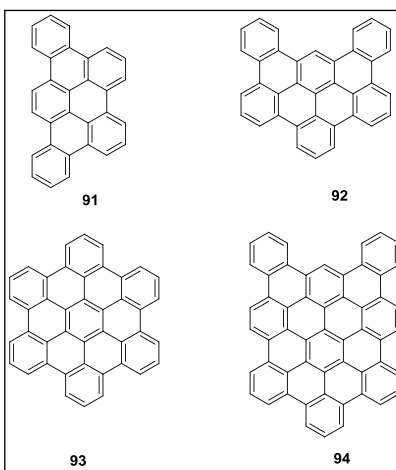


Figure 2-5. Simple synthetic polyaromatic hydrocarbons (PAHs)

Polyaromatic hydrocarbons are flat planer substances with an extended conjugated pi system. This extended pi system favors the formation of large π - π interactions between molecules, which helps them aggregate and renders them insoluble in many inorganic acids and organic solvents. Clar⁶⁶ observed that compound **92** was even insoluble in concentrated sulfuric acid. Mullen,^{64,67} who synthesized the compounds shown in Figure 2-5, reported that these compounds are yellow in color and less soluble in organic solvents like THF, dichlormethane, benzene, DMSO and DMF. He observed that PAHs consisting of 6 or more benzene rings were completely insoluble even when refluxed in THF for a couple of days. Compound **93** was found

to disperse in 1,2,4-trichlorobenzene, which allowed for the solution phase UV-visible spectra to be obtained⁶⁷.

The lack of solubility for these PAHs poses a serious problem with their characterization and identification based on solution phase analytical techniques such as NMR. In fact, no research explaining the solution-phase NMR characterization of these unsubstituted PAHs has been reported to date. Researchers have relied heavily on MALDI-TOF MS, elemental analysis and UV-visible spectroscopy for the characterization of PAHs. MALDI-TOF MS often causes fragmentation of the parent compound, which results in the loss of the molecular ion peak and thus complicates the analysis.

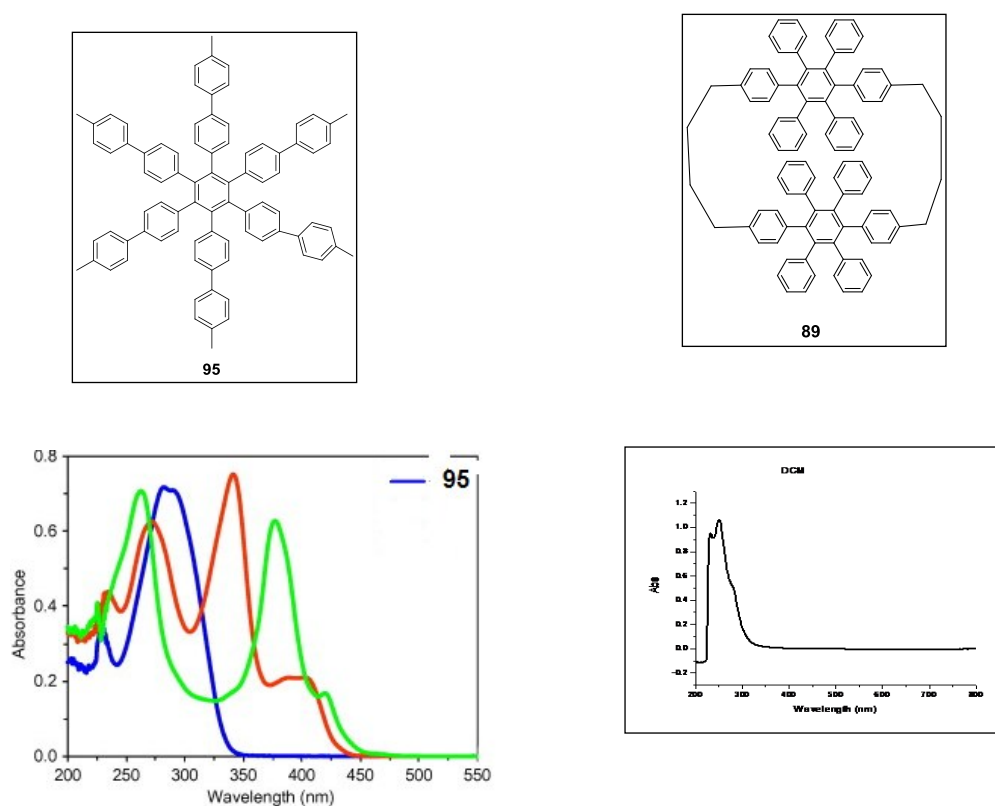


Figure 2-6. UV-visible spectra of compound 95⁶⁰ and 89 in dichloromethane

The lack of solubility for these PAHs make their purification by washing with solvents such as THF, dichloromethane, benzene, DMSO and DMF easier, and pure materials free of other organic impurities can be obtained. Thus, elemental analysis and UV-visible spectroscopy have

been the best tools for their analysis. Furthermore, the practically insoluble nature of these PAHs limits the recording of the UV-visible spectra to the solid state rather than in solution via the smearing of the sample onto the quartz substrate.

