SYNTHESIS AND BIOLOGICAL EVALUATION OF NATURAL PRODUCTS AND THEIR ANALOGS AS NEW CANCER CHEMOTHERAPEUTIC AGENTS

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SUMMARY

Cancer is a leading cause of death in the world and there is a continual search for new anti cancer drugs. Today, more than half of the clinically available drugs are either natural products or derived from natural products. This is not surprising as natural products have been used for centuries as medicine and it is clear that Nature will continue to be a source for many new drug leads. The use of natural product scaffolds to synthesize analogs has already produced many new drugs for cancer chemotherapy. Here the aim of this thesis is to develop different classes of natural product analogs as potential new chemotherapeutic agents.

In Chapter 2, we described the first reported synthesis of a class of polyenylpyrrole natural products and their analogs. The compounds were evaluated for the cell cytotoxicity against human lung cancer cells A549 and structure-activity studies showed that the 3-chloropyrrole moiety is essential as replacement of the group with other 2 or 3-chloro aromatic rings led to a complete loss of activity. 2 of these compounds displayed excellent cytotoxicity with IC_{50} of 0.6 μM and 0.01 μM respectively. In addition, these 2 compounds proved to be non-toxic to normal human lung cells Beas-2b at up to 80 μM. These results indicated that these 2 compounds have the potential to be developed as anticancer agents due to their high selectivity against A549 cells.

In Chapter 3, the synthesis of lignan natural products as potential anti-tumor agents was described. After the synthesis of racemic isochaihulactone and

nemerosin was achieved, asymmetric synthetic technique was introduced to afford all 4 lignan isomers: isochaihulactone, slyvestrin, nemerosin and its enantiomer. Of these 4 compounds synthesized, isochaihulactone and slyvestrin are natural products which had been isolated previously but never synthesized. Nemerosin is a natural product which had previously been synthesized while there are no reports on the isolation or synthesis of the enantiomer of nemerosin. Both isochaihulactone and slyvestrin displayed cytotoxicity against various cancer cells.

Chapter 4 described the microwave assisted synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones through a modified Biginelli procedure. Under microwave irradiation, the reaction time was shortened from 12 h to 15 min. These results further demonstrate the value of microwave-assisted synthesis in increasing yield, shortening reaction time and streamlining high throughput synthesis. This also represents the first reported synthesis of such a class of 5-unsubstituted 3,4-dihydropyrimidin-2-thiones.

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LIST OF ABBREVIATIONS

AcOH	acetic acid
Apaf-1	apoptotic protease activating factor 1
aq	aqueous
BCR-ABL	breakpoint cluster region-abelson
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
COD	cycloocta-1,5-diene
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*-*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DTS	diverted total synthesis
ee	enantiomeric excess

EGFR	epidermal growth factor receptor
EI	electron impact
ESI	electron spray ionization
Et	ethyl
Et_2O	diethylether
EtOAc	ethyl acetate
Fas	apoptosis stimulating fragment
FDA	Food and Drug Administration
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
KIT	c-kit protein
$_L$-DOPA	$_L$-3,4-dihydroxyphenylalanine
LCMS-IT-TOF	liquid chromatography mass spectrometer-ion trap-time of flight
LDA	lithium diisopropylamine
Me	methyl
Ms	methanesulfonyl
NBD-Cl	4-chloro-7-nitrobenzooxadiazole chloride

NCS	*N*-chlorosuccinimide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
PARP	poly (ADP-ribose) polymerase
PMA	phosphomolybdic acid
Ph	phenyl
PMA	phosphomolybdic acid
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
TNF	tumor-necrosis factor
UV	ultraviolet

Chapter 1: Introduction

1.1.1 Overview of Cancer

Cancer is a leading cause of death in the world and in the United States, about 23% of all human deaths can be attributed to it (Table 1.1)[1]. Cancer affects people of all age groups though the risk of most types of cancer increases with age. Although the many stages of carcinogenesis depend on environmental and other non-genetic factors, it is generally accepted that cancer arises from mutation in genes.[2-5] Cancer cells are defined by two heritable characteristics:[6]

1. They and their offspring reproduce with disregard for the normal restraints on cell division.

2. They invade and occupy areas normally meant for other cells.

The combination of these two traits makes cancer especially dangerous. A cell, regardless of how destructive it may be, cannot cause significant damage if it is isolated and does not proliferate faster than its normal neighbor. However when the cell proliferation is uncontrollable, it will lead to the formation of a tumor or neoplasm. A neoplasm is essentially a persisting growing mass of abnormal cell. If the cells are unable to invade other tissue, the tumor is said to be benign. Here, a complete cure can typically be achieved by removing the tumor surgically.[7] A tumor is only considered cancerous or malignant if the cells acquire the ability to invade surrounding tissue. This invasion and formation of secondary tumors at other sites of the body by the original cancer cells is known as metastasis.

Table 1.1. Leading causes of death in the United States, 2007 (thousands)[1]

	Deaths	**%**
Heart diseases	616	25.4
Malignant neoplasms	563	23.2
Cerebrovascular diseases	136	5.6
Lower respiratory infections	128	5.3
Accidents	124	5.1
Alzheimer's disease	75	3.1
Diabetes mellitus	71	2.9
Influenza and pneumonia	53	2.2
Nephritis, nephrotic syndrome	46	1.9
Septicemia	35	1.4
Sucide	35	1.4
Liver diease and cirrhosis	29	1.2
Hypertension and hypertensive renal disease	24	1.0
Parkinson's disease	20	0.8

Cancers are classified based on the tissue and cell type they originated from. Cancers arising from muscle cells or connective tissues are known as sarcomas

while those arising from epithelial cells are called carcinomas. There are also cancers that do not belong to these two categories and these include leukemia and cancer of the nervous system.[6]

1.1.2 Cancer as an Evolutionary Process

From an evolutionary perspective, a neoplasm can be viewed as a large population of genetically and epigenetically heterogeneous cells.[8] Via natural selection, neoplastic cells will undergo genetic and epigenetic modifications that are beneficial to them. Evolution of neoplastic cells is determined by their interaction with its environment and other cells. This interaction includes attempts at treating or preventing cancer. Evolution of the cancer cell generally leads to faster proliferation and metastasis as well as greater drug resistance. Evidence of this can be observed by the resistance of mutant lung cancer cells to anilinoquinazoline EGFR inhibitors.[9] Chronic myeloid leukemia and colorectal cancer have also been found to develop resistance to imatinib and 5-fluorouracil respectively.[10,11]

1.1.3 Molecular Causes of Cancer

At the molecular level, cancer results from the mutation of cancer-susceptible genes. These genes belong to one of 3 classes:[12,13] gatekeepers, caretakers and landscapers. Gatekeepers consist of oncogenes and tumor-supressor genes and they control the growth and differentiation pathways of the cell. The function of the caretakers is to maintain the genomic integrity of the cell.[14,15] A mutation of the caretakers can result in genetic instability which in turn can lead to rapid mutation of the genes that directly control cell birth and

death. Landscapers are named as such because they create an abnormal stromal environment that leads to the neoplastic transformation of cells.[16]

Despite cancer being a result of gene mutation, a single mutation is not sufficient to give rise to cancer. For full-blown cancer to develop several independent and rare mutations would have to occur.[17,18] As such, the risk of cancer development depends not only on the initial mutation but also on successive mutations driving cancer progression. One indication of this comes from the study of the incidence of cancer as a function of age. If cancer is caused by a single mutation occurring with a fixed possibility per year, the incidence of cancer should be independent of age. However the development of cancer rises steeply with age (Figure 1.1).[19] This is in line with the fact that cancer is caused by an accumulation of numerous random mutations in the cell line.

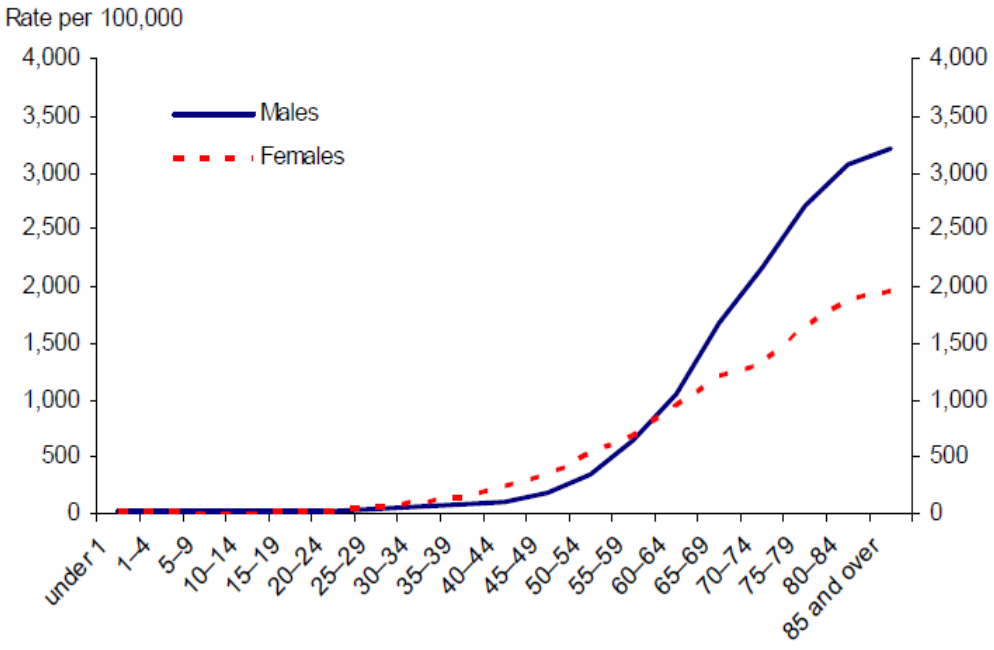


Figure 1.1. All malignant neoplasms incidence rate by age group.

1.1.4 Environment Causes of Cancer

Due to the inherent limitations in the accuracy of DNA replication, gene mutations and consequently cancer can never be completely avoided. If a person is to live long enough, the cell would eventually undergo sufficient mutations for cancer to develop. That said, evidence indicates that environmental factors play a role in the development of most types of cancer. This can be most clearly seen by comparing the cancer incidence rates in different countries. Many types of cancer vary in incidence between different countries and a cancer that is common in one country might be rare in another.[20] The convergence of cancer incidence among immigrants toward that of the local population also points to the influence of the environment rather than genetic factors. By the 1960s, the World Health Organization concluded that most cancers should be avoidable or at least delayed based on environment or lifestyle choices (Table 1.2).[21]

The most significant environmental cause of cancer in the world today is tobacco. The risk of lung cancer is the highest among those who smoke at a young age and continue to do so thereafter (Figure 1.2).[22] This is because lung cancer incidence increases rapidly for continuing smokers. In Britain, the large increase in male smokers during the First World War led to an unprecedented rise in lung cancer incidence some forty years later.[23] This pattern was repeated in the United States during the Second World War.[20] Since then, after tobacco was proven to be a carcinogen, smoking has been declining steadily especially in Britain and as such, lung cancer incidence has fallen as well.[21,24] In China, however, the rise in the number of smokers over the past two decades has led

to an increase in mortality from lung cancer.[25] The carcinogenic effects of tobacco extend beyond the lung and include the stomach, liver, mouth, esophagus, pharynx, pancreas, bladder and kidney.[25,26]

Table 1.2. US cancer deaths that would be avoided by removing known risks.[21]

Cause	**Deaths avoided (%) after removing preceding cause**	
	Smokers	Non-smokers
Smoking	60	-
Known infection	2	5
Alcohol	0.4	1
Sunlight	0.4	1
Air pollution	0.4	1
Occupation	0.4	1
Lack of exercise	0.4	1
BMI > 25 kg m^{-2}	4	10
Dietary factors	4~12	10~30
Presently unavoidable	About 25	At least 50

Another important environment cause of cancer would be diet. However it is exceedingly difficult to identify how a diet affects the incidence of cancer due to the vast variety of food and the patterns of consumption. Only the data collected from the consumption of excessive alcohol and food contaminated with aflatoxin B1 are sufficient to establish these two as significant carcinogens.[27] Aflatoxin B1 is a fungus that grows on food such as peanut and is an important cause of cancer in Africa and Asia. The only way to determine if a particular food item is deemed cancer-preventive and cancer-causing is to conduct large randomized trials that continue for many years. However the following example highlights the difficulties in obtaining conclusive results even with such a trial. There had been substantial evidence suggesting that food rich in beta-carotene can reduce the risk of lung cancer.[28] However a large randomized trial showed no benefits after 12 years of treatment.[29] Moreover two shorter trials showed that lung cancer risk was higher among those who received beta-carotene supplements.[30] Despite these conflicting data, one result that most cancer epidemiologist would agree upon is that obesity can lead to an increase in cancer risk.[31]

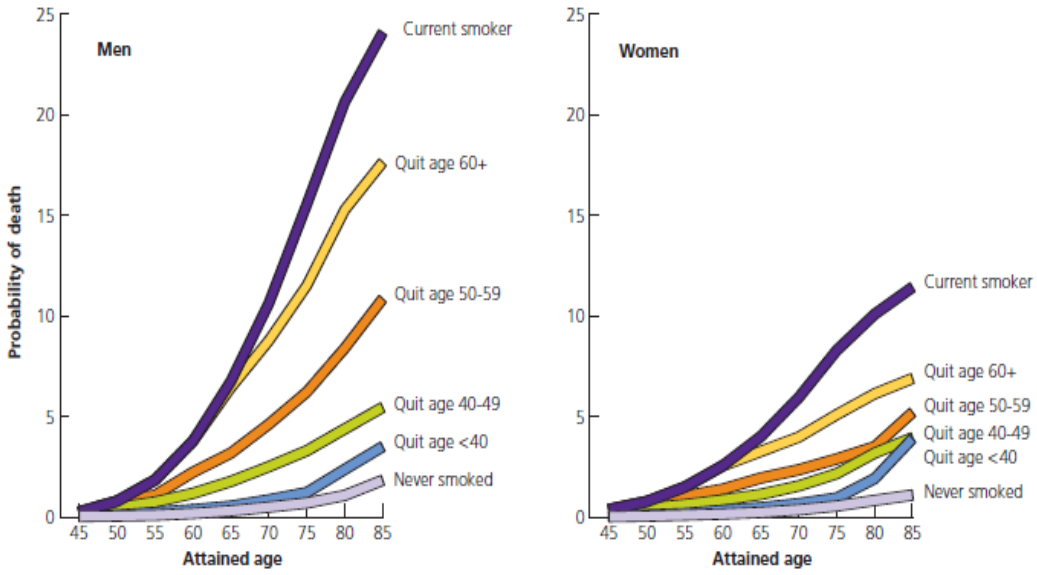


Figure 1.2. Probability of death from lung cancer in the United States, 1984-1991.[1]

About 15% of cancers in the world could be due to bacteria, viruses and parasites.[32] Chronic infection with bacteria or parasites may lead to the development of cancer. *Helicobater pylori*, which can cause chronic bacterial infection, is known to be a major cause of stomach cancer.[33] Liver cancer is common in Africa and Southeast Asia and this coincides with the higher incidence of hepatitis-B infection.[34] In fact in these areas, liver cancer occurs almost exclusively in patients who had been diagnosed with hepatitis-B infection.[21]

Another small proportion of cancer today can be due to environmental pollutants and occupational exposure to certain hazards. In the past, the lack of knowledge of certain chemicals carcinogenic effects led to workers developing cancer as a result of overexposure to such carcinogens. A classic example occurred in the early 1900s when all the male workers who were distilling 2-

napthylamine in a British factory eventually developed bladder cancer.[35] A more recent example was the mesothelioma epidemic in the 1990s. This arose from the widespread use of asbestos from the 1950s to 1970s but due to the long latency of the disease, the patients showed symptoms of the disease only decades later. Even today incidence of mesothelioma is still rising due to exposure to asbestos in the 1970s and 1980s.[36] By late 1970s, exposure limits for several industrial hazards have been reduced in many Western countries and it is believed that current occupational exposure levels would have a minimum impact on cancer incidence.[20]

1.1.5 Cancer Treatment: Chemotherapy Past & Present

One of the oldest descriptions of cancer is in the Ebers papyrus which dates back to about 1600 B.C. and it suggests cauterization for the treatment of tumor.[37] Since then mankind has come a long way in the understanding and treatment of cancer. Still, of the diseases that have plagued mankind, none have been more hard-fought than that against cancer. The treatment of a cancer has been likened to the removal of weeds in a garden. The cancer cells can be removed surgically or destroyed using radiation or chemicals but it is difficult to eliminate every one of them. The few cells that remain can proliferate again resulting in a relapse.[6] Moreover they may evolve resistance to the chemicals or radiation that was used previously. Before 1950, treatment of cancer mainly involved the removal of the tumor surgically. Radiation oncology proved to be effective for the control of localized tumor after 1960s but the drawback back then was radiation therapy, like surgery, could not treat

metastatic cancer.[37] Chemotherapy has thus become the focus for the treatment of cancer.

The beginning of effective chemotherapy dates back to World War I when autopsy findings of soldiers who died from sulphur mustard poisoning revealed that these victims had severe lymphoid hypoplasia and myelosuppression.[38] This led to the development of nitrogen mustard which was tested on a mouse with Gardner lymphosarcoma. The drug was surprisingly effective and the tumor began to regress after two injections. Although the tumor recurred, the mouse lived for 84 days when three weeks was the average survival period for a mouse with this tumor.[39] This eventually resulted in the trial on a man who was suffering from terminal stages of lymphosarcoma which radiation therapy failed to treat.[40] Treatment with nitrogen mustard caused the tumor to regress and although the remission lasted only a few weeks, it was the first concrete evidence that chemicals could be used to induce tumor suppression.

In 1956, Gordon Zubrod was appointed the head of the Division of Cancer Treatment in the United States. He had a strong interest in natural products and spearheaded a program for the collection and testing of plants and marine sources.[40] This led to the discovery of taxanes and camptothecins. Both classes of compounds encountered significant difficulties during development but eventually, paclitaxel was marketed by Bristol Myers Squibb as Taxol in 1991 and it became the first billion dollar per year drug (Figure 1.4).[41] As for camptothecin, its semi-synthetic analogue, irinotecan, finally won approval from the Food and Drug Administration (FDA) in 1996.[42] Today, paclitaxel is

used primarily to treat lung and ovarian cancer while irinotecan is used for colon, lung and ovarian cancer.[43]

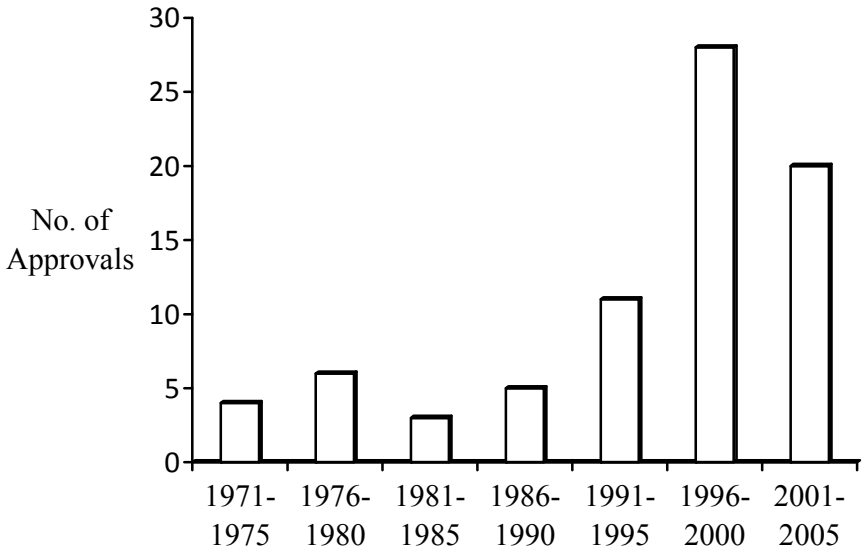


Figure 1.3. Number of approval of new drugs for cancer by FDA.[40]

Despite the development of new cancer drugs such as cisplatin and fludarabine, by the 1980s, cancer chemotherapy appeared to have slow down (Figure 1.3).[44,45] One of the main reasons is the failure of animal models to accurately predict the pharmacokinetics of cancer drugs in human.[40] Moreover cancer drug discovery requires long-term trials which often yield marginal gains. These gave cancer drug discovery a reputation for having high risks with minimal rewards. All of these changed with the advancement of cell biology at the molecular and genetic levels. New signaling networks that regulate cell survival and proliferation were discovered and many of these were significantly different in cancer cells. Small biotechnology firms sprang up as researchers attempted to fix these molecular defects in cancer cells. This heralded the beginning of the targeted-therapy era. One of the most significant

landmarks of this period was the development of imatinib. Unlike paclitaxel and irinotecan which were derived from natural products, imatinib was developed by rational drug design. Imatinib inhibits the kinase BCR-ABL as well as the KIT tyrosine kinase and platelet derived growth factor receptor-β tyrosine kinase. These effects led to the use of imatinib for the treatment of gastrointestinal stromal tumors and the hypereosinophilic syndrome.[46] When patients with chronic myeloid leukemia were treated with imatanib, 90% of them achieved total haematological remission.[47,48]

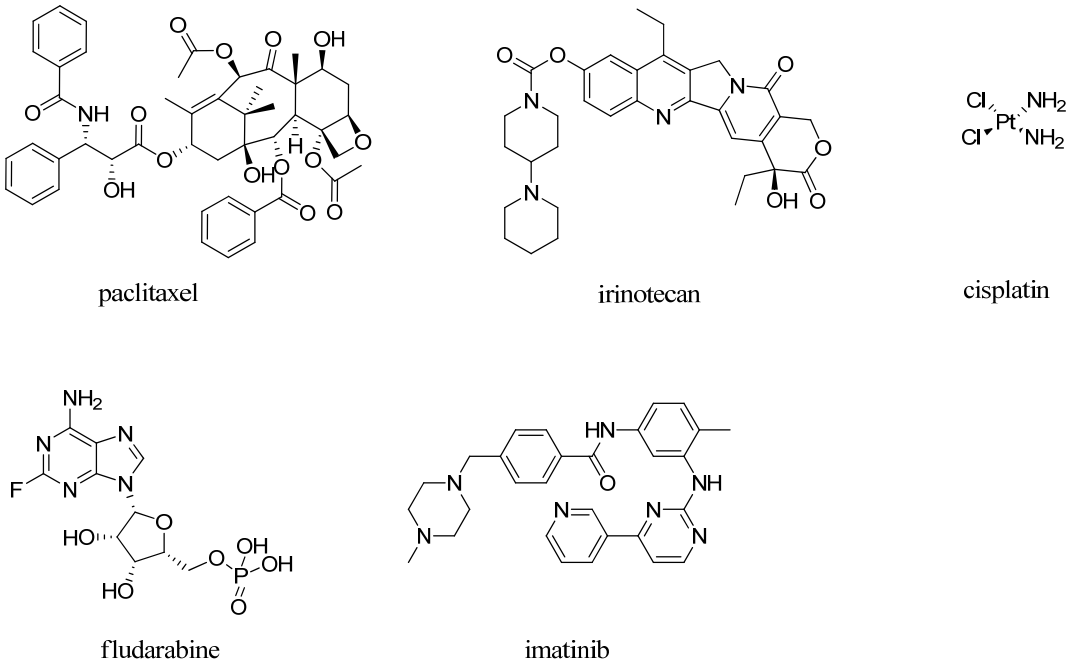


Figure 1.4. Selected drugs used in cancer chemotherapy.