Compound **90**, produced via the oxidative dehydrogenation of compound **89**, was yellow in color and insoluble in both aqueous acids and normal organic solvents, such as dichloromethane, chloroform, dimethyl sulfoxide and dimethylformamide, at both room temperature and higher temperatures. Thus, solution phase NMR characterization was of limited use and we turned our attention towards characterization by UV-Visible spectroscopy. It has been reported that HBC exhibits three distinct band types in its UV-Visible spectra, referred to as β , p , and α bands,⁶⁶ that correspond to the various pi electronic transitions and conjugations within these systems. Mullen⁶⁷ has reported the UV-Visible spectra for compound **93** in 1,2,4-trichlorobenzene at room temperature (1.0×10^{-6} M) as shown in Figure 2-7. This spectrum consists of three distinct bands at 342 nm, 359 nm and 387 nm with a weak, almost unnoticeable α band in the 500 nm region.

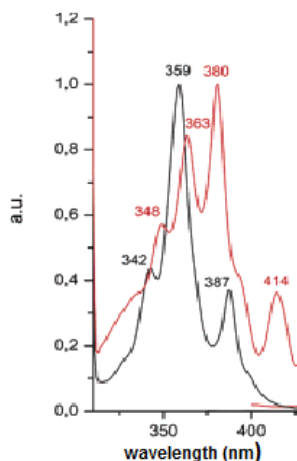


Figure 2-7. UV-Vis absorption spectra of compound **93 (black line) in 1,2,4-trichlorobenzene⁶⁷**

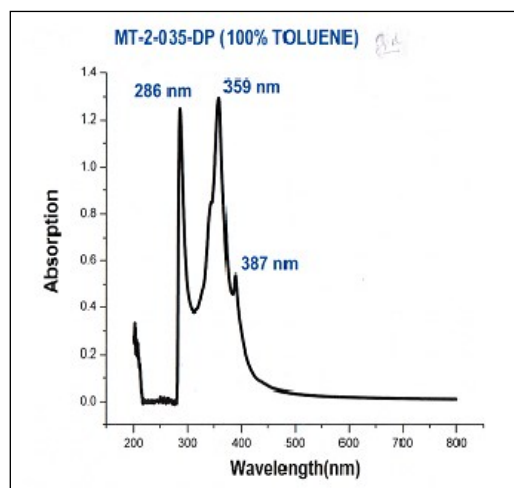


Figure 2-8. UV-Vis spectra for compound **90 in toluene**

A mixture of 1.0 mg of compound **90** in 15 mL of toluene was sonicated for 3 h and the resulting mixture of dispersed particles was filtered. The filtrate was then used to obtain the UV-visible spectra. The UV-visible spectra of compound **90** consisted of absorption bands at 342, 359 and 387 nm and resembled that of compound **93** reported in the literature.⁶⁷ The UV-Visible spectra of the starting material, **89**, (Figure 2-6) was also recorded for comparison. Compound **89** does not show any absorption bands above 310 nm; thus, the bathochromic shifted bands in compound **90** should result from an increased conjugation due to the formation of new carbon-carbon bonds between adjacent aromatic rings during oxidative hydrogenation.

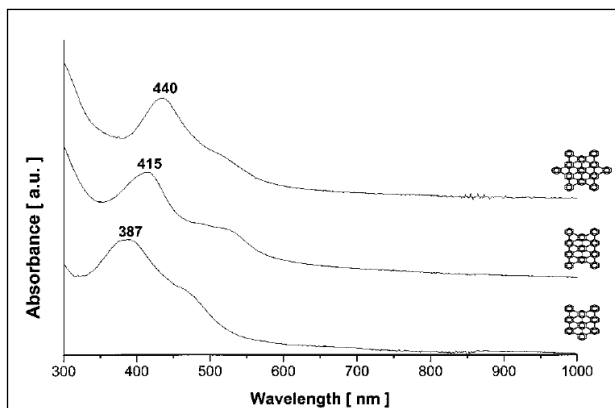


Figure 2-9. UV-Vis spectra of thin film (quartz substrate) of PAH compounds⁶⁴

UV-visible spectra of the solid PAHs were also recorded on a quartz substrate, and three similar distinct bands were observed but were relatively broad compared to the solution phase spectra.

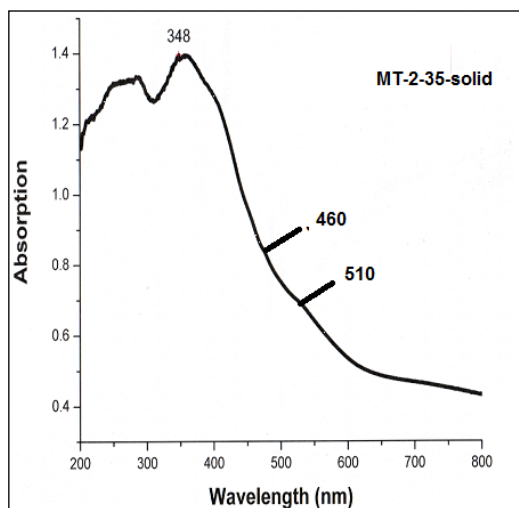


Figure 2-10. UV-Vis spectra of solid compound 90 on quartz substrate

A Cary 500 UV-vis-NIR spectrometer with a reflectance accessory was used across the range from 200–800 nm. The sample cell was made of two transparent calcium fluoride discs, a Teflon O-ring and a screw type combination where solid compound **90** was packed between the two discs and O-ring. In this technique, the absorption of a solid material was measured in the diffuse reflectance mode; the instrumentation system calculates the absorption by automatically

measuring the diffuse reflectance. Polytetrafluoroethylene (PTFE) powder with a 100 nm particle size (Sigma-Aldrich) was used as a reference.

A solid sample of compound **90** in silica quartz produced a UV-Visible spectra (Figure 2-10) with three different bands at 348, 460 and 510 nm, which correspond to the β , p and α bands, respectively. The bands corresponding to p and α are difficult to observe due to their low intensity. The blue shift relative to the compounds shown in Figure 2-9 can be explained by the presence of fewer benzene rings in compound **90**, which decreases the extent of π conjugation.

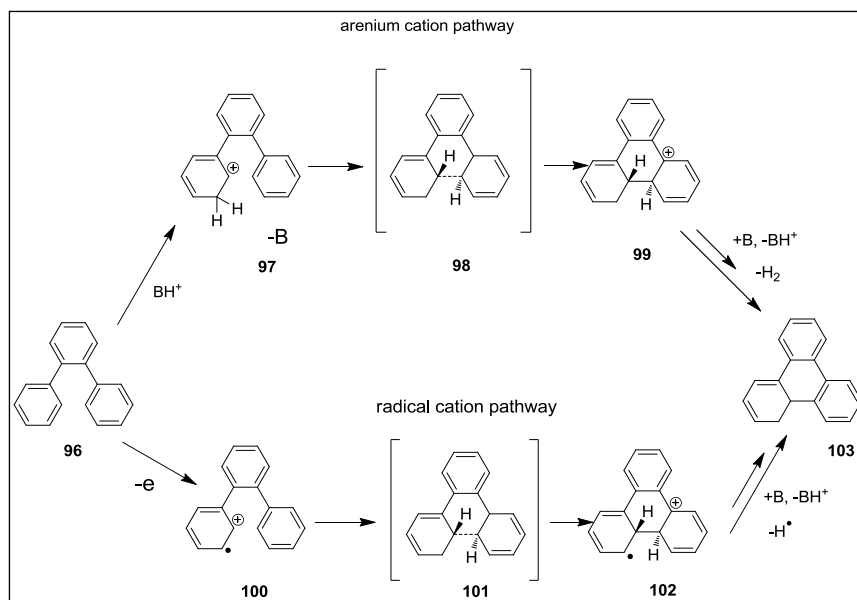


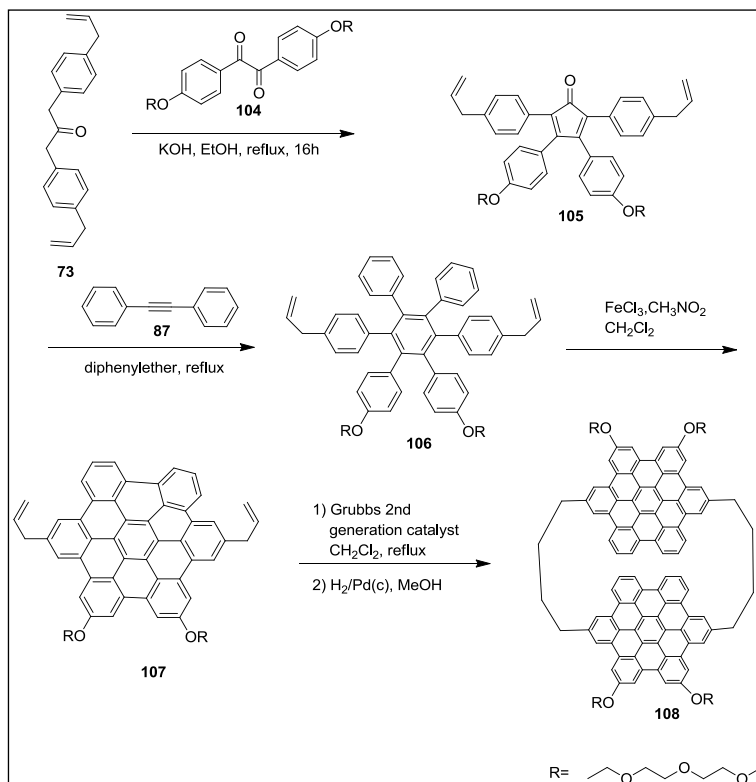
Figure 2-11. Possible reaction pathways for Scholl reaction^{65,68}

Oxidative dehydrogenation mediated by Lewis acids to yield PAHs is believed to undergo a Scholl condensation reaction.⁶⁰ Two possible mechanisms involving the arenium cation and radical ion have been proposed for this Scholl reaction as shown in Figure 2-11⁶⁵.