Along with the many success stories of drug discovery for cancer, there have been several failures as well. Nevertheless, our growing understanding of the molecular biology of cancer cell should eventually lead to better ways of preventing and treating the disease.

1.2.1 Natural Products as Medicine

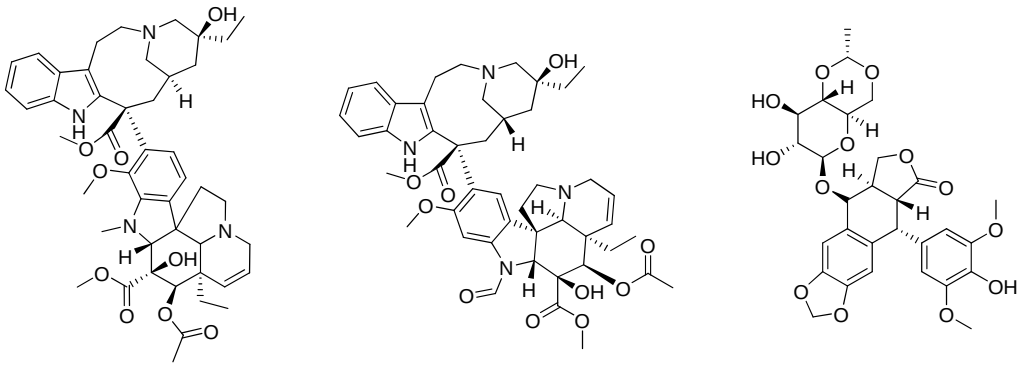
Throughout the ages, man has looked to Nature for the provision of medicine for the treatment of a wide range of diseases. Ancient civilizations such as the Egyptian, Chinese and Indian had extensive records of the use of plants in particular as medicine and some of these documentations date as far back as 2900 B.C.[49] Even today, the World Health Organization estimated that about 65% of the world's population depends on traditional medicine derived from plants as their primary health care. In developed countries, of the top 50 selling drugs sold in pharmacies, half of them are based on or derived from natural products.[50,51] Since the 1950s, natural products have attracted the interests of numerous scientists as many possess unique compounds which are biologically active.

1.2.2 Anticancer Drugs from Plants

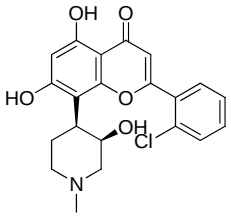
The first plant-derived anticancer drugs to be used clinically were vinblastine and vincristine (Figure 1.5).[52] These compounds were derived from the rosey periwinkle and the plant was used in many parts of Asia to treat diabetes. It was the serendipitous discovery that the plant extract caused a reduction in white blood cell counts and bone marrow depression in rats which eventually led to the isolation of vinblastine and vincristine.

Another modern anticancer drug that has its roots in traditional medicine is etoposide.[49] The Native Americans had used extracts from *podophyllum peltatum* to treat warts and skin cancer. This eventually led to the isolation of podophyllotoxin as the active agent and after extensive research, etoposide was

developed for clininal use.[49] Other examples of anticancer agents derived from plants include paclitaxel and irinotecan which was discussed in earlier sections. Flavopiridol differs from the other examples mentioned in that it is totally synthetic. However its structure is based on a natural product rohitukine. Rohitukine was isolated for its immunomodulatory and anti-inflammatory activity and flavopiridol was the result of a synthetic campaign carried out for structure-activity studies. Flavopiridol was the only compound out of more than 100 analogs synthesized to possess tyrosine kinase activity and cytotoxicity against a series of breast and lung cancer cells.[53]



vinblastine vincristine etoposide



flavopiridol

Figure 1.5. Chemotherapeutic drugs developed from plant sources.

1.2.3 Microbes as Sources of Antitumor Agents

To date, the study of natural microorganisms has been very limited and it has been estimated that less than 1% of microorganisms seen microscopically

have been cultivated.[54] Despite this small number, there have been many drugs that are derived from microbial organism. Microorganisms have traditionally been the main source of antibacterial agents but they have also led to the discovery of several anticancer drugs such as dactinomycin, mitomycin C and doxorubicin (Figure 1.6).[52]

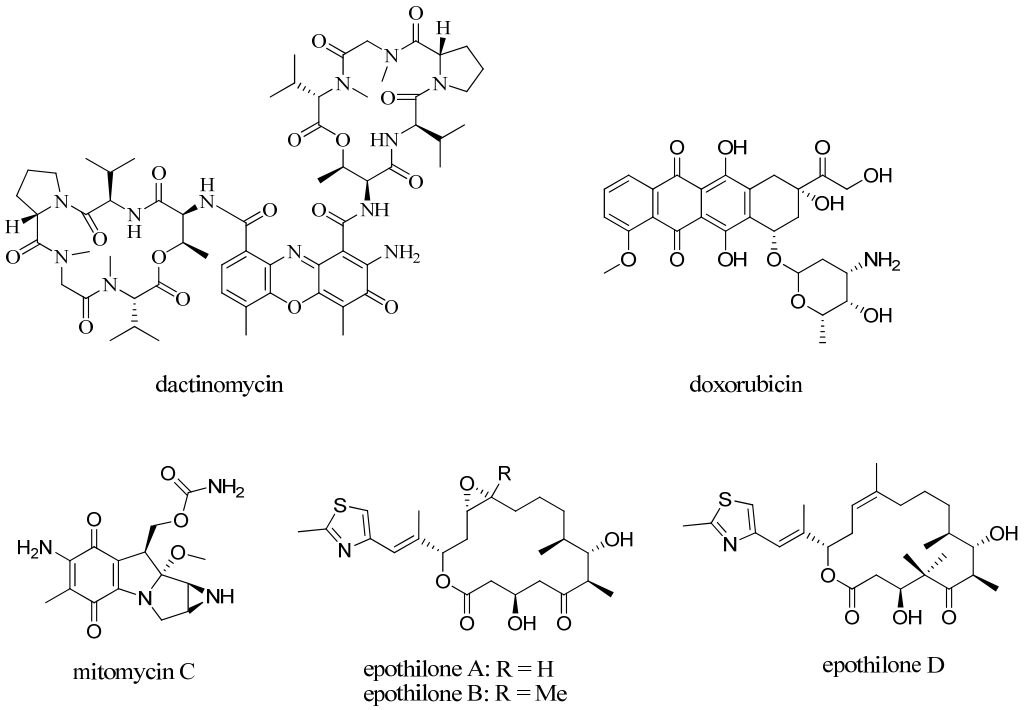


Figure 1.6. Anticancer agents from microbial organisms.

Another example of a class of microbial-derived drug is the epothilones. They were first isolated in 1993 and had a similar mode of action as paclitaxel.[55] Epothilones possessed 2 advantages in that they have greater water solubility and they can be obtained in large quantities via fermentation. The natural products epothilone A and B might be too considered too toxic for clinical use but combinatorial synthesis has allowed the production of a large number of analogs with the basic template.[56] Epothilone D has shown to be at least as cytotoxic as paclitaxel against a range of cancer cell lines and one of

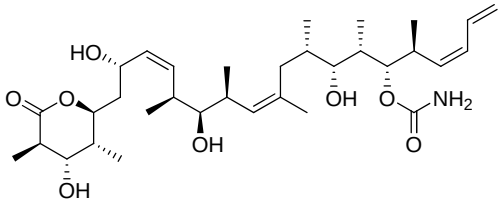
the analogs has recently entered Phase I clinical trials.[57] Given that the severely limited studies of natural microorganisms have already yielded significant benefits, it is clear that the microbial universe presents a vast untapped resource for drug discovery.

1.2.4 Anticancer Drugs from Marine Sources

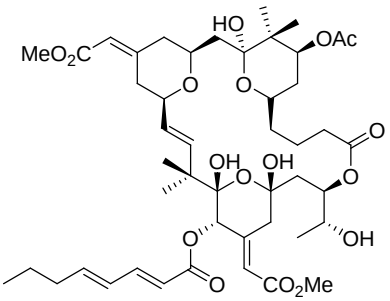
The study of natural products from marine organisms was nearly non-existent before the 1960s.[52] This can be due to the extreme difficulties in collecting materials from the marine environment. For example, marine sponges which are the sources for developmental drugs such as discodermolide are largely unculturable.[58] Therefore many natural products have to be extracted and purified from the specimens collected by scuba-diving from shallow to deep waters. This is an expensive and foreign process to most pharmaceutical industries. Nevertheless research on natural products from marine environment has yielded several potential anticancer agents which are now on Phase I and Phase II clinical trials.[59]

Bryostatin 1 is a potential anticancer drug that highlights the difficulty in obtaining sufficient materials from marine sources and the possible solution to it (Figure 1.7). Bryostatin 1 was first isolated from *B. neritina* in 1968 and was later found to possess potent *in vitro* activity against various cancer cell lines.[60] However the low abundance of compound (~10 parts per billion) prevented the clinical studies of bryostatin 1. The supply of bryostatin 1 via synthesis was also unfeasible due to the complexity of its structure. In 1991, a novel process of large scale collection and purification of 10,000 gallons of *B. neritina* afforded 18 g of bryostatin 1.[61] At the same time, the aquaculture of *B. nertina*

was explored in order to obtain a renewable source of the marine organism.[62] Currently bryostatin 1 is in several clinical trials for various types of cancer.[63]



(+)-Discodermolide



bryostatin 1

Figure 1.7. Marine sources derived anticancer drugs.

(+)-Discodermolide, like byrostatin 1, is a potential antitumor agent isolated from the marine environment and has entered clinical trials.[58] Unlike bryostatin 1, however, the supply of (+)-discodermolide could not be obtained from harvesting and purification of the rare deep-water sponge *Discodermia dissolute*. Attempts at aquaculture or biosynthesis were also unsuccessful but fortunately the supply of (+)-discodermolide could be obtained through total synthesis.[64,65]

1.2.5 Synthesis of Natural Products

The main problems of developing drugs from natural products are the latter's structural complexity and lack of supply. However recent advances in organic synthesis are overcoming the barriers presented by the structural complexity of many natural products. Moreover natural products have been termed "privileged structures" as they have been selected by evolutionary pressures to interact with biological macromolecules.[66] Therefore they

represent excellent templates for the synthesis of novel, biologically active compounds.

Although natural products frequently exhibit potent biological activity, they did not go through evolutionary selection to serve as human therapeutics.[49] Therefore optimization is usually required to fine-tune the biological activity and pharmacokinetics of the compound in a human body. This involves the modification of functional groups and stereocenters or even changing the basic scaffold of the natural product and these belong to the domain of synthetic chemistry.

The easiest approach to optimizing a natural product lead is derivatization of the natural product. A large library can be expediently generated by this method. However due to the incompatibilities of many transformations with existing functional groups, the structural diversity of the analogs may be limited. Examples of drugs developed by this method include taxanes and camptothesins previously mentioned.[41,42]

1.2.6 Semisynthesis and Total Synthesis of Natural Products

Sometimes the natural product of interest cannot be isolated in sufficient quantities and the total synthesis of it is unfeasible as well. This problem may be solved by using another readily available natural product to serve as a starting material for the semisynthesis of the target compound. An excellent example is paclitaxel (Figure 1.8). The development of paclitaxel was greatly impeded by the scarcity of its original source, the bark of *Taxus brevifolia*. Total synthesis was not feasible as well due to paclitaxel's structural

complexity. This issue was solved by semisynthesis using 10-deacetylbaccatin III, which is readily available from the needles of several *Taxus* species, as the starting material.[67]

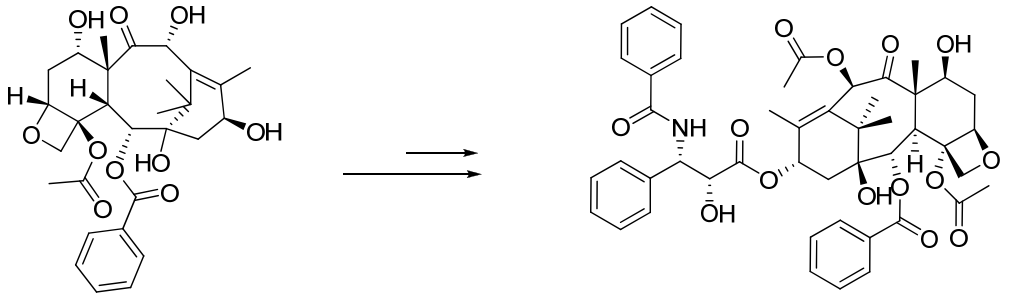


Figure 1.8. Synthesis of paclitaxel from 10-deacetylbaccatin III

The structural complexity of many natural products have also attracted the attention of many top synthetic groups in the world and their efforts at total synthesis have led to great advancements in the field of organic chemistry.[68] An efficient and economical synthetic route to a natural product can eliminate the scarcity problem a naturally derived drug might face when it comes to clinical trials. One such example was the previously discussed (+)‑discodermolide.[54,55]

Total synthesis of a natural product can frequently lead to the identification of the pharmacophore of the molecule. With this knowledge in hand, medicinal chemists will be able to modify the structure of the natural product. This can lead to the synthesis of simpler analogs with better biological activity than the natural product itself. This approach was described by Danishefsky as "diverted total synthesis" (DTS).[69,70] DTS involves the synthesis of an advanced intermediate which is less complex than the original natural product.

Based on the common pharmacophore, analogs are then synthesized either by traditional or combinatorial techniques.

An example of DTS is the development of eribulin (Figure 1.9). In 1992, Aicher and co-workers achieved the total synthesis of the marine-derived halichondrin B.[71] This led to the discovery that the right side of the molecule was responsible for most of the anticancer activity. This ultimately resulted in the discovery of eribulin which compared to halichondrin B, is structurally simpler, has lower toxicity and similar bioactivity.[72] Eribulin is currently in phase III clinical trials.

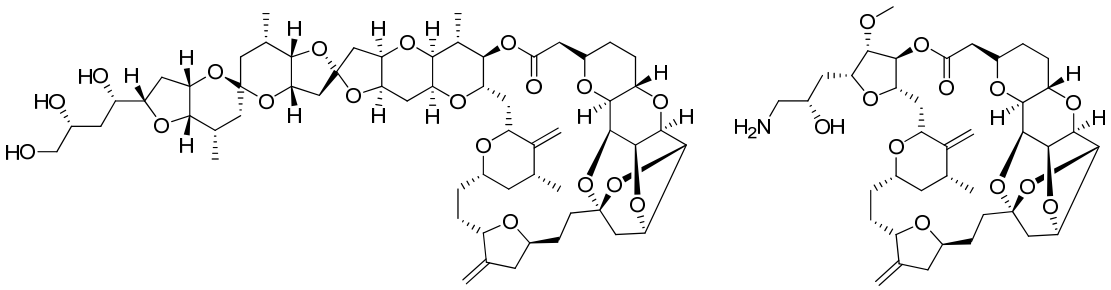


Figure 1.9. Structural similarities between halichondrin B and eribulin

1.2.7 Combinatorial Synthesis Based on Natural Products

Combinatorial synthesis is a set of techniques that allows the simultaneous or parallel synthesis of a large number of different but structural related molecules. Since the 1990s, this technology has been used by the pharmaceutical industry to generate huge libraries of compounds hoping to improve the efficiency of the drug discovery process.[49] However the results were disappointing and increasingly there is a shift of emphasis towards the more measured synthesis of libraries of fewer but well-characterized

compounds. In particular, the synthesis of complex natural product-like compounds is becoming more common.[73]

Natural product scaffolds are "privileged structures" as they have the necessary balance of rigidity and flexibility to allow functional groups to bind to biological targets in a favorable spatial arrangement.[66] Hence they are ideal for the synthesis of libraries of analogs for structure-activity studies using combinatorial techniques. One of the earliest examples was the synthesis of a library of compounds based on the sarcodictyin scaffold (Figure 1.10).[74] Other examples include the combinatorial synthesis of analogs of pepticinnamin and curacin A.[75,76] Today the synthesis of a library of compounds based on a natural product scaffold is commonplace for the optimization of the biological and pharmacokinetic properties of the original natural product.

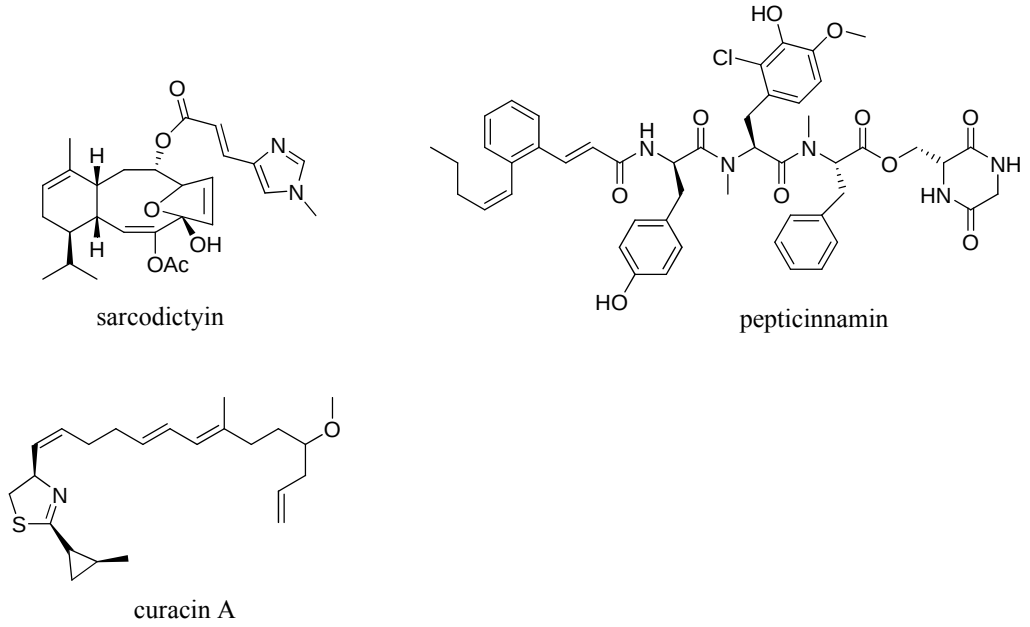


Figure 1.10. Natural product-based combinatorial synthesis.

1.3 Purpose of the Research Work in this Thesis

Cancer, being a leading cause of death in the world, has attracted the attention of the scientific community worldwide in attempts to treat the disease. Because cancer refers to a class of diseases, it is unlikely that there will ever be a single cure for cancer. Today, natural products or their derivatives account for about half of the drugs that are used for the treatment of cancer. This is not surprising as natural products have been used for centuries as medicine and it is clear that Nature will continue to be a source for many new drug leads. The use of natural product scaffolds to synthesize analogs has already produced many new drugs for cancer chemotherapy. Here the aim of this thesis is to develop different classes of natural product analogs as potential new chemotherapeutic agents.

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Chapter 2: Synthesis and Biological Evaluation of Polyenylpyrrole Derivatives as Anti-cancer Agents

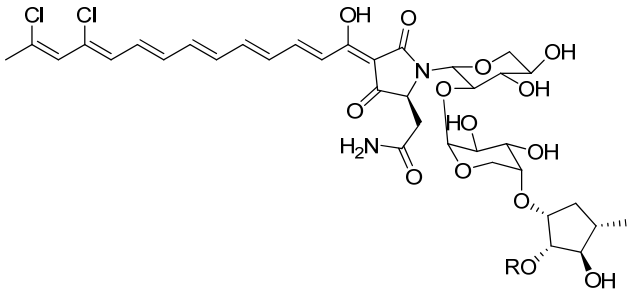
2.1 Introduction

Cancer, being one of the leading causes of death globally, is a disease of worldwide importance. Although anticancer drugs have played a major role in the success stories in cancer treatment, there are still many types of cancer where effective molecular therapeutics are non-existing. Hence there is an impetus to identify and develop more potent therapeutic agents to cancer.

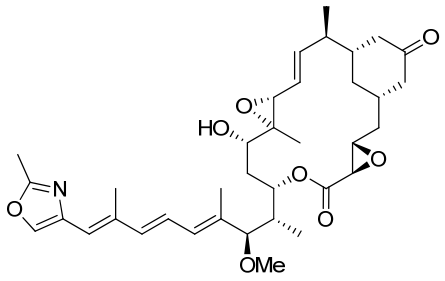
Activation of apoptotic pathways is a key method by which anticancer drugs kill tumor cells.[1,2] It is well known that anticancer drugs can stimulate apoptotic signaling through two major pathways. One is the death receptor (extrinsic) pathway involving death receptor and death ligand interaction, such as apoptosis stimulating fragment (Fas) and other members of the tumor-necrosis factor (TNF) receptor family. These receptors activate caspase-8 and subsequently caspase-3, the major caspases participating in the execution phase of apoptosis.[3] Another apoptotic pathway is the mitochondrial (intrinsic) pathway, which is activated by the release of proapoptotic factors from mitochondria intermembrane space such as cytochrome *c*.[4] The released cytochrome *c* interacts with apoptotic protease activating factor 1 (Apaf-1) and activates caspase-9 which in turn proteolytically activates downstream caspase-3.[5] Activated caspase-3 cleaves many substrates, including poly (ADP-ribose) polymerase (PARP), a DNA repair enzyme which leads to inevitable cell death. Recently, novel molecules that induce mitochondrial pathways of caspase

activation have been developed in cancer chemotherapy.[6] Our interest to investigate natural products for their potential therapeutic effects has recently spurred us to examine the influences of conjugated polyenes on anti-cancer properties.

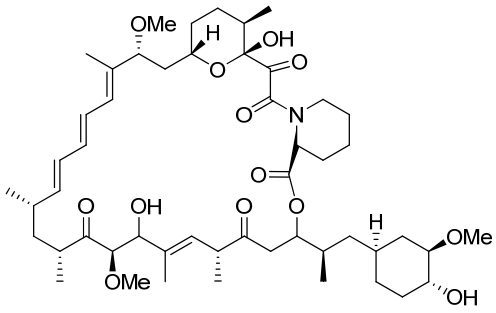
Conjugated polyenes is an interesting class of widely occurring natural products as they have been shown to possess excellent biological properties such as antibacterial, antifungal and antitumor activities.[7] Some of these polyenes that show anticancer activities include rhizoxin[8,9] and aurantosides A and B[10] (Figure 2.1). In addition, some conjugated polyenes that are sold commercially include rapamycin and fumagillin.[11-14]



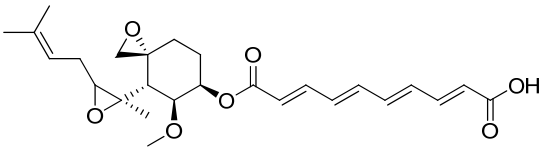
Aurantoside A: R = Me
Aurantoside B: R = H



Rhizoxin



Rapamycin



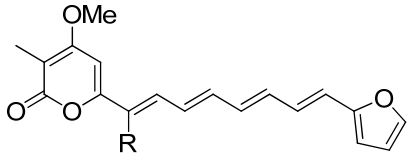
Fumagillin A

Figure 2.1. Examples of conjugated polyenes with biological activity.

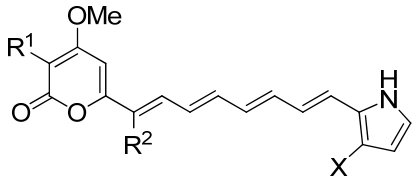
In 2006, Capon and co-workers published a report on the isolation and structure elucidation of several polyenylfurans and polyenylpyrroles from the soil microbe *Gymnoascus reessii*.[15] In that study, they discovered three new conjugated polyenes, 12*E*-isorumbrin **2-1j**, gymnoconjugatin A and B, alongside rumbrin and auxarconjugatin A **2-1b** which were isolated previously (Figure 2.2).[16-18] **2-1b** and **2-1j** were subsequently found to possess potent cytotoxicity properties against NS-1 cell line whilst earlier studies by Yamagishi and co-workers have demonstrated that rumbrin was able to provide cytoprotection against cell death caused by calcium overload. Other related polyenylpyrroles that had been isolated previously include 12*E*-bromoisorumbrin, 12*E*-dechloroisorumbrin, auxarconjugatin B **2-1a** and auxarconjugatin C.[19] Unlike **2-1b and 2-1j**, 12*E*-bromoisorumbrin, 12*E*-dechloroisorumbrin, gymnoconjugatin A and B, were absent of cytotoxicity activity, implying the importance of the 3-chloropyrrole moiety in effecting cytotoxicity in cancer cell-lines.

Thus far the main source of conjugated polyenes has been from the isolation of fungi or bacteria. The typically small quantities that can be obtained via these sources often limit the extent of biological work that can be carried out. To address this limitation as well as to provide access to structurally diverse analogs of these compounds, it would be useful to develop a synthetic strategy that allows conjugated polyenes to be synthesized expediently. To the best of our knowledge, there is presently only one reported synthesis of gymnoconjugatin A and B[20] and there is no literature describing the synthesis of polyenylpyrroles such as **2-1b and 2-1j**. This, together with the promising

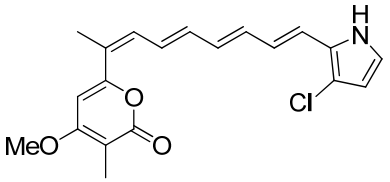
cytotoxicity properties of **2-1b and 2-1j**, prompted us to synthesize a class of polyenylpyrroles and their analogs where the 3-chloropyrrole is replaced with other 2- or 3-chlorosubstituted aromatic rings. Hence, we herein describe the synthesis of these polyenyl compounds and their *in vitro* anti-tumor activity against human non-small cell lung carcinoma cell lines A549.



Gymnoconjugatin A: R = H
Gymnoconjugatin B: R = Me



Auxarconjugatin A, **2-1b**: R^1 = Me, R^2 = H, X = Cl
Auxarconjugatin B, **2-1a**: R^1 = H, R^2 = H, X = Cl
Auxarconjugatin C: R^1 = Me, R^2 = H, X = H
12*E*-isorumbrin, **2-1j**: R^1 = Me, R^2 = Me, X = Cl
12*E*-dechloroisorumbrin: R^1 = Me, R^2 = Me, X = H
12*E*-bromoisorumbrin: R^1 = Me, R^2 = Me, X = Br



Rumbrin

Figure 2.2. Structures of auxarconjugatin, 12*E*-isorumbrin and related polyenes.

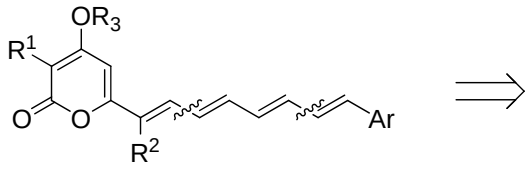
2.2 Results and Discussion

2.2.1 Retrosynthesis

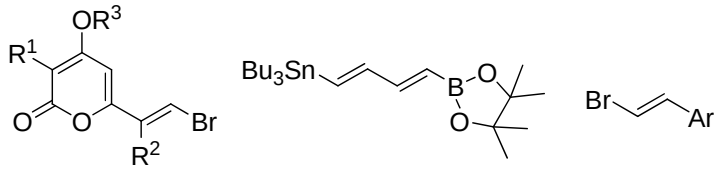
The retrosynthetic route of auxarconjugatin and its analogs **2-1** (Scheme 1) was modified from the synthesis of gymnoconjugatin.[20] Disconnection of the tetraene gave 3 fragments: pyrone **2-2**, the central butadiene connector **2-3** and vinyl bromide **2-4**. It had been shown earlier that hetero-bis-metallated butadiene **2-3** could be used for the synthesis of an extended polyene chain via

sequential Stille and Suzuki coupling reactions.[21] With this strategy in mind, we proceeded with the synthesis of **2-1**.

Scheme 2.1. Retrosynthesis of auxarconjugatin and its analogs **2-1**.



2-1

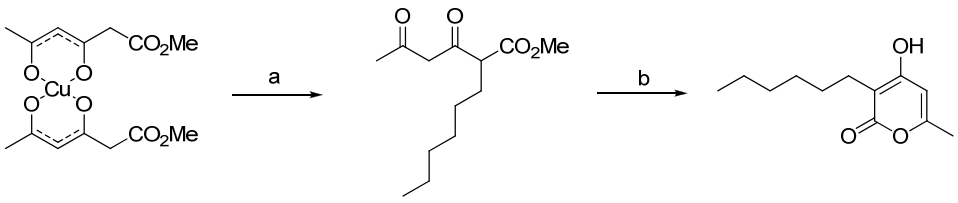


2-2 **2-3** **2-4**

2.2.2 Synthesis of Compounds 2-2

The synthesis of compound **2-7e** was adapted from the literature describing the preparation of compounds **2-7a** to **2-7d**.[22,23](Scheme 2.2 and Scheme 2.3). Regioselective alkylation of copper salt **2-5** afforded **2-6** which underwent cyclization to afford **2-7e** in excellent yield.

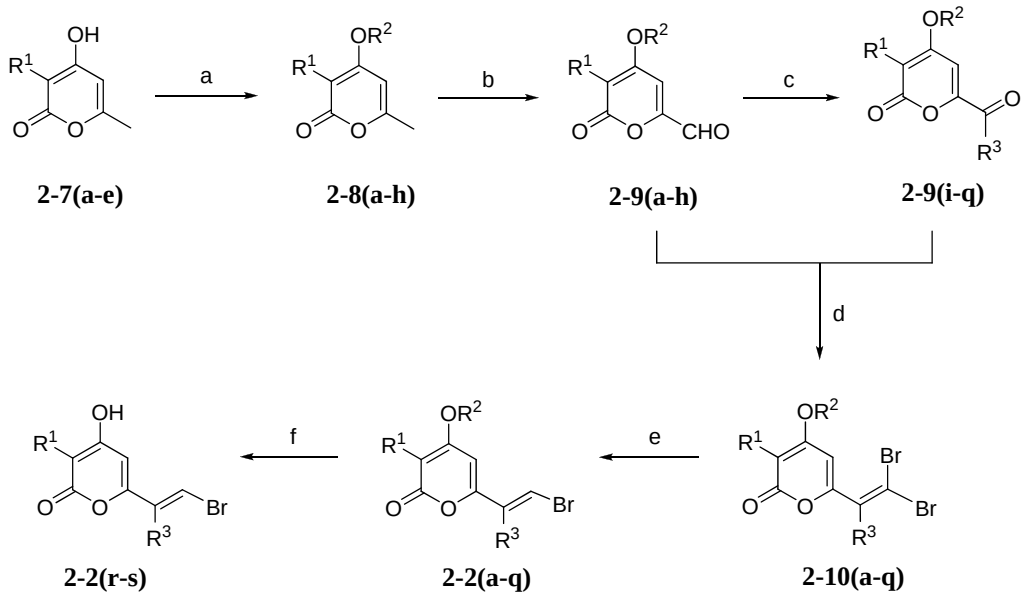
Scheme 2.2 Preparation of compound **2-7e**[a]



2-5 **2-6** **2-7e**

[a]Reagents and conditions: (a) NaH, iodohexane, THF, rt; (b) DBU, toluene, 85 °C

Scheme 2.3 Preparation of compounds **2-2(a-s)**[a]

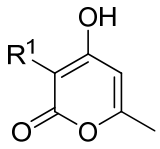


[a]Reagents and conditions: (a) $R^2_2SO_4$, K_2CO_3, DMSO, rt; (b) SeO_2, Dioxane, 150 °C-160 °C; (c) (i) R^3MgBr in Et_2O, THF, rt; (ii) DMP, CH_2Cl_2, rt; (d) CBr_4, PPh_3, CH_2Cl_2, rt; (e) dimethylphosphite, TEA, DMF, rt; (f) aq. HBr, AcOH, 90 °C

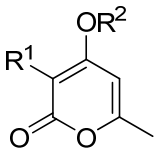
Alkylation of the hydroxyl group on **2-7** was achieved using dimethyl sulfate or diethyl sulfate to afford **2-8** (Scheme 2.3). The oxidation of **2-8** to **2-9** was modified from a procedure reported earlier.[20] Instead of conventional heating in a sealed tube, we applied microwave irradiation which resulted in shorter reaction times with improved yields. It should be noted that for the desired reaction temperature to be achieved via microwave irradiation, the concentration of **2-8** in dioxane should be relatively high (≥ 0.5 M). This is

because dioxane itself lacks dipole moment and is therefore a poor absorber of microwave radiation.

Table 2.1. Analogs of **2-7** and **2-8** synthesized



2-7



2-8

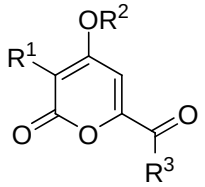
2-7	R^1
a	H
b	Me
c	*n*Bu
d	Bn
e	*n*-hexyl

2-8	R^1	R^2
a	H	Me
b	Me	Me
c	*n*Bu	Me
d	Bn	Me
e	*n*-hexyl	Me
f	H	Et
g	Me	Et
h	*n*Bu	Et

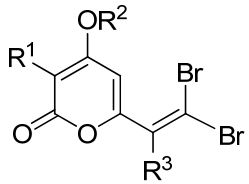
To introduce diversity at the R^3 position for **2-2**, compounds **2-9a to 2-9h** were treated with MeMgBr or EtMgBr followed by oxidation of the resulting alcohol using Dess-Martin Periodinane (DMP) to afford **2-9i** to **2-9q**. Attempts to convert the aldehyde moiety on **2-9a** and **2-9b** directly to a vinyl iodide

group via Takai olefination failed to provide the desired compound. Hence to synthesize **2-2**, compounds **2-9** were first converted to vinyl dibromide **2-10** via Corey-Fuchs olefination followed by reduction using dimethylphosphite.[24]

Table 2.2. Analogs of **2-9** and **2-10** synthesized.



2-9



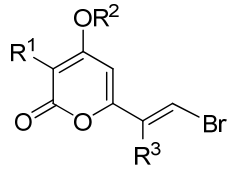
2-10

2-9	R^1	R^2	R^3
a	H	Me	H
b	Me	Me	H
c	*n*Bu	Me	H
d	Bn	Me	H
e	*n*-hexyl	Me	H
f	H	Et	H
g	Me	Et	H
h	*n*Bu	Et	H
i	H	Me	Me
j	Me	Me	Me
k	Me	Me	Et

2-10	R^1	R^2	R^3
a	H	Me	H
b	Me	Me	H
c	*n*Bu	Me	H
d	Bn	Me	H
e	*n*-hexyl	Me	H
f	H	Et	H
g	Me	Et	H
h	*n*Bu	Et	H
i	H	Me	Me
j	Me	Me	Me
k	Me	Me	Et

l	*n*Bu	Me	Me	**l**	*n*Bu	Me	Me
m	*n*Bu	Me	Et	**m**	*n*Bu	Me	Et
n	Bn	Me	Me	**n**	Bn	Me	Me
o	*n*hexyl	Me	Me	**o**	*n*hexyl	Me	Me
p	Me	Et	Me	**p**	Me	Et	Me
q	*n*Bu	Et	Me	**q**	*n*Bu	Et	Me

Table 2.3. Analogs of **2-2** synthesized



2-2

2-2	R^1	R^2	R^3	**2-2**	R^1	R^2	R^3
a	H	Me	H	**k**	Me	Me	Et
b	Me	Me	H	**l**	*n*Bu	Me	Me
c	*n*Bu	Me	H	**m**	*n*Bu	Me	Et
d	Bn	Me	H	**n**	Bn	Me	Me
e	*n*-hexyl	Me	H	**o**	*n*hexyl	Me	Me
f	H	Et	H	**p**	Me	Et	Me
g	Me	Et	H	**q**	*n*Bu	Et	Me

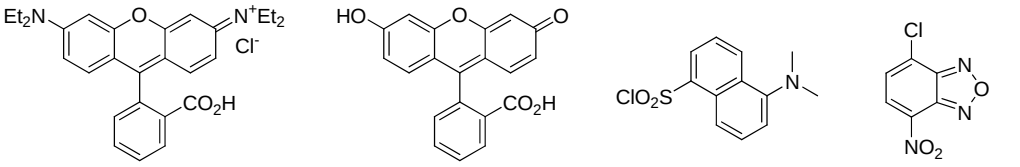
h	*n*Bu	Et	H	**r**	H	H	H
i	H	Me	Me	**s**	Me	H	H
j	Me	Me	Me				

This afforded **2-2a** to **2-2q** in excellent yields and *E/Z* ratio greater than 20:1. Further treatment of compounds **2-2a** and **2-2b** with a mixture of aqueous HBr and acetic acid gave the demethylated products **2-2r** and **2-2s** respectively.

2.2.3 Synthesis of Fluorescent Tags

Labeling of biomolecules with a radioactive or fluorescent tag is a common method used for bioanalytical purposes. The use of the latter over the former is generally preferred as the hazards of handling radioactive materials are avoided. Fluorescence microscopy is an important technique in the study of biomolecules, events and pathways in living cells and tissue. The most widely used methods, confocal microscopy and wide-field microscopy, can track proteins and other biomolecules in the cell and also resolve various cellular organelles such as the nucleus and endoplasmic reticulum.[25,26]

It was our intention to attach a fluorescent probe to the polyenyl compounds synthesized to track their mode of action in the cancer cell. Commonly used fluorescent tags include rhodamine B, fluorescein, dansyl chloride and 4-chloro-7-nitrobenzooxadiazole chloride (NBD-Cl) (Figure 2.3). For our purpose, we chose the latter two due to their smaller molecular weight to minimize the effects of the tag on the activity of the polyenyl compounds.

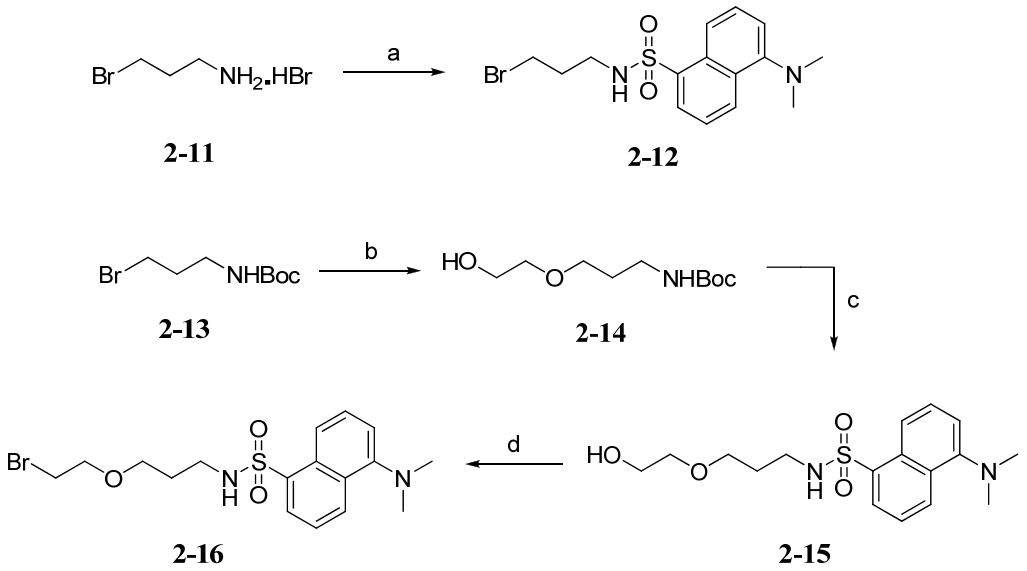


rhodamine B | fluorescein | dansyl chloride | 4-chloro-7-nitro-benzooxadiazole

Figure 2.3. Commonly used fluorescent tags.

The synthesis of 2 dansyl tags is shown in Scheme 2.4. The first tag was synthesized in excellent yield by the reaction of 3-bromopropylamine hydrobromide **2-11** with dansyl chloride.

Scheme 2.4. Synthesis of dansyl tags[a]



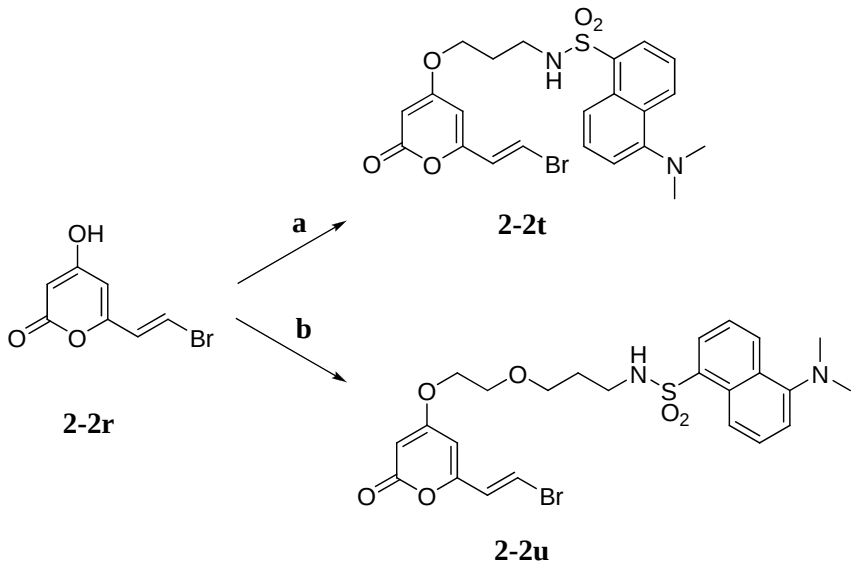
[a]Reagents and conditions: (a) dansyl chloride, TEA, DMF, rt; (b) (i) NaH, THF, rt; (ii) ethylene glycol, rt; (c) (i) TFA, CH_2Cl_2, rt; (ii) dansyl chloride, TEA, CH_2Cl_2, rt; (d) CBr_4, PPh_3, CH_2Cl_2.