Various computational calculations⁶⁸ were conducted to investigate the possible reaction pathway and indicate the arenium ion mechanism is favored over the radical cation pathway. Furthermore, the first step involving the formation of an arenium cation is the rate determining step. The chances of incomplete dehydrogenation have been investigated both theoretically and

experimentally and were less.⁶⁵ In most cases, the thermodynamically stable and completely dehydrogenated products are formed as the only product.^{65,60}

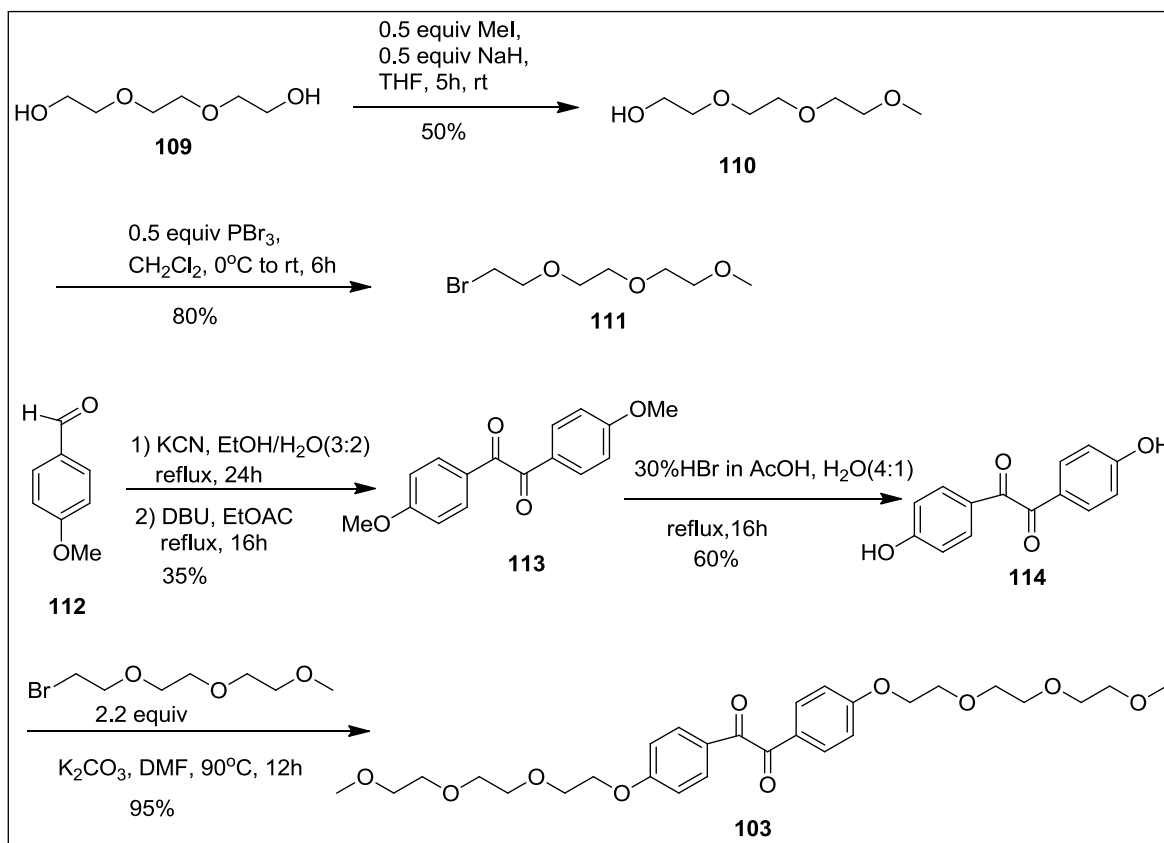
Scheme 2-9. Synthetic Scheme towards the synthesis of soluble HBC analog



Based on our UV-Visible data and the proposed Scholl reaction, we believe the yellow, insoluble product formed is our desired bilayer hexaphenyl hexabenzocoronene. However; without the NMR and other proper analytical data, we were unable to verify and identify compound **90** completely. We thus shifted our focus to synthesizing soluble analogs of compound **90**, which would lead to the complete characterization of a synthesized bilayer coronene. The synthetic approach towards a soluble analog shown in Scheme 2-9 was proposed.

It was thought that the incorporation of a long chain ether in the macrocyclic ring would make compound **90** soluble and allow for its better characterization. Keeping this in mind, a benzil containing a long chain ether group was first synthesized³⁸ as shown in Scheme 2-10.

Scheme 2-10. Synthesis of 1,2-bis[4-{2-(2-(2-methoxyethoxy)ethoxy)ethoxy}phenyl]ethane-1,2-dione