Compound **2-13** which was synthesized from known protocols[27] was used as the starting material for the preparation of the other dansyl tag. The S_N2 reaction between ethylene glycol and **2-13** afforded **2-14** in moderate yield.

The Boc protecting group on **2-14** was removed via treatment with TFA in CH_2Cl_2 and subsequent reaction with dansyl chloride provided **2-15** over 2 steps. **2-15** was then converted to **2-16** through the Appel reaction in excellent yield.

The R^2 position on **2-2r** were chosen as the point of attachment of the dansyl tags and **2-12** and **2-16** were attached to **2-2r** to afford **2-2t** and **2-2u** respectively (Scheme 2.5). However attempts at tagging **2-2r** with a NBD analogue of **2-12** failed to afford the desired compound.

Scheme 2.5. Synthesis of **2-2t** and **2-2u**[a]



[a]Reagents and conditions: (a) **2-12**, K_2CO_3 DMSO, 85 °C, (b) **2-16**, , K_2CO_3 DMSO, 85 °C.

2.2.4 Synthesis of Compounds 2-4

The second coupling partner, pyrrole **2-4a**, was synthesized from commercially available 2-methyl-1-pyrroline **2-17** (Scheme 2-6). The conversion of **2-17** to compound **2-19** was adapted from an earlier report.[28] Using THF instead of CCl_4 as a solvent for the chlorination of **2-17** led to a more than 200-fold increase in reaction rate to provide **2-18** which was used directly for the synthesis of **2-19** in excellent yield. Initial attempts to reduce **2-19** directly to the aldehyde **2-20** in a single step by using diisobutylaluminium hydride (DIBAL) failed and the fully reduced alcohol was obtained as the major product. To obtain **2-20**, we therefore attempted to reduce **2-19** completely to the alcohol with $LiAlH_4$ and then oxidize the alcohol to the aldehyde **2-20** with DMP. Unfortunately, the addition of DMP led to the

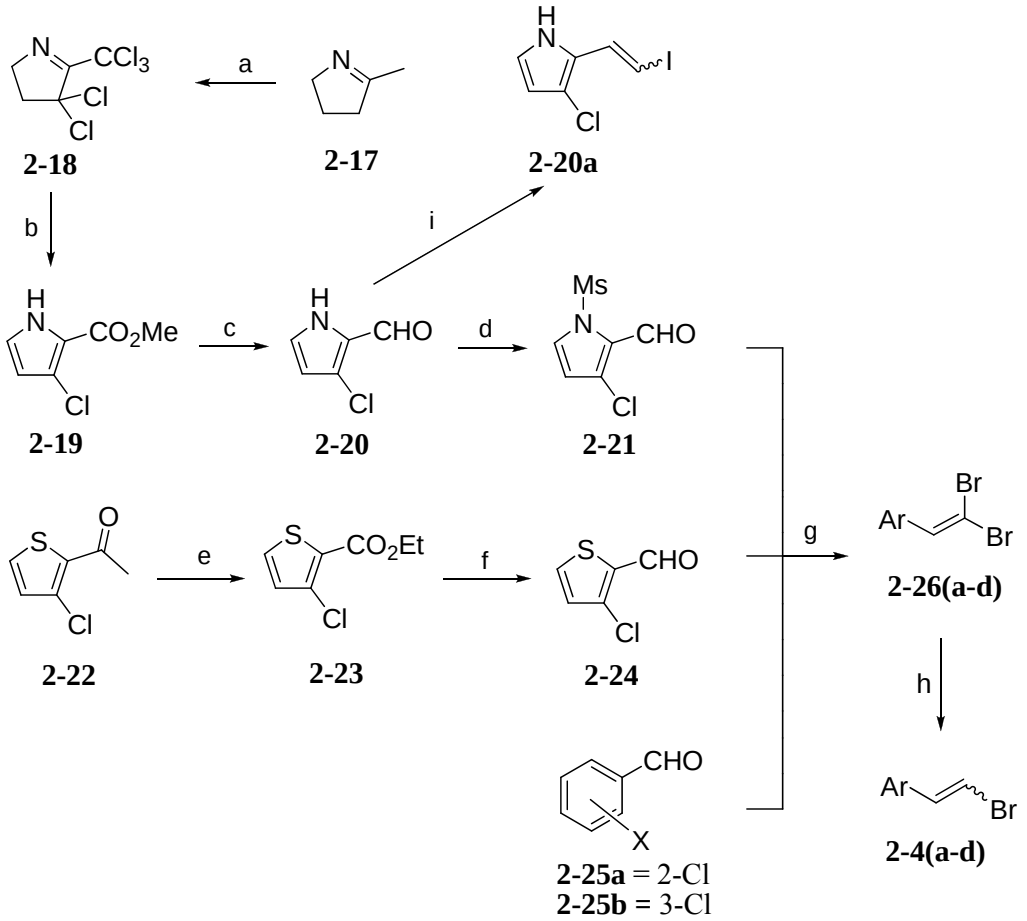
immediate decomposition of the alcohol. This could be attributed to the polymerization of pyrrole in the presence of the acetic acid which was formed as a byproduct of the DMP oxidation.[29] However the addition of sodium bicarbonate[30,31] and pyridine[32,33] to neutralize the acetic acid byproduct did not resolve the problem. Swern oxidation, another commonly used method to oxidize an alcohol to an aldehyde also failed to give the desired product. Thus to circumvent this problem, we tried 2-iodoxybenzoic acid (IBX) which gratuitously gave **2-20** in moderate yields. The addition of excess sodium bicarbonate to the reaction mixture to neutralize the acidic conditions further improved the yield of **2-20**.

With compound **2-20** in our hands, we proceeded to synthesize the corresponding vinyl iodide **2-20a** via Takai olefination. However in the course of drying the vinyl iodide, polymerization occurred and a dark tar was obtained. This problem was partially solved by storing **2-20a** in a solution of THF. However the yield for the final step of the synthesis involving Sukuzi coupling between **2-30a** and **2-20a** was disappointingly low (< 30%). This was very likely due to the instability of **2-20a** as the yield for the similar Suzuki coupling of **2-30a** and **2-4b** was significantly higher. This problem was subsequently resolved by first protecting **2-20** with a mesyl group whose electron-withdrawing property served to stabilize the pyrrole for subsequent transformations.

Earlier studies have shown that the 3-chloropyrrole group plays an important role in the cytotoxicity effects of **2-1b** and **2-1e**. When the chloro group was substituted with a bromo or hydrogen or when the 3-chloropyrrole

moiety was substituted with a furan ring, the activity was drastically reduced.[19,20] To study other ring systems besides pyrrole, we replaced 3-chloropyrrole with other 2- or 3-chlorosubstituted aromatic rings.

Scheme 2.6. Synthesis of **2-4(a-d)**[a]

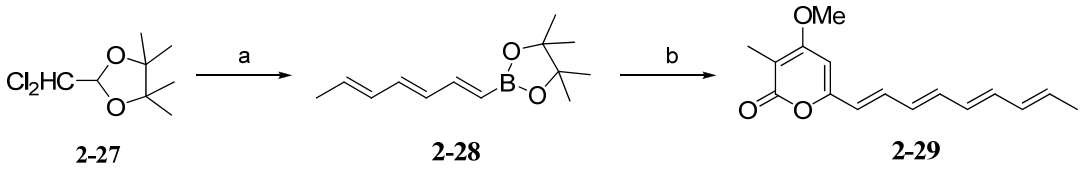


[a]Reagents and conditions: (a) NCS, THF, 55 °C; (b) (i) MeONa, MeOH, 0 °C–rt; (ii) aq. HCl; (c) (i) $LiAlH_4$, THF, -20 °C–rt; (ii) IBX, $NaHCO_3$, DMSO, rt; (d) NaH, MsCl, THF, rt; (e) (i) CuO, I_2, Pyridine, EtOH, reflux; (ii) K_2CO_3, reflux; (f) (i) $LiAlH_4$, THF, 0 °C; (ii) DMP, CH_2Cl_2, rt; (g) CBr_4, PPh_3, CH_2Cl_2, rt; (h) dimethylphosphite, TEA, DMF, rt; (i) $CrCl_2$, CHI_3, THF, rt.

Compound **2-23** was prepared by the oxidation of 2-acetyl-3-chlorothiophene **2-22** (Scheme 3).[34] Reduction of **2-23** with $LiAlH_4$ followed by oxidation with DMP gave compound **2-24**. Corey-Fuchs olefination of **2-21**, **2-24, 2-25a** and **2-25b** gave the corresponding vinyl dibromide **2-26(a-d)** and subsequent reduction of **2-26(a-d)** with dimethylphosphite afforded **2-4(a-d)**. Compound **2-4a** and **2-4b** were obtained as a *ca.* 2:1 mixture of *E* and *Z* stereoisomers but for **2-4c** and **2-4d**, the *E* isomer was obtained in greater than 9:1 ratio.

To establish if the cytotoxic effects of **2-1a** would be affected if the 3-chloropyrrole group was replaced by a methyl group (Scheme 4), compound **2-28** was synthesized. This synthesis involved the Takai olefination of 2,4-hexadienal with **2-27**[35] to afford **2-28** which was then reacted with **2-2b** via Suzuki coupling to provide **2-29**.

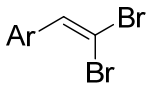
Scheme 2.7. Synthesis of **2-29**[a]



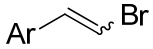
2-27 **2-28** **2-29**

[a]Reagents and conditions: (a) 2,4-hexadienal, $CrCl_2$, LiI, THF, rt; (b) **2-2b**, Pd_2dba_3, $AsPh_3$, aq. KOH, THF.

Table 2.4. Analogs of **2-4** synthesized.



2-26



2-4

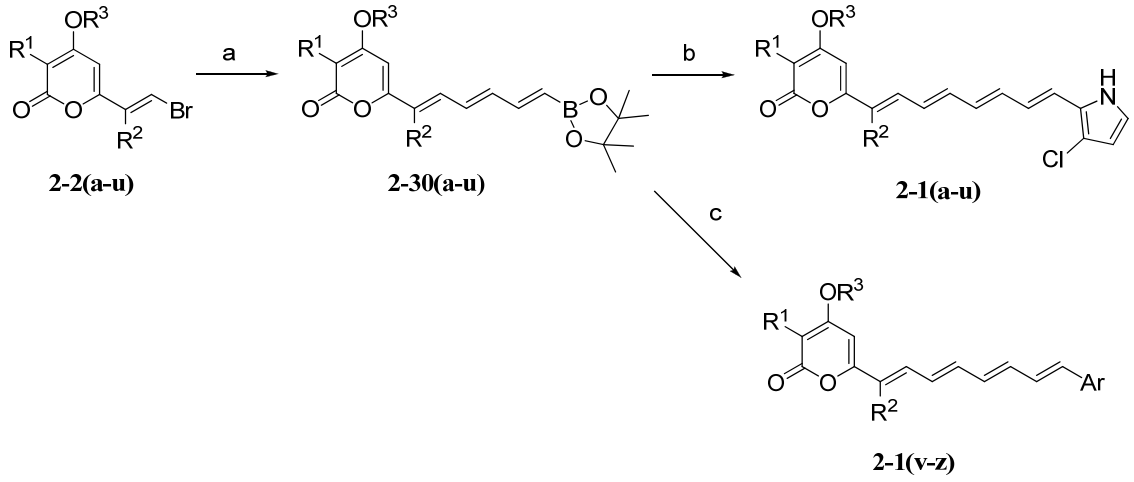
2-26	Ar	**2-4**	Ar
a	3-chloro-1-mesyl-pyrrol-2-yl	**a**	3-chloro-1-mesyl-pyrrol-2-yl
b	3-chlorothiophen-2-yl	**b**	3-chlorothiophen-2-yl
c	2-chlorophenyl	**c**	2-chlorophenyl
d	3-chlorophenyl	**s**	3-chlorophenyl

2.2.5 Synthesis of Compounds 2-1

Pyrones **2-2(a-u)** were treated with **2-3** via Stille coupling to afford trienes **2-30(a-u)**. Suzuki coupling of **2-30(a-u)** with **2-4a** followed by treatment with tetrabutylammonium fluoride (TBAF) to remove the mesyl group afforded **2-30(a-u)** (Scheme 2.8). Other attempts at removing the mesyl group on the pyrrole via basic hydrolysis were less successful as the reaction proceeded much slower. Compounds **2-1(v-z),** bearing other aromatic rings besides 3-chloropyrrole, were synthesized in a similar manner. Interestingly, the ^{1}H NMR of crude **2-1(a-z)** showed that the *E* stereoisomer of the respective compound was present in 75-85%. As the *E* stereoisomers of **2-4a**, **2-4b** and **2-4(c-d)** were present in *ca*. 66%, 66% and >90% respectively, this indicated that

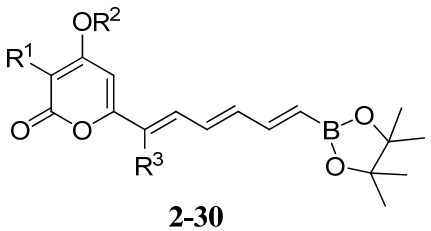
isomerization could have occurred during the coupling process. Table 2.6 shows the 27 auxarconjugatin analogs **2-1(a-z)** and **2-29** synthesized.

Scheme 2.8. Synthesis of **2-1**.



[a]Reagents and conditions: (a) **2-3**, Pd_2dba_3, $AsPh_3$, NMP, rt; (b) (i) **2-4a**, Pd_2dba_3, $AsPh_3$, aq. KOH, THF, rt; (ii) TBAF, THF, rt; (c) **2-4(a-d)**, Pd_2dba_3, $AsPh_3$, aq. KOH, THF, rt.

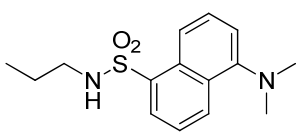
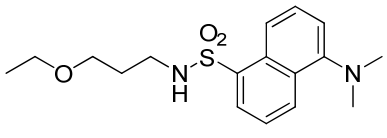
Table 2.5. Analogs of **2-30** synthesized.



2-30

2-30	R^1	R^2	R^3
a	H	Me	H
b	Me	Me	H
c	*n*Bu	Me	H
d	Bn	Me	H
e	*n*-hexyl	Me	H
f	H	Et	H
g	Me	Et	H
h	*n*Bu	Et	H
i	H	Me	Me
j	Me	Me	Me

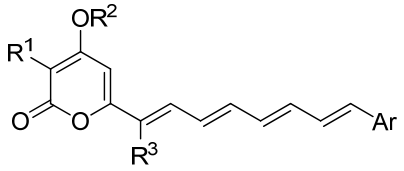
2-30	R^1	R^2	R^3
k	Me	Me	Et
l	*n*Bu	Me	Me
m	*n*Bu	Me	Et
n	Bn	Me	Me
o	*n*hexyl	Me	Me
p	Me	Et	Me
q	*n*Bu	Et	Me
r	H	H	H
s	Me	H	H
t[a]	H	R^4	H
u[a]	H	R^5	H

[a] **R^4** =  **R^5** = 

2.3 Biological Results[a]

[a]All the biological results were obtained as a result of a collaboration with another research group.

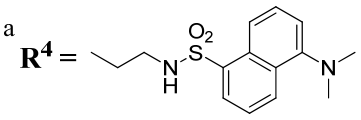
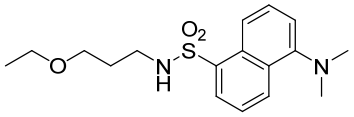
Table 2.6. Cytotoxicity of conjugated polyenes against human lung cancer A549 cells[a]



2-1

Compd	R^1	R^2	R^3	Ar	IC_{50} (μM)
2-1a	H	Me	H	3-chloropyrrol-2-yl	0.6
2-1b	Me	Me	H	3-chloropyrrol-2-yl	1.2
2-1c	*n*Bu	Me	H	3-chloropyrrol-2-yl	5.0
2-1d	Bn	Me	H	3-chloropyrrol-2-yl	>1.0[c]
2-1e	*n*-hexyl	Me	H	3-chloropyrrol-2-yl	>1.0[c]
2-1f	H	Et	H	3-chloropyrrol-2-yl	>1.0[c]
2-1g	Me	Et	H	3-chloropyrrol-2-yl	>1.0[c]
2-1h	*n*Bu	Et	H	3-chloropyrrol-2-yl	>1.0 [c]
2-1i	H	Me	Me	3-chloropyrrol-2-yl	2.5
2-1j	Me	Me	Me	3-chloropyrrol-2-yl	5.2

2-1k	Me	Me	Et	3-chloropyrrol-2-yl	5.6
2-1l	*n*Bu	Me	Me	3-chloropyrrol-2-yl	0.01
2-1m	*n*Bu	Me	Et	3-chloropyrrol-2-yl	>1.0[c]
2-1n	Bn	Me	Me	3-chloropyrrol-2-yl	>1.0[c]
2-1o	*n*hexyl	Me	Me	3-chloropyrrol-2-yl	>1.0[c]
2-1p	Me	Et	Me	3-chloropyrrol-2-yl	>1.0[c]
2-1q	*n*Bu	Et	Me	3-chloropyrrol-2-yl	>1.0[c]
2-1r	H	H	H	3-chloropyrrol-2-yl	>20[b]
2-1s	Me	H	H	3-chloropyrrol-2-yl	>20[b]
2-1t[a]	H	R^4	H	3-chloropyrrol-2-yl	>20[b]
2-1u[a]	H	R^5	H	3-chloropyrrol-2-yl	>20[b]
2-1v	H	Me	H	3-chlorothiophen-2-yl	>20[b]
2-1w	Me	Me	H	3-chlorothiophen-2-yl	>20[b]
2-1x	Me	Me	H	2-chlorophenyl	>20[b]
2-1y	Me	Me	H	3-chlorophenyl	>20[b]
2-1z	Me	Me	H	3-chloro-1-mesyl-pyrrol-2-yl	>20[b]
2-29	Me	H	Me	Me	>20[b]

[a] $R^4 =$  $R^5 =$ 

[a]All treatment media contained the final DMSO concentration of 0.1%. AlamarBlue® assay was used to determine the cytotoxicity of the test compounds after 48 h of incubation. The procedure was conducted following the protocol described in the manufacturer's instructions (AbD Serotec, Oxford).

[b]The IC_{50} values of these compounds were not determined due to their lack of potency.

[c]These compounds were synthesized and tested at a later date. As they displayed less activity than **2-1a** and **2-1l**, their exact IC_{50} values were not determined.

Compounds **2-1(a-z)** and **2-29** were evaluated for their cytotoxicities against the human lung cancer cell line A549 after 48 h treatment. As shown in Table 2.6, the two most potent compounds are **2-1a** and **2-1l** with IC_{50} values of 0.6 and 0.01 μM respectively, indicating that these compounds are more potent against A549 cell lines than anti-tumor drugs like Gleevec (IC_{50} = 2-3 μM) and cisplatin (IC_{50} = 64 μM).[36] The loss of activity in compounds **2-1v** to **2-1z**, where other chloro-substituted aromatic rings were present instead of 3-chloropyrrole, supported our hypothesis that the later group played an important role in effecting cytotoxicity.

Fluorescence imaging of the cell could not be carried out due to the lost of cytotoxicity when the dansyl tags were attached in **2-1t** and **2-1u**. In addition,

the lack of cytotoxicity in compounds **2-1r** and **2-1u** also illustrated the importance of a methyl group at the R^3 position. The difference in cytotoxicity between compounds **2-1a** and **2-1f** as well as **2-ll** and **2-1q** when the methyl group was replaced by an ethyl group at the R^3 position further highlights the importance of a methyl group at the R^3 position.

To further explore the selectivity of the polyenyl compounds against A549 cells, compounds **2-1a** and **2-1l** were further examined against Beas-2b cells which were derived from normal human lung tissue. As can be seen in Figure 2 compounds **2-1a** and **2-1l**, despite being very potent against A549 cells (0.6 and 0.01 μM respectively), were found to be non-cytotoxic towards Beas-2b cells at up to 80 μM.

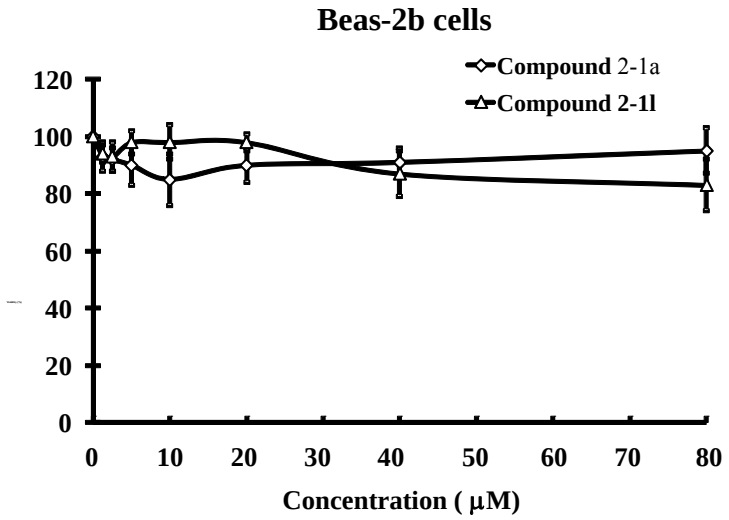


Figure 2.4 Compounds **2-1a** and **2-1l** were non-cytotoxic to normal human lung cells.[a]

[a]All treatment media contained the final DMSO concentration of 0.1%. AlamarBlue® assay was used to determine the cytotoxicity of the test

compounds after 48 h of incubation. The procedure was conducted following the protocol described in the manufacturer's instructions (AbD Serotec, Oxford).

2.4 Conclusion

In our efforts to develop potential chemotherapeutic agents from natural products, we have herein provided the first reported synthesis of a class of polyenylpyrrole natural products and their analogs. The compounds were evaluated for the cell cytotoxicity against human lung cancer cells A549. Two compounds, **2-1a** and **2-1l**, displayed potent effects in the inhibition of tumor cell proliferation with IC_{50} values of 0.6 μM and 0.01 μM respectively. In addition, these two compounds were found to be non-toxic to normal lung cells. These results indicated that compounds **2-1a** and **2-1l** have the potential to be developed as anticancer agents due to their high selectivity against A549 cells.

2.5 Experimental Section

General Procedures. All chemical reagents and solvents were obtained from Sigma Aldrich, Merck, Alfa Aesar, or Fluka and were used without further purification. The microwave-assisted reactions were performed using the Biotage Initiator microwave synthesizer. Analytical TLC was carried out on precoated silica plates (Merck silica gel 60, F254) and visualized with UV light or stained with phosphomolybdic acid (PMA) stain. Flash column chromatography was performed with silica (Merck, 70-230 mesh). The purities of the compounds were determined via HPLC using a Shimadzhu LCMS-IT-TOF system with a Phenomenex Luma C18 column (50 mm × 3.0 mm, 5 μm).

Compounds used in the biological assays have purities of at least 95%. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker ACF 300 or AMX 500 Fourier transform spectrometer. Chemical shifts were reported in parts per million (δ) relative to the internal standard of tetramethylsilane (TMS). The signals observed were described as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet). The number of protons (n) for a given resonance was indicated as nH. Mass spectra were performed on a Finnigan/MAT LCQ mass spectrometer under electron spray ionization (ESI) or electron impact (EI) techniques.

Synthesis of methyl-2-3-hydroxybut-2-enoyl)octanoate (2-6). 60% NaH in mineral oil (1.44 g, 36.1 mmol) was added portionwise to **2-5** (6.20 g, 16.4 mmol) in THF (50 mL) and the reaction mixture was stirred at room temperature for 30 min. Next, iodohexane (20.9 g, 98.4 mmol) was added and the reaction mixture was stirred at 65 °C for 5 h. The reaction was quenched with aqueous 3 M HCl and extracted with Et_2O. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc:hexane = 1:10) to afford **2-6** (5.80 g, 73%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (s, 1H), 3.71 (s, 3H), 3.23 (t, J = 7.3 Hz, 1H), 2.05 (s, 3H), 1.92-1.88 (m, 2H), 1.87-1.78 (m, 2H), 1.27-1.25 (m, 8H), 0.86 (t, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 189.5, 170.8, 99.3, 55.4, 52.3, 31.5, 29.3, 28.9, 27.3, 24.1, 22.5, 13.9; HRMS (EI): calcd for $C_{13}H_{22}O_4$, 242.1518; found 242.1514.

Synthesis of 3-hexyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (2-7e). DBU (3.27 g, 21.5 mmol) was added to **2-6** (5.20 g, 21.5 mmol) in toluene (30 mL)

and the mixture was stirred at 85 °C for 2 h. The reaction was quenched with aqueous 3 M HCl and extracted with EtOAc. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated and purified by column chromatography (EtOAc:hexane = 1:1) to afford **2-7e** (4.11 g, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (s, 1H), 2.45 (t, *J* = 7.6 Hz, 2H), 2.21 (s, 3H), 1.52-1.46 (m, 2H), 1.34-1.27 (m, 6H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 167.4, 159.7, 103.4, 101.8, 31.8, 29.3, 28.0, 23.0, 22.6, 19.6, 14.1; ; HRMS (EI): calcd for $C_{12}H_{18}O_3$, 210.1256; found 210.1260.

General Procedure for the Synthesis of 2-8a to 2-8e. To a mixture of K_2CO_3 (1.73 g, 12.5 mmol) and the corresponding pyrone **2-7** (5.00 mmol) in DMSO (10 mL) was added dimethyl sulfate (0.693 g, 5.50 mmol). The mixture was stirred at room temperature for 1 h and poured into water (60 mL). The mixture was extracted with EtOAc and the combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated and purified by column chromatography.

4-methoxy-6-methyl-2*H*-pyran-2-one (2-8a). The residue was purified using flash chromatography (EtOAc:hexane = 2:1) to afford **2-8a** (0.588 g, 86%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (d, *J* = 1.3 Hz, 1H), 5.36 (d, *J* = 1.9 Hz, 1H), 3.75 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 164.8, 161.9, 100.2, 87.2, 55.7, 19.7; HRMS (EI): calcd for $C_7H_8O_3$, 140.0473; found 140.0472.

4-methoxy-3,6-dimethyl-2*H*-pyran-2-one (2-8b). The residue was purified using flash chromatography (EtOAc:hexane = 1:1) to afford **2-8b** (0.593 g,

77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (s, 1H), 3.83 (s, 3H), 2,21 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 165.8, 160.7, 100.5, 95.0, 56.2, 20.2, 8.3; HRMS (EI): calcd for $C_8H_{10}O_3$, 154.0630; found 154.0629.

3-butyl-4-methoxy-6-methyl-2*H*-pyran-2-one (2-8c). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-8c** (0.725 g, 74%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (s, 1H), 3.82 (d, J = 3.2 Hz, 3H), 2.39-2.34 (m, 2H), 2.21 (d, J = 3.8 Hz, 3H), 1.41-1.40 (m, 2H), 1.32-1.28 (m, 2H), 0.89-0.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 165.4, 160.8, 105.6, 94.9, 56.1, 30.1, 22.9, 22.6, 20.2, 13.9; HRMS (EI): calcd for $C_{11}H_{16}O_3$, 196.1099; found 196.1098.

3-benzyl-4-methoxy-6-methyl-2*H*-pyran-2-one (2-8d). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-8d** (0.891 g, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.30 (m, 2H), 7.24-7.21(m, 2H), 7.15-7.13 (m, 1H), 6.02 (s, 1H), 3.85 (s, 3H), 3.74 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.2, 161.6, 140.1, 128.5, 128.0, 125.8, 104.2, 94.9, 56.2, 28.8, 20.2; HRMS (EI): calcd for $C_{14}H_{14}O_3$, 230.0943; found 230.0952.

3-hexyl-4-methoxy-6-methyl-2*H*-pyran-2-one (2-8e). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-8e** (1.02 g, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 3.80 (s, 3H), 2.34 (t, J = 7.9 Hz, 2H), 2.19 (s, 3H), 1.40 (m, 2H), 1.26-1.23 (m, 6H), 0.82 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 165.4, 160.7,

105.4, 94.9, 56.0, 31.6, 29.1, 27.8, 23.1, 22.5, 20.1, 14.0; HRMS (EI): calcd for $C_{13}H_{20}O_3$, 224.1412; found 224.1409.

General Procedure for the Synthesis of 2-8f to 2-8h. To a mixture of K_2CO_3 (1.73 g, 12.5 mmol) and the corresponding pyrone **2-7** (5.00 mmol) in DMSO (10 mL) was added diethyl sulfate (0.693 g, 5.50 mmol). The mixture was stirred at room temperature for 90 min and poured into water (60 mL). The mixture was extracted with EtOAc and the combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated and purified by column chromatography.

4-ethoxy-6-methyl-2*H*-pyran-2-one (2-8f). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-8f** (0.601 g, 78%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (s, 1H), 5.31 (s, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 2.14 (s, 3H), 1.34 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 164.9, 161.8, 100.4, 87.5, 64.4, 19.6, 13.9; HRMS (EI): calcd for $C_8H_{10}O_3$, 154.0630; found 154.0628.

4-ethoxy-3,6-dimethyl-2*H*-pyran-2-one (2-8g). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-8g** (0.622 g, 74%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (s, 1H), 4.07 (q, *J* = 6.9 Hz, 2H), 2.21 (s, 3H), 1.87 (s, 3H), 1.38 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.3, 160.3, 100.6, 95.5, 64.7, 20.1, 14.7, 8.3 ; HRMS (EI): calcd for $C_9H_{12}O_3$, 168.0786; found 168.0785.

3-butyl-4-ethoxy-6-methyl-2*H*-pyran-2-one (2-8h). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-8h**

(0.767 g, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (s, 1H), 4.06 (q, *J* = 6.9 Hz, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 1.43-1.25 (m, 7H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 165.3, 160.5, 105.4, 95.5, 64.5, 30.0, 22.8, 22.4, 20.1, 14.7, 13.8; HRMS (EI): calcd for $C_{12}H_{18}O_3$, 210.1256; found 210.1259.

General Procedure for the Synthesis of 2-9a to 2-9h. SeO_2 (1.11 g, 10.0 mmol) was added to the corresponding pyrone **2-8** (2.00 mmol) in 1,4-dioxane (4 mL). The reaction mixture containing **2-8b** to **2-8h** was heated at 160 °C for 15 min while **2-8a** was heated at 150 °C for 15 min using microwave irradiation in a sealed tube. After which, the mixture was allowed to cool, saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined organic extract was dried over $MgSO_4$, concentrated and purified by column chromatography.

4-methoxy-6-oxo-6*H*-pyran-2-carbaldehyde (2-9a). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2 = 1:3:6) to afford **2-9a** (0.188 g, 61%) as a pale brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.14 (d, *J* = 1.9 Hz, 1H), 6.01 (d, *J* = 1.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 184.3, 169.0, 161.2, 153.7, 112.6, 94.6, 57.1; HRMS (EI): calcd for $C_7H_6O_4$, 154.0266; found 154.0265.

4-methoxy-5-methyl-6-oxo-6*H*-pyran-2-carbaldehyde (2-9b). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2= 1:4:8) to afford **2-9b** (0.239 g, 71%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.00 (s, 1H), 3.97 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 183.2, 163.3, 162.8, 152.3, 111.1, 101.9, 56.8, 9.5; HRMS (EI): calcd for $C_8H_8O_4$, 168.0423; found 168.0424.

5-butyl-4-methoxy-6-oxo-6*H*-pyran-2-carbaldehyde (2-9c). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2 = 1:6:12) to afford **2-9c** (0.319 g, 76%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.99 (s, 1H), 3.96 (s, 3H), 2.48 (t, *J* = 7.6 Hz, 2H), 1.47-1.41 (m, 2H), 1.35-1.31 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 163.3, 162.3, 152.4, 115.9, 101.8, 56.7, 29.7, 23.9, 22.6, 13.8; HRMS (EI): calcd for $C_{11}H_{14}O_4$, 210.0892; found 210.0893.

3-benzyl-4-methoxy-2-oxo-2*H*-pyran-6-carbaldehyde (2-9d). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2 = 1:4:8) to afford **2-9d** (0.366g, 75%) as a pale brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.65 (s, 1H), 7.26-7.15 (m, 5H), 4.03 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 184.0, 164.5, 161.9, 152.7, 138.7, 128.3, 128.2, 126.1, 111.6, 108.1, 57.6, 29.1; HRMS (EI): calcd for $C_{14}H_{12}O_4$, 244.0736; found 244.0735.

3-hexyl-4-methoxy-2-oxo-2*H*-pyran-6-carbaldehyde (2-9e). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2 = 1:6:12) to afford **2-9e** (0.338g, 71%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.99 (s, 1H), 3.95 (s, 3H), 2.48 (t, *J* = 7.9 Hz, 2H), 1.49-1.43 (m, 2H), 1.32-1.27 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 163.2, 162.5, 152.4, 115.9, 101.6, 56.7, 31.6, 29.2, 27.5, 24.2, 22.5, 14.0; HRMS (EI): calcd for $C_{13}H_{18}O_4$, 238.1205; found 238.1202.

4-ethoxy-2-oxo-2*H*-pyran-6-carbaldehyde (2-9f). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2 = 1:5:10) to afford **2-9f** (0.211 g g, 63%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 5.71 (d, *J* = 2.5 Hz, 1H), 4.8 (q, *J* = 6.9 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 168.1, 161.7, 153.8, 108.9, 94.9, 65.5, 13.9; HRMS (EI): calcd for $C_8H_8O_4$, 168.0423; found 168.0427.

4-ethoxy-3-methyl-2-oxo-2*H*-pyran-6-carbaldehyde (2-9g). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2 = 1:5:10) to afford **2-9g** (0.254 g, 70%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 6.96 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.97 (s, 1H), 1.43 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 162.9, 162.8, 152.2, 111.1, 103.1, 65.7, 14.8, 9.6; HRMS (EI): calcd for $C_9H_9O_3Br$, 182.0579; found 182.0581.

3-butyl-4-ethoxy-2-oxo-2*H*-pyran-6-carbaldehyde (2-9h). The residue was purified using flash chromatography (EtOAc:hexane:CH_2Cl_2 = 1:6:12) to afford **2-9h** (0.323 g, 77%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (s,1H), 6.94 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H), 1.48-1.41 (m, 5H), 1.35-1.28 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 162.7, 162.5, 152.3, 115.8, 102.6, 65.5, 29.6, 23.8, 22.5, 14.7, 13.8; HRMS (EI): calcd for $C_{12}H_{16}O_4$, 224.1049; found 224.1049.

General Procedure for the Synthesis of 2-9i to 2-9q. 3 M MeMgBr or 3 M EtMgBr in Et_2O (2.20 mmol) was added dropwise to the corresponding pyrones **2-9** (2.00 mmol) in THF. The mixture was allowed to stir at room

temperature for 30 min before quenching with saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2 and the combined organic extract was washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a brown residue. DMP (1.02 g, 2.40 mmol) was added to the residue dissolved in CH_2Cl_2 (5 mL) and the reaction mixture was stirred at room temperature for 1 hr. Subsequently, saturated $NaHCO_3$ solution (5 mL) and 15% $Na_2S_2O_3$ solution (5 mL) were added and the mixture was allowed to stir for an additional 15 min. After which, the mixture was extracted with CH_2Cl_2 and the combined organic extract was dried over $MgSO_4$, concentrated and purified by column chromatography.

6-acetyl-4-methoxy-2*H*-pyran-2-one (2-9i). The residue was purified using flash chromatography (EtOAc:hexane = 2:3) to afford **2-9i** (0.228 g, 68%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, J = 1.9 Hz, 1H), 5.70 (d, J = 1.9 Hz, 1H), 3.84 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 169.7, 162.2, 154.5, 103.9, 93.6, 56.4, 25.9; HRMS (EI): calcd for $C_8H_8O_4$, 168.0423; found 168.0425.

6-acetyl-4-methoxy-3-methyl-2*H*-pyran-2-one (2-9j). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-9j** (0.277 g, 76%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (s, 1H), 3.94 (s, 3H), 2.54 (s, 3H), 2.00 (d, J = 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 164.0, 163.2, 153.0, 109.7, 98.0, 56.7, 25.9, 9.4; HRMS (EI): calcd for $C_9H_{10}O_4$, 182.0579; found 182.0578.

4-methoxy-3-methyl-6-propionyl-2*H*-pyran-2-one (2-9k). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-9k**

(0.278 g, 71%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 1H), 3.91 (s, 3H), 2.90 (q, *J* = 7.2 Hz, 2H), 1.93 (s, 3H), 1.11 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 164.0, 163.1, 152.9, 109.2, 97.8, 56.6, 31.4, 9.2, 7.1; HRMS (EI): calcd for $C_{10}H_{12}O_4$, 196.0736; found 196.0739.

6-acetyl-3-butyl-4-methoxy-2*H*-pyran-2-one (2-9l). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-9l** (0.327 g, 73%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 3.89 (s, 3H), 2.46 (s, 3H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.41-1.36 (m, 2H), 1.31-1.23 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 163.9, 162.7, 153.1, 114.1, 98.0, 56.5, 29.6, 25.7, 23.6, 22.5, 13.7; HRMS (ESI) $[M+Na]^+$: calcd for $C_{12}H_{16}O_4Na$ 247.0946; found 247.0942.

3-butyl-4-methoxy-6-propionyl-2*H*-pyran-2-one (2-9m). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-9m** (0.290 g, 61%) as a pale yellow sticky liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1H), 3.91 (s, 3H), 2.92 (q, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 1H), 1.45-1.39 (m, 2H), 1.33-1.27 (m, 2H), 1.13 (t, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 164.1, 162.9, 153.1, 114.0, 97.9, 56.6, 31.5, 29.7, 23.7, 22.6, 13.8, 7.1; HRMS (EI): calcd for $C_{13}H_{18}O_4$, 238.1205; found 238.1208.

6-acetyl-3-benzyl-4-methoxy-2*H*-pyran-2-one (2-9n). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-9n** (0.384 g, 74%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.31 (m, 2H), 7.26-7.22 (m, 2H), 7.18-7.17 (m, 1H), 7.06 (s, 1H), 3.96 (s, 3H), 3.82

(s, 2H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 164.2, 162.7, 153.6, 138.9, 128.7, 128.3, 126.3, 112.7, 98.1, 56.8, 29.6, 25.8; HRMS (EI): calcd for $C_{15}H_{14}O_4$, 258.0892; found 258.0891.

6-acetyl-3-hexyl-4-methoxy-2*H*-pyran-2-one (2-9o). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-9o** (0.413 g, 82%) as a pale yellow sticky liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1H), 3.91 (s, 3H), 2.51 (s, 3H), 2.45 (t, *J* = 7.9 Hz, 2H), 1.45-1.41 (m, 2H), 1.28-1.25 (m, 6H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 164.0, 162.8, 153.2, 114.3, 98.1, 56.6, 31.6, 29.1, 27.5, 25.8, 24.0, 22.5, 14.0; HRMS (EI): calcd for $C_{14}H_{20}O_4$, 252.1362; found 252.1360.

6-acetyl-4-ethoxy-3-methyl-2*H*-pyran-2-one (2-9p). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-9p** (0.313 g, 80%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.56 (s, 3H), 2.03 (s, 3H), 1.46 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 163.4, 163.2, 152.8, 109.4, 98.6, 65.3, 25.7, 14.7, 9.3; HRMS (EI): calcd for $C_{10}H_{12}O_4$, 196.0736; found 196.0739.

6-acetyl-3-butyl-4-ethoxy-2*H*-pyran-2-one (2-9q). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-9q** (0.325 g, 68%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.50 (s, 3H), 2.48 (t, *J* = 7.6 Hz, 2H), 1.47-1.38 (m, 5H), 1.35-1.27 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 163.4, 163.0, 153.0, 114.3, 98.7, 65.3, 29.7, 25.8, 23.6, 22.5, 14.7, 13.8; HRMS (EI): calcd for $C_{13}H_{18}O_4$, 238.1205; found 238.1204.

General Procedure for the Synthesis of 2-10a to 2-10q. CBr_4 (0.464 g, 1.40 mmol) in CH_2Cl_2 (4 mL) was added to a solution of the corresponding pyrone **2-9** (1.00 mmol) and PPh_3 (0.734 g, 2.80 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred at room temperature for 30 min and thereafter, the solvent was removed under reduced pressure and the residue was purified by column chromatography.

6-(2,2-dibromovinyl)-4-methoxy-2*H*-pyran-2-one (2-10a). The residue was purified using flash chromatography (EtOAc:CH_2Cl_2 = 1:40) to afford **2-10a** (0.285 g, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09, (s, 1H), 6.35 (d, *J* = 2.6 Hz, 1H), 5.53 (d, *J* = 1.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 162.8, 155.4, 128.5, 103.5, 97.3, 89.9, 56.1; HRMS (EI): calcd for $C_8H_6O_3Br_2$, 307.8684; found 307.8678.

6-(2,2-dibromovinyl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-10b). The residue was purified using flash chromatography (EtOAc:CH_2Cl_2 = 1:50) to afford **2-10b** (0.295 g, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.64 (s, 1H), 3.89 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 163.9, 154.0, 128.9, 104.9, 98.1, 96.3, 56.4, 9.0; HRMS (EI): calcd for $C_9H_8O_3Br_2$, 321.8847; found 321.8840.

3-butyl-6-(2,2-dibromovinyl)-4-methoxy-2*H*-pyran-2-one (2-10c). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-10c** (0.347 g, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 1.9 Hz, 1H), 6.63 (s, 1H), 3.87 (d, *J* = 1.3 Hz, 3H), 2.40-2.39 (m, 2H), 1.45-1.42 (m, 2H), 1.32-1.31 (m, 2H), 0.91-0.88 (m, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 164.6, 163.5, 154.1, 128.9, 109.7, 98.2, 96.2, 56.4, 29.9, 23.5, 22.6, 13.9; HRMS (EI): calcd for $C_{12}H_{14}O_3Br_2$, 363.9310; found 363.9320.