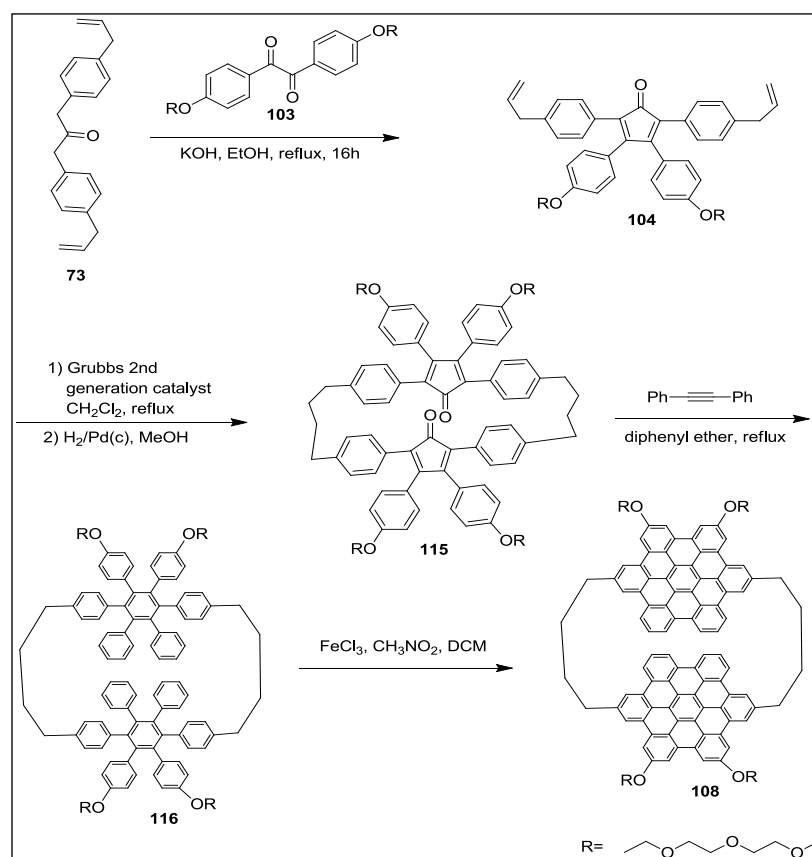


The Knoevenagel reaction between benzil compound **104** and compound **73** in ethanol and KOH under reflux yielded the desired cyclopentanone **105**. Refluxing compound **105** with phenyl acetylene in diphenyl ether gave the Diels-Alder adduct **106** in low yield. The FeCl_3 mediated oxidative dehydrogenation of compound **106** was performed but no product was isolated. Because of the small amount of compound **106** available, the Scholl reaction could not be performed under varying conditions.

2.6. Work in progress

Currently, the reaction to produce compound **106** is being optimized. With enough compound **106** in hand; the Scholl reaction will be repeated using varying conditions to obtain compound **107**. The Grubb's macrocyclization of compound **107** followed by a reduction in Pd/C will provide the desired compound, **108**, which is most likely soluble in organic solvents and will allow a proper characterization.

Scheme 2-11. Alternative route to the synthesis of compound 108



Macrocyclization using Grubb's second generation catalyst has low yields and is affected by the presence of bulkier groups. Furthermore, this reaction requires two reactant molecules to approach each other in such a way that produces a homo dimer and prevents polymerization.

Macrocyclic ring formation using compound **107** may prove difficult because of the planar central aromatic core and may form a polymerized product. We know from our previous experience that cyclopentadienone can undergo macrocyclization using Grubb's catalyst. To avoid polymerization and possibly increase the yield of the Diels-Alder reaction, an alternative route to compound **108**, shown in Scheme 2-11, can be followed.

2.7. Conclusions

A rational, stepwise synthetic approach to bilayer hexabenzocoronene, or “pieces of graphenes”, with a predefined distance between the two layers has been investigated and presented. Despite its insolubility in organic solvents, UV-Visible spectra similar to those reported in the literature have been obtained. The similarity in the UV-visible spectra indicates the yellow, insoluble compound may be the desired bilayer HBCC; however, both MALDI-TOF MS and elemental analysis should be performed to further characterize the compound. The synthesis of soluble analogs that can be characterized by conventional analytical techniques, such as NMR, would help in further identifying and characterizing this compound.

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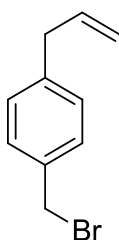
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2.9. Experimental Section.

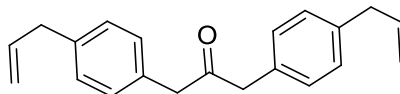
General Methods. NMR spectra were obtained from a 400-MHz spectrometer (Varian Inc.), in CDCl₃, unless otherwise indicated, and reported in ppm. Infrared spectra were taken from a Nicolet 380 FT-IR instrument (Thermo Scientific) in solid forms and are reported in wave numbers (cm⁻¹). Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer (from Applied Biosystems). High-resolution Mass spectra were obtained from a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. The instrument was operated at 10,000 resolutions (W mode) with dynamic range enhancement that attenuates large intensity signals. The cone voltage was 60 eV. Spectra were acquired at 16666 Hz pusher frequency covering the mass range 100 to 1200 μ and accumulating data for 2 seconds per cycle. Mass correction for exact mass determinations was made automatically with the lock mass feature in the MassLynx data system. A reference compound in an auxiliary sprayer is sampled every third cycle by toggling a “shutter” between the analysis and reference needles. The reference mass is used for a linear mass correction of the analytical cycles.