3-benzyl-6-(2,2-dibromovinyl)-4-methoxy-2*H*-pyran-2-one (2-10d). The residue was purified using flash chromatography (EtOAc:hexane = 1:5) to afford **2-10d** (0.288 g, 72%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.32 (m, 2H), 7.24-7.23 (m, 2H), 7.18-7.14 (m, 2H), 6.63 (s, 1H), 3.91 (s, 3H), 3.76 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 163.4, 154.8, 139.5, 128.8 (2 carbons), 128.3, 126.2, 108.3, 98.3, 96.8, 56.6, 29.4; HRMS (EI): calcd for $C_{15}H_{12}O_3{}^{79}Br^{81}Br$, 399.9133; found 399.9136.

6-(2,2-dibromovinyl)-3-hexyl-4-methoxy-2*H*-pyran-2-one (2-10e). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-10e** (0.319 g, 81%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.63 (s, 1H), 3.87 (s, 3H), 2.40 (t, *J* = 7.6 Hz, 2H), 1.45-1.41 (m, 2H), 1.27 (s, 6H), 0.86 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 163.5, 154.1, 128.9, 109.7, 98.2, 96.1, 56.3, 31.6, 29.2, 27.6, 23.7, 22.6, 14.0; HRMS (EI): calcd for $C_{14}H_{18}O_3Br_2$, 391.9623; found 391.9638.

6-(2,2-dibromovinyl)-4-ethoxy-2*H*-pyran-2-one (2-10f). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-10f** (0.249 g, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.35 (s, 1H), 5.50 (s, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 163.0, 155.4, 128.5, 103.8, 97.1, 90.3, 64.9, 14.0; HRMS (EI): calcd for $C_9H_8O_3Br_2$, 321.8840; found 321.8841.

6-(2,2-dibromovinyl)-4-ethoxy-3-methyl-2*H*-pyran-2-one (2-10g). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-10g** (0.269 g, 80%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.61 (s, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 1.90 (s, 1H), 1.41 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 163.9, 153.7, 128.8, 104.8, 98.8, 96.0, 65.0, 14.7, 9.0; HRMS (EI): calcd for $C_{10}H_{10}O_3Br_2$, 335.8997; found 335.8996.

3-butyl-6-(2,2-dibromovinyl)-4-ethoxy-2*H*-pyran-2-one (2-10h). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-10h** (0.321 g, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 1H), 6.59 (s, 1H), 4.10 (q, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 1.46-1.37 (m, 5H), 1.34-1.26 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 163.6, 153.9, 128.9, 109.5, 98.9, 95.9, 64.9, 29.8, 23.3, 22.4, 14.7, 13.8; HRMS (EI): calcd for $C_{13}H_{16}O_3Br_2$, 377.9466; found 377.9468.

6-(1,1-dibromoprop-1-en-2-yl)-4-methoxy-2*H*-pyran-2-one (2-10i). The residue was purified using flash chromatography (EtOAc:CH_2Cl_2 = 1:40) to afford **2-10i** (0.285 g, 88%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (d, *J* = 2.5 Hz, 1H), 5.48 (d, *J* = 1.9 Hz, 1H), 3.81 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 163.5, 159.2, 134.7, 103.3, 94.9, 89.0, 56.1, 22.6; HRMS (EI): calcd for $C_9H_8O_3Br_2$, 321.8850; found 321.8840.

6-(1,1-dibromoprop-1-en-2-yl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-10j). The residue was purified using flash chromatography (EtOAc:CH_2Cl_2 = 1:50) to afford **2-10j** (0.287 g, 85%) as a white solid. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 6.42, (s, 1H), 3.89 (s, 3H), 2.14 (s, 3H), 1.93 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 164.5, 157.7, 135.3, 103.5, 98.1, 94.5, 56.4, 22.7, 8.7; HRMS (EI): calcd for $C_{10}H_{10}O_3Br_2$, 335.8997; found 335.8998.

6-(1,1-dibromobut-1-en-2-yl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-10k). The residue was purified using flash chromatography (EtOAc:CH_2Cl_2 = 1:50) to afford **2-10k** (0.292 g, 83%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (s, 1H), 3.88 (s, 3H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.90 (s, 3H), 1.03 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 (2 carbons), 157.1, 141.0, 103.3, 98.6, 94.2, 56.4, 29.8, 11.4, 8.7; HRMS (EI): calcd for $C_{11}H_{12}O_3Br_2$, 349.9153; found 349.9152.

3-butyl-6-(1,1-dibromoprop-1-en-2-yl)-4-methoxy-2*H*-pyran-2-one (2-10l). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-10l** (0.338 g, 89%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, 1H), 3.85 (s, 3H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H) 1.44-1.38 (m, 2H), 1.33-1.25 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H), NMR (125 MHz, $CDCl_3$) δ 164.6, 164.1, 157.7, 135.2, 108.0, 98.1, 94.3, 56.3, 29.8, 23.2, 22.6, 22.5, 13.8; HRMS (ESI) $[M+H]^+$: calcd for $C_{13}H_{17}O_3Br_2$ 378.9544; found 378.9532.

3-butyl-6-(1,1-dibromobut-1-en-2-yl)-4-methoxy-2*H*-pyran-2-one (2-10m). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-10m** (0.362 g, 93%) as a colorless sticky liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (s, 1H), 3.87 (s, 3H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 1.47-1.41 (m, 2H), 1.36-1.29 (m, 2H), 1.05 (t, *J* = 7.6 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 164.3, 157.4,

141.2, 108.1, 98.7, 94.1, 56.4, 29.9, 29.8, 23.3, 22.6, 13.9, 11.5; HRMS (EI): calcd for $C_{14}H_{18}O_3Br_2$, 391.9623; found 391.9635.

3-benzyl-6-(1,1-dibromoprop-1-en-2-yl)-4-methoxy-2*H*-pyran-2-one (2-10n). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-10n** (0.380 g, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.35 (m, 2H), 7.28-7.24 (m, 2H), 7.19-7.17 (m, 1H), 6.44 (s, 1H), 3.91 (s, 3H), 3.78 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.0, 158.4, 139.6, 135.2, 128.7, 128.2, 126.0, 106.9, 98.2, 94.6, 56.6, 29.2, 22.7; HRMS (EI): calcd for $C_{16}H_{14}O_3Br_2$, 413. 9289; found 413.9298.

6-(1,1-dibromoprop-1-en-2-yl)-3-hexyl-4-methoxy-2*H*-pyran-2-one (2-10o). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-10o** (0.318 g, 81%) as a colorless sticky liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, 1H), 3.85 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 2.11 (s, 3H), 1.44-1.41 (m, 2H), 1.26-1.25 (m, 6H), 0.83 (t, J = 5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 164.1, 157.7, 135.3, 108.2, 98.1, 94.3, 56.3, 31.6, 29.1, 27.6, 23.5, 22.6, 22.5, 14.0; HRMS (EI): calcd for $C_{15}H_{20}O_3Br_2$, 405.9779; found 405.9780.

6-(1,1-dibromoprop-1-en-2-yl)-4-ethoxy-3-methyl-2*H*-pyran-2-one (2-10p). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-10p** (0.266 g, 76%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (s, 1H), 4.13 (q, J = 6.9 Hz, 2H), 2.13 (s, 3H), 1.92 (s, 3H), 1.41 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 164.0, 157.4, 135.4, 103.5, 98.8, 94.3, 65.0, 22.7, 14.8, 8.8; HRMS (EI): calcd for $C_{11}H_{12}O_3Br_2$, 349.9153; found 349.9161.

3-butyl-6-(1,1-dibromoprop-1-en-2-yl)-4-ethoxy-2*H*-pyran-2-one (2-10q). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-10q** (0.320 g, 79%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 1H), 4.11 (q, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.12 (s, 3H), 1.47-1.37 (m, 5H), 1.35-1.28 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 164.0, 157.6, 135.4, 108.2, 98.8, 94.2, 64.9, 29.8, 23.2, 22.6, 22.5, 14.7, 13.9; HRMS (EI): calcd for $C_{14}H_{18}O_3Br_2$, 391.9623; found 391.9640.

General Procedure for the Synthesis of 2-2a to 2-2q. To a solution of the corresponding pyrone **2-10** (0.80 mmol) and triethylamine (0.364 g, 3.60 mmol) in DMF (1.5 mL) was added dimethylphosphite (0.352g, 3.20 mmol). The reaction mixture was stirred at room temperature for 1 h following which water was added to the mixture and extracted with Et_2O. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography.

(*E*)-6-(2-bromovinyl)-4-methoxy-2*H*-pyran-2-one (2-2a). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-2a** (0.181 g, 98%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 13.9 Hz, 1H), 6.62 (d, *J* = 13.3 Hz, 1H), 5.83 (d, *J* = 2.5 Hz, 1H), 5.49 (d, *J* = 2.6 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 163.1, 156.3, 128.2, 116.3, 101.4, 89.5, 56.0; HRMS (EI): calcd for $C_8H_7O_3Br$, 229.9579; found 229.9585.

(*E*)-6-(2-bromovinyl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-2b). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to

afford **2-2b** (0.182 g, 93%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 13.2 Hz, 1H), 6.64 (d, *J* = 13.3 Hz, 1H), 6.05 (s, 1H), 3.87 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.0, 154.9, 128.5, 115.4, 104.0, 96.0, 56.3, 8.8; HRMS (EI): calcd for $C_9H_9O_3Br$, 243.9735; found 243.9746.

(*E*)-6-(2-bromovinyl)-3-butyl-4-methoxy-2*H*-pyran-2-one (2-2c). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-2c** (0.218 g, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 13.9 Hz, 1H), 6.66 (d, *J* = 13.3 Hz, 1H), 6.08 (s, 1H), 3.87 (s, 3H), 2.41 (t, *J* = 7.6 Hz, 2H), 1.47-1.41 (m, 2H), 1.36-1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 165.0, 163.8, 155.1, 128.6, 115.4, 108.9, 96.2, 56.3, 30.0, 23.4, 22.6, 13.9; HRMS (EI): calcd for $C_{12}H_{15}O_3Br$, 286.0205; found 286.0200.

(*E*)-3-benzyl-6-(2-bromovinyl)-4-methoxy-2*H*-pyran-2-one (2-2d). The residue was purified using flash chromatography (EtOAc:hexane = 1:5) to afford **2-2d** (0.210 g, 82%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H), 7.18-7.15 (m, 1H), 6.64 (d, *J* = 13.9 Hz, 1H), 6.06 (s, 1H), 3.88 (s, 3H), 3.76 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 163.6, 155.7, 139.6, 128.6, 128.4, 128.2, 126.0, 116.0, 107.5, 96.1, 56.4, 29.3; HRMS (EI): calcd for $C_{15}H_{13}O_3Br$, 320.0048; found 320.0039.

***(E)*-6-(2-bromovinyl)-3-hexyl-4-methoxy-2*H*-pyran-2-one (2-2e).** The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-2e** (0.226 g, 90%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 13.9 Hz, 1H), 6.63 (d, *J* = 13.9 Hz, 1H), 6.05 (s, 1H), 3.84 (s, 3H),

2.38 (t, *J* = 7.9 Hz, 2H), 1.43-1.30 (m, 2H), 1.29-1.25 (m, 6H), 0.85 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 163.7, 155.0, 128.5, 115.3, 108.9, 96.1, 56.2, 31.6, 29.1, 27.8, 23.6, 22.5, 14.0; HRMS (EI): calcd for $C_{14}H_{19}O_3Br$, 314.0518; found 314.0517.

***(E)*-6-(2-bromovinyl)-4-ethoxy-2*H*-pyran-2-one (2-2f).** The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-2f** (0.178 g, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 13.9 Hz, 1H), 6.61 (d, *J* = 13.9 Hz, 1H), 5.81 (d, *J* = 1.9 Hz, 1H), 5.45 (d, *J* = 1.9 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 163.2, 156.1, 128.2, 116.0, 101.6, 89.8, 64.8, 13.9; HRMS (EI): calcd for $C_9H_9O_3Br$, 243.9735; found 243.9736.

***(E)*-6-(2-bromovinyl)-4-ethoxy-3-methyl-2*H*-pyran-2-one (2-2g).** The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-2g** (0.171 g, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 13.3 Hz, 1H), 6.62 (d, *J* = 13.9 Hz, 1H), 6.02 (s, 1H), 4.10 (q, *J* = 6.9 Hz, 2H), 1.98 (s, 3H), 1.40 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 164.1, 154.7, 128.5, 115.2, 104.0, 96.7, 64.9, 14.7, 8.9; HRMS (EI): calcd for $C_{10}H_{11}O_3Br$, 257.9892; found 257.9890

***(E)*-6-(2-bromovinyl)-3-butyl-4-ethoxy-2*H*-pyran-2-one (2-2h).** The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-2h** (0.192 g, 80%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 13.9 Hz, 1H), 6.62 (d, *J* = 13.9 Hz, 1H), 6.01 (s, 1H), 4.09 (q, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 1.46-1.38 (m, 5H), 1.35-1.27 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 163.8, 154.9,

128.6, 115.2, 108.9, 96.8, 64.8, 29.9, 23.3, 22.5, 14.7, 13.9; HRMS (EI): calcd for $C_{13}H_{17}O_3Br$, 300.0361; found 300.0355.

(*E*)-6-(1-bromoprop-1-en-2-yl)-4-methoxy-2*H*-pyran-2-one (2-2i). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-2i** (0.180 g, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 1.3 Hz, 1H), 6.02 (d, *J* = 1.9 Hz, 1H), 5.49 (d, *J* = 1.9 Hz, 1H), 3.82 (s, 3H), 2.03 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 163.3, 158.3, 131.5, 115.5, 99.1, 89.1, 56.0, 15.6; HRMS (EI): calcd for $C_9H_9O_3Br$, 243.9735; found 243.9741.

(*E*)-6-(1-bromoprop-1-en-2-yl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-2j). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-2j** (0.196 g, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 1.3 Hz, 1H), 6.21 (s, 1H), 3.91 (s, 3H), 2.07 (d, *J* = 1.3 Hz, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 164.2, 157.0, 131.8, 114.9, 103.6, 93.4, 56.2, 15.7, 8.7; HRMS (EI): calcd for $C_{10}H_{11}O_3Br$, 257.9892; found 257.9892.

(*E*)-6-(1-bromobut-1-en-2-yl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-2k). The residue was purified using flash chromatography (EtOAc:hexane = 1:5) to afford **2-2k** (0.205 g, 94%) as a white solid. 1H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.23 (s, 1H), 3.89 (s, 3H), 2.53 (q, *J* = 7.6 Hz, 2H), 1.89 (s, 3H), 1.09 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 164.4, 156.5, 137.9, 114.1, 103.5, 93.4, 56.3, 23.2, 12.3, 8.7; HRMS (EI): calcd for $C_{11}H_{13}O_3Br$, 272.0048; found 272.0038.

(*E*)-6-(1-bromoprop-1-en-2-yl)-3-butyl-4-methoxy-2*H*-pyran-2-one (2-2l). The residue was purified using flash chromatography (EtOAc:hexane = 1:8) to afford **2-2l** (0.232 g, 96%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 1.3 Hz, 1H), 6.20 (s, 1H), 3.89 (s, 3H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.06 (d, *J* = 1.3 Hz, 1H), 1.46-1.39 (m, 2H), 1.35-1.28 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 163.9, 157.2, 131.8, 114.8, 108.4, 93.5, 56.2, 30.0, 23.2, 22.6, 15.7, 13.9; HRMS (EI): calcd for $C_{13}H_{17}O_3Br$, 300.0361; found 300.0357.

(*E*)-6-(1-bromobut-1-en-2-yl)-3-butyl-4-methoxy-2*H*-pyran-2-one (2-2m). The residue was purified using flash chromatography (EtOAc:hexane = 1:8) to afford **2-2m** (0.231 g, 92%) as a colorless sticky liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.25 (s, 1H), 3.91 (s, 3H), 2.56 (q, *J* = 7.6 Hz, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 1.48-1.42 (m, 2H), 1.38-1.30 (m, 2H), 1.13 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 164.0, 156.6, 137.9, 114.0, 108.4, 93.4, 56.2, 30.0, 23.2, 23.1, 22.6, 13.9, 12.2; ; HRMS (EI): calcd for $C_{14}H_{19}O_3Br$, 314.0518; found 314.0515.

(*E*)-3-benzyl-6-(1-bromoprop-1-en-2-yl)-4-methoxy-2*H*-pyran-2-one (2-2n). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-2n** (0.238 g, 89%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 3H), 7.29-7.25 (m, 2H), 7.20-7.17 (m, 1H), 6.25 (s, 1H), 3.95 (s, 3H), 3.79 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 163.7, 157.8, 139.7, 131.8, 128.6, 128.2, 126.0, 115.3, 107.1, 93.5, 56.4, 29.2, 15.7; HRMS (EI): calcd for $C_{16}H_{15}O_3Br$, 334.0205; found 334.0203.

(*E*)-6-(1-bromoprop-1-en-2-yl)-3-hexyl-4-methoxy-2*H*-pyran-2-one (2-2o). The residue was purified using flash chromatography (EtOAc:hexane = 1:8) to afford **2-2o** (0.241 g, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.20 (s, 1H), 3.89 (s, 3H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.06 (s, 3H), 1.44-1.41 (m, 2H), 1.30-1.27 (m, 6H), 0.86 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 163.8, 157.2, 131.8, 114.8, 108.4, 93.5, 56.2, 31.7, 29.2, 27.8, 23.5, 22.6, 15.7, 14.0; HRMS (EI): calcd for $C_{15}H_{21}O_3Br$, 328.0674; found 328.0665.

(*E*)-6-(1-bromoprop-1-en-2-yl)-4-ethoxy-3-methyl-2*H*-pyran-2-one (2-2p). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-2p** (0.196 g, 90%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.17 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.04 (s, 3H), 1.89 (s, 3H), 1.41 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 164.3, 156.8, 131.7, 114.6, 103.5, 94.1, 64.9, 15.6, 14.7, 8.8; HRMS (EI): calcd for $C_{11}H_{13}O_3Br$, 272.0048; found 272.0044.

(*E*)-6-(1-bromoprop-1-en-2-yl)-3-butyl-4-ethoxy-2*H*-pyran-2-one (2-2q). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-2q** (0.216 g, 86%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.17 (s, 1H), 4.13 (q, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 2.05 (s, 3H), 1.47-1.39 (m, 5H), 1.35-1.28 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 163.9, 157.0, 131.8, 114.7, 108.4, 94.2, 64.8, 30.0, 23.1, 22.5, 15.7, 14.7, 13.9; HRMS (EI): calcd for $C_{14}H_{19}O_3Br$, 314.0518; found 314.0516.

General Procedure for the Synthesis of 2-2r and 2-2s. Acetic acid (1 mL) and 45% aqueous HBr (1 mL) were added to **2-2a** or **2-2b** (0.500 mmol) and the mixture was stirred at 90 °C for 45 min and 2 h for **2-2a** and **2-2b** respectively. Thereafter, the mixture was cooled to room temperature and 3 M aqueous NaOH was added until the reaction mixture achieved pH 4~5. Saturated NaCl solution (5 mL) was then added and the mixture was extracted with EtOAc. The combined organic extract was dried over $MgSO_4$ and purified using flash chromatography (MeOH:CH_2Cl_2 = 1:30 with 0.5% AcOH).

(*E*)-6-(2-bromovinyl)-4-hydroxy-2*H*-pyran-2-one (2-2r). 2-2r (76 mg, 70%) was obtained as a brown solid. ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.31-7.28 (d, J = 13.9 Hz, 1H), 6.94 (d, J = 13.9 Hz, 1H), 6.19 (d, J = 1.9 Hz, 1H), 5.45 (d, J = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 169.1, 162.0, 156.8, 128.7, 114.3, 101.2, 90.7; HRMS (EI): calcd for $C_7H_5O_3Br$, 215.9422; found 215.9421.

(*E*)-6-(2-bromovinyl)-4-hydroxy-3-methyl-2*H*-pyran-2-one (2-2s). 2-2s (0.106 g, 92%) was obtained as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4, (br, 1H), 7.24 (d, J = 13.9 Hz, 1H), 7.06 (d, J = 13.9 Hz, 1H), 6.23 (s, 1H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 163.5, 153.5, 129.1, 113.9, 101.7, 99.6, 8.7; HRMS (EI): calcd for $C_8H_7O_3Br$, 229.9579; found 229.9589.

Synthesis of *N*-(3-bromopropyl)-5-(dimethylamino)naphthalene-1-sulfonamide (2-12). To dansyl chloride (0.270 g, 1.00 mmol) and compound **2-11** (0.438 g, 2.00 mmol) in DMF (2 mL) was added triethylamine (0.202 g, 2.00 mmol). The reaction mixture was stirred at room temperature for 20 min

after which water was added and the mixture was extracted with Et_2O. The combined organic extract organic extract was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated. The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-12** (0.368 g, 99%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.9 Hz, 1H), 8.30-8.25 (m, 2H), 7.58-7.51 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 5.00 (t, *J* = 6.6 Hz, 2H), 3.30 (t, *J* = 6.3 Hz, 2H), 3.08-3.04 (m, 2H), 2.89 (s, 6H), 1.96-1.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 134.4, 130.6, 129.9, 129.7, 129.5, 128.5, 123.2, 118.5, 115.2, 45.4, 41.4, 32.3, 30.1; HRMS (EI): calcd for $C_{15}H_{19}N_2O_2BrS$, 370.0351; found 370.0341.