1-allyl-4-(bromomethyl)benzene (74)



To a solution of 8.0 g (0.03 mol) of dibromide **73** in 150 mL of 1:1 mixture of dry THF and ether, 31 mL (0.03 mol) of 1.0 molar vinyl magnesium bromide in THF and 15 mL (0.09 mol) of dry HMPA were added at room temperature. Reaction was maintained at 40°C for 24 h, diluted with 100 mL of aqueous NH₄Cl, extracted with ether (50 mL x 4 times), brine washed, dried (MgSO₄), concentrated and column chromatographed on silica gel using 10% ether in hexane as eluent to give 3.6 g (56% yield) of colorless liquid product. ¹H NMR δ 7.33 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 6.00 - 5.90 (m, 1 H), 5.11 (dd, *J* = 3.9, 2.3 Hz, 1 H), 5.07 (s, 1 H), 4.49 (s, 2 H), 3.39 (d, *J* = 6.6 Hz, 2 H); ¹³C NMR δ 140.74, 137.19, 135.80, 129.36, 129.25, 116.36, 40.13, 33.81.

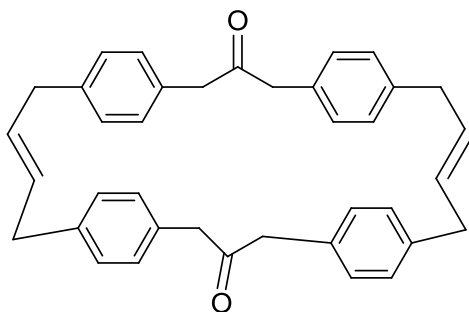
1, 3-bis (4-allylphenyl) propan-2-one (75)



To the mixture of 1.0 g (5.10 mmol) of bromide **74**, 0.35 g (4.74 mmol) of Ca(OH)₂ and 0.40 g of (1.18 mmol) n-Bu₄N⁺H⁻SO₄ in 1:1 mixture of degassed dichloromethane and water (35 mL each), 0.50 g (2.55 mmol) iron pentacarbonyl was syringed. Argon was bubbled into the reaction mixture and left to stir at room temperature for 3 h. After constant bubbling of air for 15 min, reaction was diluted with 50 mL of aqueous NH₄Cl, extracted with ethyl acetate (50 mL x three times), brine washed, dried (MgSO₄), concentrated and column chromatographed on silica gel using 20% ether in hexane as eluent to give 0.34 g (50% yield) of solid product. ¹H NMR δ

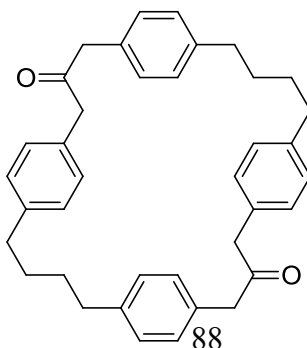
7.16 (d, $J = 8.4$ Hz, 2 H), 7.09 (d, $J = 8.0$ Hz, 2 H), 6.02 - 5.92 (m, 1 H), 5.12 - 5.10 (m, 1 H), 5.07 (t, $J = 1.2$ Hz, 1 H), 3.70 (s, 2 H), 3.39 (d, $J = 6.6$ Hz, 2 H); ^{13}C NMR δ 206.17, 139.09, 137.53, 131.96, 129.77, 129.16, 116.11, 48.90, 40.07.

Synthesis of 2.21-Dioxo-11,30-diene(3,4,3,4)paracyclophane (**82**)



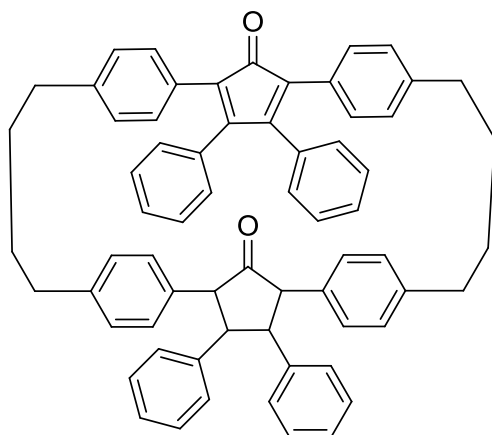
To a solution of 200.0 mg (0.69 mmol) of ketone **75**, dissolved in 40 mL of dry degassed dichloromethane, 17.5 mg (0.02 mmol) of Grubb's second generation catalyst dissolved in 10 mL of dry dichloromethane was added drop wise over a period of 30 min. After refluxing for 18 h, reaction was diluted with 30 mL of water, extracted with dichloromethane (30 mL x three times), brine washed, dried (MgSO_4), concentrated and column chromatographed on silica gel using hexane and ether as eluent to give 108.0 mg (60% yield) of **82** solid product. ^1H NMR δ 7.11(d, $J = 7.0$ Hz, 8 H), 7.03 (d, $J = 6.6$ Hz, 8 H), 5.63 (dd, $J = 3.3, 1.8$ Hz, 4 H), 3.68 (s, 8 H), 3.35 (d, $J = 3.5$ Hz, 8 H); ^{13}C NMR δ 206.41, 139.50, 131.82, 130.58, 129.67, 129.10, 48.67, 38.61.

Synthesis of 2.21-Dioxo (3,4,3,4)paracyclophane (**86**)



To 50.0 mg (0.095 mmol) of cyclized product **82**, in 2 mL of ethanol, 5.0 mg (10% by weight) of Pd/C was added and reaction was left to stir at room temperature under 1 atm. of hydrogen for 2 h. The reaction was filtered through celite, concentrated to dryness and column chromatographed on silica gel using 10% ether in hexane as eluent to give 45.0 mg (89% yield) of **86** as solid product. ^1H NMR δ 7.02 (d, $J = 7.8$ Hz, 8 H), 6.94 (d, $J = 7.8$ Hz, 8 H), 3.65 (s, 8 H), 2.66 (s, 8 H), 1.56 (s, 8 H); ^{13}C NMR δ 206.53, 141.21, 131.43, 129.60, 128.96, 48.79, 35.45, 30.47.

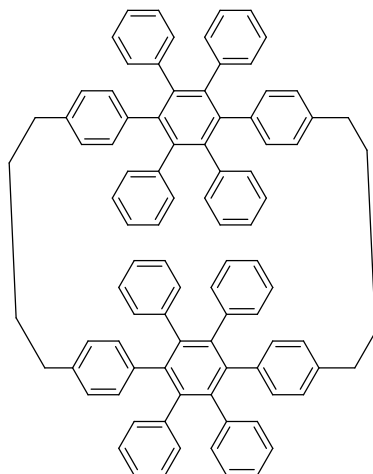
Synthesis of macrocyclic cyclopentadienone (**87**)



Mixture of 130.0 mg (0.25 mmol) of diketone **86**, 130.0 mg (0.62 mmol) of benzil and 13.8 mg (0.25 mmol) of crushed KOH in 25 mL of dry ethanol was refluxed for 5 h. Reaction was cooled to room temperature, diluted with aqueous NH_4Cl , and extracted with dichloromethane (20 mL x 3 times), brine washed, dried (MgSO_4) and concentrated in rotary evaporator. Crude product was diluted with 25 mL of ethyl acetate and centrifuged for 10 min

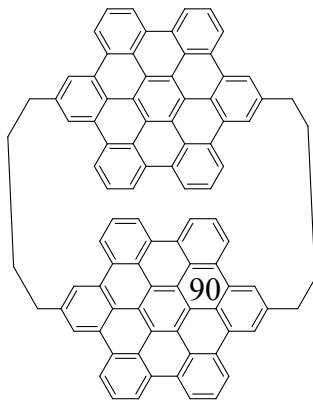
(10,000 rpm), solid precipitate was collected and dried to give 130.0 mg (60% yield) of crude product **87**.

Synthesis of 12,13,15,16,34,35,37,38-octaphenyl(4,4)triphenylophane (**89**)



Mixture of 340.0 mg (0.39 mmol) of cyclopentadienone **87**, and 172.73 mg (0.97 mmol) of diphenyl acetylene in 3.88 mL of diphenyl ether was gradually heated to reflux using sand bath for 16 h. After 16 h, solvent was distilled off; residue was diluted with 10 mL of ether and centrifuged for 10 min (10,000 rpm) two times. Solid precipitate obtained was collected and dried to give 225.4 mg (51% yield) of product. ^1H NMR δ 6.89 (s, 40 H), 6.55 (s, 12 H), 6.18 (s, 4 H), 2.32 (s, 8 H), 1.38 (s, 8 H); ^{13}C NMR δ 141.10, 140.69, 140.39, 137.57, 131.89, 125.43, 33.37, 26.06.

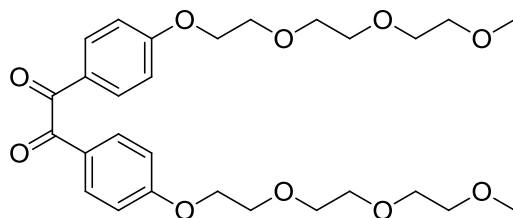
Synthesis of (4,4)Hexa-peri-hexabenzocoronenophane (**90**)



To 35.0 mg (0.03 mmol) of hexabenzene **89**, 860.1 mg (2.37 mmol) of copper triflate and 317.1 mg (2.37 mmol) of Aluminum trichloride were added in a glove box. Reaction mixture was diluted with 29.5 mL of dry carbon disulfide and left to stir at room temperature for 2 days, diluted with 15 mL of 2 N HCl and 40 mL of aqueous NH₄OH. Solid precipitate was washed with water several times to give 24.2 mg of brownish yellow solid in soluble in organic solvents like benzene, dichlorobenzene, DMF, DMSO, dichloromethane, chloroform, THF and hexanes.

20.0 mg (0.02 mmol) of hexabenzene **89**, in 17 mL of dry dichloromethane was added drop wise to 275.5 mg (1.7 mmol) anhydrous Iron trichloride in 17 mL of dry nitromethane under argon. Reaction was left to stir at room temperature for 16 h with constant flow of argon. After 16 h, reaction was diluted with 110 mL of methanol and centrifuged for 10 min (10,000 rpm) to obtain brownish yellow solid insoluble in organic solvents. Because of the insoluble nature of the compound solution state ¹H NMR and ¹³C NMR was not possible to obtain.