Synthesis of *tert*-butyl 3-(2-hydroxyethoxy)propylcarbamate (2-14). 60% NaH in mineral oil (0.192 g, 4.80 mmol) was added to ethylene glycol (0.297 g, 4.80 mmol) in DMF. After the evolution of hydrogen gas had ceased, compound **2-13** (0.571 g, 2.40 mmol) was added and the reaction mixture was stirred overnight at room temperature. EtOAc was added and the mixture was washed with H_2O thrice followed by saturated NaCl. The organic layer was dried over $MgSO_4$, concentrated and purified using flash chromatography (EtOAc:hexane = 1:1) to afford **2-14** (0.273 g, 54%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (s, 1H), 3.67 (t, *J* = 4.7 Hz, 2H), 3.52-3.47 (m, 4H), 3.19 (s, 2H), 2.82 (s, 1H), 1.73-1.68 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 79.0, 72.3, 68.6, 61.5, 37.8, 29.8, 28.3; HRMS (EI): calcd for $C_{10}H_{21}NO_4$, 219.1471; found 219.1474.

Synthesis of 5-(dimethylamino)-*N*-(3-(2-hydroxyethoxy)propyl)naphthalene-1-sulfonamide (2-15). TFA (0.50 mL)

was added to **2-14** (0.262 g, 1.20 mmol) in CH_2Cl_2 and stirred for 1 h at room temperature and after which TFA and CH_2Cl_2 were removed under reduced pressure. To the residue was added CH_2Cl_2 (2 mL), dansyl chloride (0.389 g, 1.44 mmol) and triethylamine (0.30 mL) and the reaction mixture was stirred at room temperature for 30 min. Water was added and the mixture was extracted with EtOAc. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$ and purified using flash chromatography to afford **2-15** (0.321 g, 76%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.8 Hz, 1H), 8.31 (d, *J* = 8.2, 1H), 8.22-8.20 (m, 1H), 7.54-7.47 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 5.78 (t, *J* = 6.0 Hz, 1H), 3.65 (t, *J* = 4.7 Hz, 2H), 3.41-3.37 (m, 4H), 3.03-2.99 (m, 2H), 2.86 (s, 6H), 1.66-1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 134.8, 130.2, 129.8, 129.5, 129.3, 128.2, 123.1, 118.9, 115.1, 71.9, 68.9, 61.5, 45.3, 41.3, 28.9; HRMS (EI): calcd for $C_{17}H_{24}N_2O_4S$, 352.1457; found 352.1451.

Synthesis of *N*-(3-(2-bromoethoxy)propyl)-5-(dimethylamino)naphthalene-1-sulfonamide (2-16). CBr_4 (0.370 g, 1.12 mmol) in CH_2Cl_2 (2 mL) was added to a solution of **2-15** (0.282 g, 0.80 mmol) and PPh_3 (0.587 g, 2.24 mmol) in CH_2Cl_2 (4 mL) and stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-16** (0.249 g, 75%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.2 Hz, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 8.2 (d, *J* = 7.0 Hz, 1H), 7.55-7.48 (m, 2H), 7.17 (d, *J* = 7.6 Hz, 1H), 5.46 (s, 1H), 3.54 (m, 2H), 3.39-3.31 (m, 4H), 3.04-3.01 (m, 2H), 2.87 (s, 6H), 1.66-1.64 (m, 2H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 151.8, 134.7, 130.2, 129.8, 129.5, 129.4, 128.2, 123.1, 118.9, 115.1, 70.4, 69.2, 45.3, 41.5, 30.4, 28.9; HRMS (EI): calcd for $C_{17}H_{23}N_2O_3BrS$, 414.0607; found 414.0613. HRMS (EI): calcd for $C_{17}H_{23}N_2O_3BrS$, 414.0613; found 414.0607.

General Procedure for the Synthesis of 2-2t and 2-2u Compounds **2-12** or **2-16** (0.39 mmol) was added to a mixture of **2-2r** (0.30 mmol) and K_2CO_3 (0.39 mmol) in DMSO and stirred at 85 °C for 45 min. Water was added and the mixture was extracted with Et_2O. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$ and purified using flash chromatography**.**

(*E*)-*N*-(3-(6-(2-bromovinyl)-2-oxo-2*H*-pyran-4-yloxy)propyl)-5-(dimethylamino)naphthalene-1-sulfonamide (2-2t). The residue was purified using flash chromatography to afford **2-2t** (79.0 mg, 52%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.8 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 7.51-7.47 (m, 2H), 7.24 (d, *J* = 13.9 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.54 (d, *J* = 13.3 Hz, 1H), 5.62-5.57 (m, 2H), 5.19 (d, *J* = 1.9 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.09-3.06 (m, 2H), 2.86 (m, 6H), 1.86-1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 163.0, 156.0, 152.0, 134.2, 130.6, 129.8, 129.7, 129.5, 128.4, 128.1, 122.9, 118.4, 116.1, 115.1, 101.3, 89.9, 65.7, 45.3, 39.4, 28.2; HRMS (EI): calcd for $C_{22}H_{23}N_2O_5BrS$, 506.0511; found 506.0518.

(*E*)-*N*-(3-(2-(6-(2-bromovinyl)-2-oxo-2*H*-pyran-4-yloxy)ethoxy)propyl)-5-(dimethylamino)naphthalene-1-sulfonamide (2-2u). The residue was purified using flash chromatography to afford **2-2u** (82.7 mg, 50%) as a pale

yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.2 Hz, 1H), 8.27 (d, *J* = 8.8 Hz, 1H), 8.21 (d, *J* = 6.3 Hz, 1H), 7.51-7.47 (m, 2H), 7.23 (d, *J* = 13.9 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 13.9 Hz, 1H), 6.02 (d, *J* = 1.9 Hz, 1H), 5.62 (t, *J* = 5.7 Hz, 1H), 5.49 (d, *J* = 2.6 Hz, 1H), 4.01 (t, *J* = 4.4 Hz, 2H), 3.61 (t, *J* = 4.4 Hz, 2H), 3.45 (t, *J* = 5.7 Hz, 2H), 3.04-3.00 (m, 2H), 2.87 (s, 6H), 1.69-1.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 163.1, 156.3, 151.9, 134.7, 130.3, 129.8, 129.6, 129.5, 128.3, 128.1, 123.1, 118.7, 116.1, 115.1, 101.6, 90.0, 69.9, 68.0, 68.0, 45.3, 41.8, 28.6; HRMS (ESI) $[M+Na]^+$: calcd for $C_{24}H_{27}N_2O_6BrS$, 573.0665; found 573.0656.

Synthesis of methyl 3-chloro-1*H*-pyrrole-2-carboxylate (2-19). 2-Methyl-1-pyrroline **2-17** (0.831 g, 10.0 mmol) was added to a suspension of *N*-cholorosuccinimide (10.7 g, 80.0 mmol) in THF (25 mL) and the reaction mixture was heated at 55 °C for 20 min. After the reaction mixture was cooled to room temperature, water was added and the mixture was extracted with hexane. The combined organic extract was concentrated under reduced pressure to afford **2-18** which was directly used for the next step. Compound **2-18** was dissolved in MeOH (10 mL) and cooled to 0 °C. 3 M MeONa in MeOH (20 mL, 60.0 mmol) was added dropwise over 5 min and thereafter, the reaction mixture was warmed to room temperature and stirred for an additional 30 min. The mixture was acidified using 2 M HCl and extracted with EtOAc. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated and the residue purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-19** (1.50 g, 94%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (br, 1H), 6.86 (s, 1H), 6.23 (s, 1H), 3.89 (s, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 160.9, 122.0, 119.2, 118.2, 111.9, 51.6; HRMS (EI): calcd for $C_6H_6NO_2Cl$, 159.0087; found 159.0088.

Synthesis of 3-chloro-1*H*-pyrrole-2-carbaldehyde (2-20). 2 M $LiAlH_4$ in THF solution (4.80 mL, 9.60 mmol) was added dropwise to **2-19** (1.28 g, 8.00 mmol) in THF (15 mL) at -20 °C. The reaction mixture was warmed to 0 °C and stirred for 30 min before quenching with EtOAc (5 mL). Water (20 mL) and 2 M aqueous NaOH (20 mL) was added to the reaction mixture and the solid formed was filtered and washed with EtOAc. The filtrate was extracted with EtOAc and the combined organic extract was washed with saturated NaCl solution and then concentrated to obtain the crude alcohol product. 2-iodoxybenzoic acid (5.60 g, 20.0 mmol) was dissolved in DMSO (20 mL) before the addition of $NaHCO_3$ (4.03 g, 48.0 mmol) and the crude alcohol product. The mixture was stirred at room temperature for 16 h and quenched with 0.5 M aqueous NaOH (150 mL). The solid was filtered and washed with EtOAc and the filtrate was extracted with EtOAc. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated and the residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-20** (0.777 g, 75%) as a pale brown solid. ^1H NMR (500 MHz, $CDCl_3$) δ 10.7 (br, 1H), 9.63 (s, 1H), 7.10-7.08 (m, 1H), 6.29-6.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 127.7, 126.3, 125.3, 111.6; HRMS (EI): calcd for $C_5H_4NO_2Cl$, 128.9981; found 129.9977.

Synthesis of 3-chloro-1-(methylsulfonyl)-1*H*-pyrrole-2-carbaldehyde (2-21). 60% NaH in mineral oil (0.132 g, 3.30 mmol) was added to **2-20** (0.388 g, 3.00 mmol) in THF portionwise. After evolution of hydrogen gas had ceased,

methanesulfonyl chloride (0.378 g, 3.30 mmol) was added and the reaction mixture was stirred at room temperature for 20 min. Subsequently, the solvent was removed and the residue was purified by flash chromatography (EtOAc:hexane = 1:3) to afford **2-21** (0.573 g, 92%) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.58-7.57 (d, *J* = 3.2 Hz, 1H), 6.37 (d, *J* = 3.2 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 132.5, 129.2, 127.2, 112.2, 42.9; HRMS (EI): calcd for $C_6H_6NO_3ClS$, 206.9757; found 206.9755.

Synthesis of ethyl 3-chlorothiophene-2-carboxylate (2-23), To a solution of 2-acetyl-3-chlorothiophene **2-22** (0.321 g, 2.00 mmol) in EtOH was added CuO (0.318 g , 4.00 mmol), I_2 (1.02 g , 4.00 mmol) and pyridine (0.632 g, 8.00 mmol) and the mixture was refluxed for 16 h. After which, K_2CO_3 (0.552 g, 4.00 mmol) was added carefully and the mixture was refluxed for an additional 2 h. The mixture was then cooled to room temperature, filtered and the filtrate was concentrated under reduced pressure. 5% $Na_2S_2O_3$ was added to the residue and the reaction mixture was extracted with EtOAc. The combined organic extract was dried over $MgSO_4$, concentrated and purified using flash chromatography (EtOAc:hexane = 1:20) to afford **2-23** (0.294 g, 77%) as a yellow syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.7 Hz, 1H), 6.99 (d, *J* = 5.1 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 131.3, 130.1, 130.1, 125.9, 61.3, 14.2; HRMS (EI): calcd for $C_7H_7O_2ClS$, 189.9855; found 189.9858.

Synthesis of 3-chlorothiophene-2-carbaldehyde (2-24). 2 M $LiAlH_4$ in THF solution (0.912 mL, 1.83 mmol) was added dropwise to **2-23** (0.290 g,

1.52 mmol) in THF (6 mL) at 0 °C. The reaction mixture was stirred for 30 min before quenching with EtOAc (2 mL). Water (10 mL) and 2 M aqueous NaOH (10 mL) was added to the reaction mixture and the solid that formed was filtered and washed with EtOAc. The filtrate was extracted with EtOAc and the combined organic extract was washed with saturated NaCl solution and concentrated. The residue obtained was dissolved in CH_2Cl_2 (8 mL). DMP (0.776 g, 1.83 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. Subsequently, saturated $NaHCO_3$ solution (5 mL) and 15% $Na_2S_2O_3$ solution (5 mL) was added and the mixture was allowed to stir for an additional 15 min. After which, the mixture was extracted with CH_2Cl_2 and the combined organic extract was dried over $MgSO_4$ and concentrated. The residue was purified using flash chromatography (EtOAc:hexane = 1:15) to afford **2-24** (0.189 g, 85%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0, (s, 1H), 7.71 (d, *J* = 5.0 Hz, 1H), 7.06(d, *J* = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.7, 135.6, 134.4, 134.2, 129.4; HRMS (EI): calcd for C_5H_3OClS, 145.9593; found 145.9592.

General Procedures for the Synthesis of 2-26a to 2-26d. CBr_4 (0.345 g, 1.04 mmol) in CH_2Cl_2 (2 mL) was added to a solution of PPh_3 (0.545 g, 2.08 mmol) and **2-21**, **2-24**, **2-25a** or **2-25b** (0.800 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 30 min, concentrated and purified by column chromatography

3-chloro-2-(2,2-dibromovinyl)-1-(methylsulfonyl)-1*H*-pyrrole (2-26a). The residue was purified using flash chromatography (EtOAc:hexane = 1:10) to afford **2-26a** (0.194 g, 85%) as a pale brown solid. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.40 (s, 1H), 7.19 (d, *J* = 3.2 Hz, 1H), 6.33 (d, *J* = 3.8 Hz, 1H), 3.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.1, 124.7, 122.1, 119.3, 113.4, 98.5, 42.9; HRMS (EI): calcd for $C_7H_6NO_2Br_2ClS$, 360.8175; found 360.8177.

3-chloro-2-(2,2-dibromovinyl)thiophene (2-26b). The residue was purified using flash chromatography (EtOAc:hexane = 1:60) to afford **2-26b** (0.205 g, 92%) as a pale yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.38 (d, *J* = 5.7 Hz, 1H), 6.96 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.9, 128.1, 127.2, 127.0, 126.1, 89.0; calcd for $C_6H_3Br_2ClS$, 299.8011; found 299.8013.

1-chloro-2-(2,2-dibromovinyl)benzene (2-26c). The residue was purified using flash chromatography with hexane as the eluent to afford **2-26c** (0.226 g, 95%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.64 (m, 1H), 7.57 (s, 1H), 7.41-7.39 (m, 1H), 7.30-7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 134.1. 133.0. 130.1. 129.7. 129.5. 126.5. 92.8; HRMS (EI): calcd for $C_8H_5Br_2Cl$, 293.8447; found 293.8443.

1-chloro-3-(2,2-dibromovinyl)benzene (2-26d). The residue was purified using flash chromatography with hexane as the eluent to afford **2-26d** (0.228 g, 96%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.43 (s, 1H), 7.40-7.39 (m, 1H), 7.31-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 135.5, 134.3, 129.6, 128.6, 128.2, 126.6, 91.3; HRMS (EI): calcd for $C_8H_5Br_2Cl$, 293.8447; found 293.8443.

General Procedure for the Synthesis of 2-4a to 2-4d. To a solution of **2-26** (0.735 mmol) and triethylamine (0.334 g, 0.331 mmol) in DMF (1.5 mL)

was added dimethylphosphite (0.323 g, 0.294 mmol) and the reaction mixture was stirred at room temperature for 1 h. Thereafter, water was added to the mixture and extracted with Et_2O. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography.

2-(2-bromovinyl)-3-chloro-1-(methylsulfonyl)-1*H*-pyrrole (2-4a). The residue was purified using flash chromatography (EtOAc:hexane = 1:10) to afford a pale brown solid **2-4a** (0.147 g, 97%) as a mixture of E/Z isomers in *ca.* 2:1 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of E/Z isomers) δ 7.40 (d, *J* = 13.9 Hz, 1H), 7.19 (d *J* = 3.2 Hz, 1H), 7.16-7.13 (m, 1.8H), 6.77 (d, *J* = 7.6 Hz, 0.4H), 6.34 (d, *J* = 3.2 Hz, 0.4 H), 6.30 (d, *J* = 3.8 Hz, 1H), 3.14 (s, 3H), 3.08 (s, 1.3H); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of E/Z isomers) δ 125.2, 124.2, 122.8, 122.6, 122.0, 121.6, 118.8, 117.5, 115.5, 113.6, 113.3, 112.6, 42.8, 42.7; HRMS (EI): calcd for $C_7H_7NO_2BrClS$, 282.9069; found 282.9069.

2-(2-bromovinyl)-3-chlorothiophene (2-4b). The residue was purified using flash chromatography with hexane as the eluent to afford a pale yellow liquid **2-4b** (0.150 g, 92%) as a mixture of E/Z isomers in *ca* 2:1 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.2 Hz, 0.4H), 7.44 (d, *J* = 5.7 Hz, 0.4H), 7.30 (d, *J* = 13.9 Hz, 1H), 7.20 (d, *J* = 5.0 Hz, 1H), 7.02 (d, *J* = 5.7 Hz, 0.4H), 6.92 (d, *J* = 5.1 Hz, 1H), 6.765 (d, *J* = 14.5 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 0.4H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6, 131.0, 128.3, 127.4, 127.1, 127.0, 125.9, 123.8, 123.8, 123.4, 107.2, 106.1; HRMS (EI): calcd for C_6H_4BrClS, 221.8096; found 221.8095.

(*E*)-1-(2-bromovinyl)-2-chlorobenzene (2-4c). The residue was purified using flash chromatography with hexane as the eluent to afford **2-4c** (0.150 g, 94%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 13.9 Hz, 1H), 7.41-7.36 (m, 2H), 7.24-7.22 (m, 2H), 6.81 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 133.8, 132.5, 129.9, 129.3, 127.0, 126.9, 109.2; HRMS (EI): calcd for C_8H_6BrCl, 215.9341; found 215.9342.

(*E*)-1-(2-bromovinyl)-3-chlorobenzene (2-4d). The residue was purified using flash chromatography with hexane as the eluent to afford **2-4d** (0.153 g, 96%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 3H), 7.20-7.19 (m, 1H), 7.07 (d, *J* = 13.9 Hz, 1H), 6.83 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 135.9, 134.8, 130.0, 128.2, 126.0, 124.3, 108.1; HRMS (EI): calcd for C_8H_6BrCl, 215.9341; found 215.9343.

Synthesis of 2-((1*E*,3*E*,5*E*)-hepta-1,3,5-trienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2-28). A mixture of boronate **2-27** (1.27 g, 6.00 mmol) and 2,4-hexadienal (0.192 g, 2.00 mmol) in THF (3 mL) was added to a suspension of $CrCl_2$ (2.46 g, 20.0 mmol) and LiI (1.61 g, 12.0 mmol) in THF (20 mL) and the mixture was stirred at room temperature for 6 h. Thereafter the reaction mixture was poured into water (120 mL) and the mixture was extracted with Et2O. The combined organic extract was washed with saturated NaCl solution,dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified using a short column (*ca.* 5 cm) of silica gel (EtOAc:hexane = 1:40) to afford **2-28** (0.361 g, 82%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 10.7, 17.7 Hz, 1H), 6.32 (dd, *J* = 10.7, 15.1 Hz, 1H), 6.19-6.07 (m, 2H), 5.84-5.77 (m, 1H), 5.50 (d, *J* = 17.7 Hz,

1H), 1.80-1.77 (m, 3H), 1.26 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 136.7, 132.5, 131.9, 131.5, 83.1, 24.7, 18.4; HRMS (EI): calcd for $C_{13}H_{21}O_2B$, 220.1635; found 220.1634.

Synthesis of 4-methoxy-3-methyl-6-((1*E*,3*E*,5*E*,7*E*)-nona-1,3,5,7-tetraenyl)-2*H*-pyran-2-one (2-29). Pd_2dba_3 (5.5 mg, 6.0 μmol) and $AsPh_3$ (9.2 mg, 30 μmol) was added to THF (2 mL), followed by **2-2b** (48.6 mg, 0.200 mmol) and 1.8 M aqueous KOH (0.222 mL, 0.400 mmol). **2-28** (48.4 mg, 0.220 mmol) was dissolved in THF (0.5 mL) and added dropwise to the reaction mixture over 5 min with stirring. The reaction mixture was stirred for 1 h at room temperature and quenched with saturated NH_4Cl. EtOAc was added and the mixture was washed with H_2O thrice followed by saturated NaCl solution. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified using flash chromatography (acetone:CH_2Cl_2 = 1:100) to afford **2-29** (44.4 mg, 86%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 11.3, 15.1 Hz, 1H), 6.50 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.37-6.24 (m, 2H), 6.20-6.10 (m, 2H), 6.03-6.00 (m, 2H), 5.87-5.80 (m, 1H), 3.87 (s, 3H), 1.94 (s, 3H), 1.81 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 164.8, 157.6, 138.8, 136.5, 135.7, 132.5, 131.7, 130.2, 129.8, 121.2, 102.6, 95.3, 56.1, 18.5, 8.8; HRMS (ESI) $[M+Na]^+$: calcd for $C_{16}H_{18}O_3Na$, 281.1154; found 281.1145.

General Procedure for the Synthesis of 2-30. Pd_2dba_3 (5.5 mg, 6.0 μmol) and $AsPh_3$ (7.3 mg, 24 μmol) were added to a mixture of the respective compound **2-2** (0.20 mmol) and 2-**3** (0.169 g, 0.36 mmol) in NMP (1 mL) and allowed to stir at room temperature for 6 h. After which, water was added and

the mixture was extracted with Et_2O. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated. The residue obtained was dissolved in CH_3CN (15 mL) and washed with pentane (15 mL x 5) to remove the tributyltin bromide byproduct. Following that, CH_3CN was removed under reduced pressure and the residue was purified using a short column (*ca.* 5 cm) of silica gel.