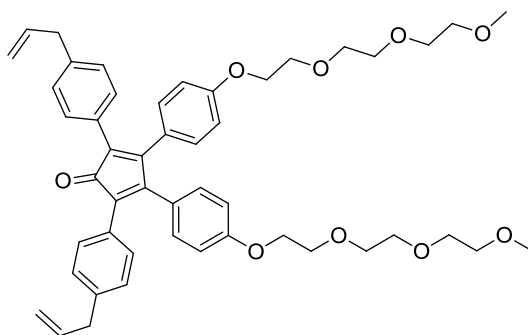
Synthesis of 1,2-bis[4-{2-(2-(2-methoxyethoxy)ethoxy)phenyl}ethane-1,2-dione (103)



A solution of 320.0 mg (1.32 mmol) of diketone **114**, 600.0 mg (2.64 mmol) of bromide **111** and 728.0 mg (5.28 mmol) of K₂CO₃ in 30 mL of dry DMF was heated to 70°C for 16 h.

reaction was cooled to room temperature, diluted with 100 mL of water, extracted with ether (30 mL x 3 times), brine washed, dried (MgSO₄) and silica gel column chromatographed using ether, dichloromethane and methanol as eluent to give 650.0 mg (97% yield) of solid product. ¹H NMR δ 7.79 (d, *J* = 9.2 Hz, 4 H), 6.87 (d, *J* = 9.2 Hz, 4 H), 4.08 (t, *J* = 4.0 Hz, 4 H), 3.75 (t, *J* = 4.0 Hz, 4 H), 3.62 - 3.59 (m, 4 H), 3.56 - 3.51 (m, 4 H), 3.42 - 3.40 (m, 8 H), 3.23 (s, 6 H); ¹³C NMR δ 193.20, 163.89, 131.95, 125.98, 114.64, 71.60, 70.54, 70.29, 69.09, 67.58, 58.66.

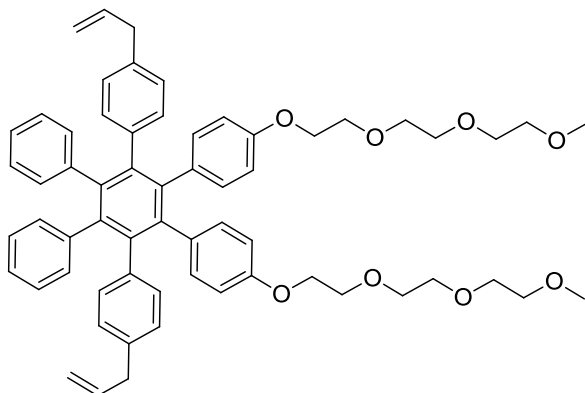
Synthesis of 2,5-bis[(4-allylphenyl)-3,4-bis{4-2-(2-methoxyethoxy)ethoxy}phenyl]cyclopentanone (104)



A mixture of 56.0 mg (0.19 mmol) of ketone **75**, 113.3mg (0.21 mmol) of benzil and 16.2 mg (0.29 mmol) of powder KOH in 4 mL of dry ethanol was left to reflux for 16 h. Reaction was cooled to room temperature, diluted with 20 mL of aqueous NH₄Cl, extracted with dichloromethane (10 mL x 3 times), brine washed, dried (MgSO₄), concentrated and silica gel column chromatographed using hexane, ethyl acetate and methanol as eluent to give 55.0 mg (36% yield) of solid product. ¹H NMR δ 7.16 (d, *J* = 8.0 Hz, 4 H), 7.06 (d, *J* = 8.4 Hz, 4 H), 6.83 (d, *J* = 8.4 Hz, 4 H), 6.71 (d, *J* = 8.4 Hz, 4 H), 6.00-5.59 (m, 2 H), 5.10-5.04 (m, 4 H), 4.09 (t, *J* = 4.8 Hz, 4 H), 3.85 (t, *J* = 4.8 Hz, 4 H), 3.75-3.73 (m, 4 H), 3.70-3.65 (m, 4 H), 3.57-3.54 (m, 4 H), 3.38 (s, 6 H), 3.35 (d, *J* = 6.8 Hz, 4 H); ¹³C NMR δ 200.79, 159.11, 153.82, 139.23, 137.40,

131.25, 130.31, 129.14, 128.43, 125.76, 124.61, 116.06, 114.17, 72.17, 71.02, 70.86, 70.77, 69.89, 67.48, 59.25, 40.24.

Synthesis of 4-allyl-4'-(4-allylphenyl)-4''-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)phenyl)-5',6'-diphenyl-1,1':2',1''-terphenyl (106)



Mixture of 30.0 mg (0.04 mmol) of cyclopentanone **104** and 7.5 mg (0.04 mmol) of phenyl acetylene in 1 mL of diphenyl ether was heated to 210°C for 16 h. Reaction mixture was cooled to room temperature and directly purified by silica gel column chromatography using hexane, ether and dichloromethane (4:2:1) as eluent to give 25.0 mg of product (not pure). ^1H NMR δ 7.04-6.97 (m, 10H), 6.74 - 6.58 (m, 8 H), 6.50 - 6.47(m, 8 H), 6.00 - 5.87 (m, 2 H), 5.10 - 5.00 (m, 4 H), 4.09 (t, J = 4.8 Hz, 4 H), 3.85 (t, J = 4.8 Hz, 4 H), 3.75 - 3.73 (m, 4 H), 3.70 - 3.65 (m, 4 H), 3.57 - 3.54 (m, 4 H), 3.38 (s, 6 H), 3.35 (d, J = 6.8 Hz, 4 H)

^1H and ^{13}C NMR spectra of synthesized compounds