4-methoxy-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30a). The residue was purified using flash chromatography (EtOAc:hexane = 1:1) to afford **2-30a** (48.2 mg, 73%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 10.7, 15.1 Hz, 1H), 7.03 (dd, *J* = 10.7, 17.8 Hz, 1H), 6.51 (dd, *J* = 10.8, 14.5 Hz, 1H), 6.41 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.09 (d, *J* = 15.2 Hz, 1H), 5.84 (d, *J* = 1.9 Hz, 1H), 5.70 (d, *J* = 17.7 Hz, 1H), 5.45 (d, *J* = 2.5 Hz, 1H), 3.79 (s, 3H), 1.26 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 163.8, 158.3, 148.4, 139.5, 135.4, 133.9, 123.5, 101.5, 88.9, 83.3, 55.9, 24.7; HRMS (ESI) $[M+Na]^+$: calcd for $C_{18}H_{23}O_5BNa$, 353.1536; found 353.1522.

4-methoxy-3-methyl-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30b). The residue was purified using flash chromatography (EtOAc:hexane = 1:1) to afford **2-30b** (48.8 mg, 71%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 10.7, 15.1 Hz, 1H), 7.04 (dd, *J* = 10.7, 17.7 Hz, 1H), 6.51 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.40 (dd, *J* = 11.4, 15.2 Hz, 1H), 6.12 (d, *J* = 15.1 Hz, 1H), 6.06 (s, 1H), 5.74 (d, *J* =17.7 Hz, 1H), 3.85 (s, 3H), 1.92 (s, 3H), 1.26 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 164.5, 156.9, 148.4, 139.2, 134.7, 134.1,

123.9, 103.3, 96.2, 83.3, 56.1, 24.7, 8.8; HRMS (ESI) $[M+Na]^+$: calcd for $C_{19}H_{25}O_5BNa$, 367.1693; found 367.1685.

3-butyl-4-methoxy-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30c). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-30c** (52.5 mg, 68%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 11.4, 15.1 Hz, 1H), 7.04 (dd, *J* = 10.8, 17.7 Hz, 1H), 6.51 (dd, *J* = 10.1, 14.5 Hz, 1H), 6.41 (dd, *J* = 11.4, 15.2 Hz, 1H), 6.11 (d, *J* = 15.2, 1H), 6.05 (s, 1H), 5.74 (d, *J* = 17.7 Hz, 1H), 3.84 (s, 3H), 2.41 (t, *J* = 7.6 Hz, 2H), 1.45-1.39 (m, 2H), 1.35-1.28 (m, 2H), 1.26 (s, 12H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 164.2, 157.1, 148.4, 139.2, 134.7, 134.1, 123.9, 108.2, 96.3, 83.2, 56.1, 30.2, 24.7, 23.3, 22.6, 13.9; HRMS (ESI) $[M+H]^+$: calcd for $C_{22}H_{32}O_5B$, 387.2343; found 387.2352.

3-benzyl-4-methoxy-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30d). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-30d** (63 mg, 75%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.6 Hz, 2H), 7.24-7.21 (m, 2H), 7.16-7.13 (m, 2H), 7.05 (dd, *J* = 10.1, 17.0 Hz, 1H), 6.53 (dd, *J* = 10.8, 15.2 Hz, 1H), 6.41 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.11 (d, *J* = 15.1 Hz, 1H), 6.06 (s, 1H), 5.72 (d, *J* = 17.7 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 2H), 1.27 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 164.1, 157.7, 148.4, 140.0, 139.5, 135.2, 134.0, 128.6, 128.2, 125.9, 123.8, 106.8, 96.2, 83.3, 56.3, 29.3, 24.7; HRMS (EI): calcd for $C_{25}H_{29}O_5B$, 420.2108; found 420.2116.

3-hexyl-4-methoxy-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30e). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-30e** (58.8 mg, 71%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 11.4, 15.2 Hz, 1H), 7.04 (dd, *J* = 10.7, 17.7 Hz, 1H), 6.51 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.40 (dd, *J* =10.7, 14.5 Hz, 1H), 6.11 (d, *J* = 15.2 Hz, 1H), 6.05 (s, 1H), 5.69 (d, *J* = 17.7 Hz, 1H), 3.84 (s, 3H), 2.40 (t, *J* = 7.6 Hz, 2H), 1.45-1.40 (m, 2H), 1.30-1.26 (m, 18H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 164.2, 157.1, 148.4, 139.2, 134.7, 134.1, 123.9, 108.3, 96.3, 83.3, 56.1, 31.7, 29.2, 28.0, 24.7, 23.6, 22.6, 14.0; HRMS (EI): calcd for $C_{24}H_{35}O_5B$, 414.2578; found 414.2574.

4-ethoxy-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30f). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-30f** (57.1 mg, 83%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 10.8, 15.2 Hz, 1H), 7.03 (dd, *J* = 10.7, 17.7 Hz, 1H), 6.51 (dd, *J* =10.8, 14.5 Hz, 1H), 6.41 (dd, *J* = 11.4, 15.1 Hz, 1H), 6.09 (d, *J* = 15.2 Hz, 1H), 5.83 (d, *J* = 1.3 Hz, 1H), 5.70 (d, *J* = 17.7 Hz, 1H), 5.41 (d, *J* = 1.9 Hz, 1H), 4.00 (q, *J* = 6.9 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 163.9, 158.2, 148.4, 139.5, 135.3, 134.0, 123.6, 101.7, 89.3, 83.3, 64.6, 24.7, 14.0; HRMS (EI): calcd for $C_{19}H_{25}O_5B$, 344.1795; found 344.1802.

4-ethoxy-3-methyl-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30g). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-30g**

(56.6 mg, 79%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 10.8, 15.1 Hz, 1H), 7.02 (dd, *J* = 10.1, 17.7 Hz, 1H), 6.48 (dd, *J* = 10.7, 15.2 Hz, 1H), 6.39 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.09 (d, *J* = 15.1 Hz, 1H), 6.02 (s, 1H), 5.67 (d, *J* = 17.7 Hz, 1H), 4.03 (q, *J* = 6.9 Hz, 1H), 1.91 (s, 3H); 1.38 (t, *J* = 7.3 Hz, 3H), 1.25 (s, 12H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 164.6, 156.7, 148.4, 139.1, 134.5, 134.1, 123.9, 103.3, 96.9, 83.3, 64.7, 24.7, 14.7, 8.9; HRMS (EI): calcd for $C_{20}H_{27}O_5B$, 358.1952; found 358.1958.

3-butyl-4-ethoxy-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30h). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-30h** (64.8 mg, 81%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13(dd, *J* = 10.7, 15.2 Hz, 1H), 7.03 (dd, *J* = 10.1, 17.1 Hz, 1H), 6.50 (dd, *J* = 10.7, 15.1 Hz, 1H), 6.40 (dd, *J* = 11.4, 15.2 Hz, 1H), 6.09 (d, *J* = 15.1 Hz, 1H), 6.01 (s, 1H), 5.69 (d, *J* = 17.7 Hz, 1H), 4.08 (q, *J* = 6.9 Hz, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 1.47-1.33 (m, 5H), 1.29-1.25 (m, 14H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 164.3, 156.9, 148.5, 139.1, 134.6, 134.1, 124.0, 108.3, 97.0, 83.3, 64.6, 30.1, 24.7, 23.3, 22.5, 14.7, 13.9; HRMS (EI): calcd for $C_{23}H_{33}O_5B$, 400.2421; found 400.2423.

4-methoxy-6-((2*E*,4*E*,6*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2*H*-pyran-2-one (2-30i). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-30i** (46.8 mg, 68%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13-7.05 (m, 2H), 6.66 (dd, *J* = 12.0, 15.2 Hz, 1H), 6.53 (dd, *J* = 10.8, 14.5 Hz, 1H), 5.98 (d, *J* = 1.9 Hz, 1H), 5.68 (d, *J* = 17.7 Hz, 1H), 5.44 (d, *J* = 1.9 Hz, 1H), 3.78 (s, 3H),

1.93 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 163.8, 160.4, 148.8, 139.5, 131.6, 130.9, 127.3, 98.8, 88.6, 83.2, 55.9, 24.7, 12.4; HRMS (ESI) $[M+Na]^+$: calcd for $C_{19}H_{25}O_5BNa$, 367.1693; found 367.1679.

4-methoxy-3-methyl-6-((2*E*,4*E*,6*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2*H*-pyran-2-one (2-30j). The residue was purified using flash chromatography (EtOAc:hexane = 1:2) to afford **2-30j** (47.2 mg, 66%) an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-7.08 (m, 2H), 6.69 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.58 (dd, *J* = 10.8, 14.5 Hz, 1H), 6.20 (s, 1H), 5.71 (d, *J* = 17.7 Hz, 1H), 3.91 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H), 1.28 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 164.7, 159.3, 148.9, 139.4, 131.3, 131.1, 127.5, 103.1, 93.1, 83.3, 56.1, 24.8, 12.6, 8.8; HRMS (ESI) $[M+H]^+$: calcd for $C_{20}H_{28}O_5B$, 359.2030; found 359.2022.

4-methoxy-3-methyl-6-((3*E*,5*E*,7*E*)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-3,5,7-trien-3-yl)-2*H*-pyran-2-one (2-30k). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-30k** (46.1 mg, 62%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, 2H), 6.68 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.57 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.25 (s, 1H), 5.70 (d, *J* = 17.7 Hz, 1H), 3.90 (s, 3H), 2.47 (q, *J* = 7.6 Hz, 2H), 1.93 (s, 3H), 1.27 (s, 12H), 1.11 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 164.8, 158.6, 149.0, 139.4, 134.5, 130.8, 130.6, 102.9, 92.9, 83.3, 56.1, 24.8, 20.2, 14.3, 8.7; HRMS (ESI) $[M+H]^+$: calcd for $C_{21}H_{30}O_5B$, 373.2186; found 373.2210.

3-butyl-4-methoxy-6-((2*E*,4*E*,6*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2*H*-pyran-2-one (2-30l). The

residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-30l** (48.8 mg, 61%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.10 (m, 2H), 6.71 (dd, *J* = 12.0, 15.1 Hz, 1H), 6.60 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.21 (s, 1H), 5.72 (d, *J* = 17.7 Hz, 1H), 3.91 (s, 3H), 2.45 (t, *J* = 7.6 Hz, 2H), 2.01 (s, 3H), 1.49-1.44 (m, 2H), 1.38-1.29 (m, 2H), 1.25 (s, 12H), 0.93-0.90 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 164.3, 159.3, 148.9, 139.3, 131.1, 131.2, 127.6, 107.9, 93.1, 83.3, 56.0, 30.2, 24.7, 23.2, 22.6, 13.9, 12.6; HRMS (ESI) $[M+Na]^+$: calcd for $C_{23}H_{33}O_5BNa$, 423.2319; found 423.2334.

3-butyl-4-methoxy-6-((3*E*,5*E*,7*E*)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-3,5,7-trien-3-yl)-2*H*-pyran-2-one (2-30m). The residue was purified using flash chromatography (EtOAc:hexane = 1:6) to afford **2-30m** (58.8 mg, 71%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14-7.06 (m, 2H), 6.68 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.57 (dd, *J* = 10.8, 15.2 Hz, 1H), 6.23 (s, 1H), 5.75 (d, *J* = 17.7 Hz, 1H), 3.88 (s, 3H), 2.48-2.41 (m, 4H), 1.47-1.41 (m, 2H), 1.33-1.27 (m, 14H), 1.10 (t, *J* = 7.6 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 164.4, 158.7, 149.0, 139.3, 134.5, 130.9, 130.6, 107.9, 92.9, 83.3, 56.0, 30.2, 24.7, 23.2, 22.6, 20.2, 14.3, 13.9; HRMS (EI): calcd for $C_{24}H_{35}O_5B$, 414.2578; found 414.2576.

3-benzyl-4-methoxy-6-((2*E*,4*E*,6*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2*H*-pyran-2-one (2-30n). The residue was purified using flash chromatography (EtOAc:hexane = 1:3) to afford **2-30n** (63.3 mg, 73%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.0 Hz, 2H), 7.24-7.21 (m, 2H), 7.18-7.08 (m, 3H), 6.71 (dd, *J* =

12.0, 15.2 Hz, 1H), 6.58(dd, *J* = 10.1, 14.5 Hz, 1H), 6.20 (s, 1H), 5.71 (d, *J* = 17.7 Hz, 1H), 3.90 (s, 3H), 3.77 (s, 2H), 1.98 (s, 3H), 1.27 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 164.1, 160.0, 148.9, 140.1, 139.5, 131.6, 131.0, 128.6, 128.1, 127.5, 125.9, 106.5, 93.1, 83.3, 56.2, 29.2, 24.7, 12.5; HRMS (EI): calcd for $C_{26}H_{31}O_5B$, 434.2265; found 434.2271.

3-hexyl-4-methoxy-6-((2*E*,4*E*,6*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2*H*-pyran-2-one (2-30o). The residue was purified using flash chromatography (EtOAc:hexane = 1:5) to afford **2-30o** (63.3 mg, 74%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.08 (m, 2H), 6.69 (dd, *J* = 12.0, 15.2 Hz, 1H), 6.57 (dd, *J* = 10.8, 14.5 Hz, 1H), 6.19 (s, 1H), 5.70 (d, *J* = 17.7 Hz, 1H), 3.88 (s, 3H), 2.42 (t, *J* = 7.9 Hz, 2H), 1.99 (s, 3H), 1.46-1.41 (m, 2H), 1.28-1.27 (m, 18H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 164.3, 159.3, 148.9, 139.3, 131.2, 131.1, 127.6, 108.0, 93.1, 83.3, 56.0, 31.7, 29.2, 28.0, 24.7, 23.5, 22.6, 14.1, 12.6; HRMS (EI): calcd for $C_{25}H_{37}O_5B$, 428.2734; found 428.2732.

4-ethoxy-3-methyl-6-((2*E*,4*E*,6*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2*H*-pyran-2-one (2-30p). The residue was purified using flash chromatography (EtOAc:hexane = 1:4) to afford **2-30p** (52.1 mg, 70%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14-7.06 (m, 2H), 6.69-6.63 (m, 1H), 6.54 (dd, *J* = 10.1, 13.9 Hz, 1H), 6.15 (s, 1H), 5.68 (d, *J* = 17.1 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 1.96 (s, 3H), 1.92 (s, 3H), 1.40 (t, *J* = 6.9 Hz, 3H), 1.25 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.7, 159.0, 148.9, 139.2, 131.0, 131.0, 127.6, 103.0, 93.8, 83.3, 64.7,

24.7, 14.8, 12.5, 8.8; HRMS (EI): calcd for $C_{21}H_{29}O_5B$, 372.2108; found 372.2114.

3-butyl-4-ethoxy-6-((2*E*,4*E*,6*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2*H*-pyran-2-one (2-30q). The residue was purified using flash chromatography (EtOAc:hexane = 1:5) to afford **2-30q** (60.4 mg, 73%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14-7.05 (m, 2H), 6.68-6.63 (m, 1H), 6.54 (dd, *J* = 10.8, 14.5 Hz, 1H), 6.14 (s, 1H), 5.67 (d, *J* = 17.0 Hz, 1H), 4.11 (q, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.95 (s, 3H), 1.44-1.38 (m, 5H), 1.37-1.25 (m, 14H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.4, 159.1, 148.9, 139.1, 131.1, 131.0, 127.6, 107.9, 93.9, 83.2, 64.5, 30.1, 24.7, 23.1, 22.4, 14.7, 13.9, 12.5; HRMS (EI): calcd for $C_{24}H_{35}O_5B$, 414.2578; found 414.2582.

4-hydroxy-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30r). The residue was purified using flash chromatography (MeOH:CH_2Cl_2 = 1:20) to afford **2-30r** (41.1 mg, 65%) as an orange solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (br, 1H), 7.04-6.97 (m, 2H), 6.70-6.60 (m, 2H), 6.44 (d, *J* = 15.1 Hz, 1H), 6.19 (s, 1H), 5.63 (d, *J* = 17.7 Hz, 1H), 5.31 (s, 1H), 1.21 (s, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.9, 162.7, 158.6, 148.8, 138.7, 134.8, 133.9, 124.9, 102.2, 90.2, 83.0, 24.5; HRMS (ESI) $[M-H]^-$: calcd for $C_{17}H_{20}O_5B$, 315.1404; found 315.1394.

4-hydroxy-3-methyl-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-2-one (2-30s). The residue was purified using flash chromatography (MeOH:CH_2Cl_2 = 1:20) to afford **2-**

30s (43.6 mg, 66%) as an orange solid. $_1$H NMR (500 MHz, Acetone-d_6) δ 7.06-7.01 (m, 2H), 6.66 (dd, J = 10.1, 15.1 Hz, 1H), 6.58 (dd, J = 10.7, 15.2 Hz, 1H), 6.34 (d, J =15.1 Hz, 1H), 6.20 (s, 1H), 5.67 (d, J = 17.7 Hz, 1H), 1.90 (s, 3H), 1.25 (s, 12H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 163.7, 163.6, 155.6, 148.5, 138.2, 134.4, 133.1, 124.4, 101.4, 100.1, 82.8, 23.9, 7.9; HRMS (ESI) $[M-H]^-$: calcd for $C_{18}H_{22}O_5B$, 329.1560; found 329.1546.

5-(dimethylamino)-*N*-(3-(2-oxo-6-((1*E*,3*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2*H*-pyran-4-yloxy)propyl)naphthalene-1-sulfonamide (2-30t). The residue was purified using flash chromatography (EtOAc:hexane = 1:1) to afford **2-30t** (75.5 mg, 60%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 8.2 Hz, 1H), 8.27-8.24 (m, 2H), 7.53-7.48 (m, 2H), 7.16-7.02 (m, 3H), 6.52 (dd, J = 10.7, 14.5 Hz, 1H), 6.42 (dd, J = 11.3, 15.1 Hz, 1H), 6.04 (d, J = 15.2 Hz, 1H), 5.72 (d, J = 17.7 Hz, 1H), 5.62 (d, J = 1.9 Hz, 1H), 5.22-5.14 (m, 2H), 3.77 (t, J = 5.7 Hz, 2H), 3.11-3.07 (m, 2H), 2.86 (s, 6H), 1.88-1.83 (m, 2H), 1.28 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 163.6, 158.2, 152.1, 148.4, 139.6, 135.4, 134.2, 133.9, 130.7, 129.8 (2 carbons), 129.5, 128.5, 123.4, 123.0, 118.4, 115.2, 101.3, 89.4, 83.4, 65.6, 45.3, 39.7, 28.4, 24.7; HRMS (ESI) $[M+Na]^+$: calcd for $C_{32}H_{39}N_2O_7BSNa$, 629.2463; found 629.2494.

General Procedure for the Synthesis of 2-1a to **2-1t.** Pd_2dba_3 (2.7 mg, 3.0 μmol) and $AsPh_3$ (4.6 mg, 15 μmol) was added to THF (1 mL) followed by **2-4a** (56 mg, 0.195 mmol) and 1.8 M aqueous KOH (0.167 mL, 0.300 mL). The respective compound **2-30** (0.150 mmol) was dissolved in THF (0.5 mL) and added dropwise to the reaction mixture over 5 min with stirring. The reaction

mixture was stirred for 20 min at room temperature and quenched with saturated NH_4Cl. EtOAc was added and the mixture was washed thrice with water followed by saturated NaCl solution. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure and the residue obtained was dissolved in THF (1 mL) and 1 M TBAF in THF (0.300 mL, 0.300 mmol) was added. The mixture was stirred at room temperature for 30 min and thereafter EtOAc was added and the mixture was washed thrice with water followed by saturated NaCl solution. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography.

Auxarconjugatin B (2-1a). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:5:10) to afford **2-1a** (36.8 mg, 74%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.05 (dd, J = 11.4, 15.1 Hz, 1H), 6.90-6.89 (m, 1H), 6.79-6.69 (m, 2H), 6.60 (dd, J = 11.4, 14.5 Hz, 1H), 6.54-6.37 (m, 3H), 6.29 (d, J = 15.1 Hz, 1H), 6.23 (d, J = 1.9 Hz, 1H), 6.14-6.13 (m, 1H), 5.59 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.7, 162.6, 158.4, 138.8, 136.8, 135.1, 131.1, 130.5, 126.0, 124.7, 121.6, 120.8, 120.5, 111.9, 109.1, 100.6, 88.4, 56.3; HRMS (ESI) $[M-H]^-$: calcd for $C_{18}H_{15}NO_3Cl$, 328.0740; found 328.0738.

Auxarconjugatin A (2-1b). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:5:10) to afford **2-1b** (34.7 mg, 70%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.46 (br, 1H), 7.07 (dd, J = 11.4, 15.1 Hz, 1H), 6.90-6.89 (m, 1H), 6.80-6.70 (m, 2H), 6.65-6.59 (m, 2H), 6.54-6.47 (m, 2H), 6.42 (dd, J = 11.4, 14.5 Hz, 1H), 6.33 (d, J = 15.2 Hz, 1H), 6.13-6.12 (m, 1H), 3.90 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (125 MHz,

DMSO-d_6) δ 165.9, 163.4, 157.0, 138.5, 136.7, 134.5, 131.1, 130.7, 126.0, 124.7, 121.9, 120.7, 120.5, 111.8, 109.1, 100.5, 96.5, 56.7, 8.8; HRMS (ESI) $[M-H]^-$: calcd for $C_{19}H_{17}NO_3Cl$, 342.0915; found 342.0897.

3-butyl-6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-methoxy-2*H*-pyran-2-one (2-1c). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:8:16) to afford **2-1c** (45.9 mg, 75%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.47 (br, 1H), 7.07 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.91-6.90 (m, 1H), 6.81-6.70 (m, 2H), 6.64-6.60 (m, 2H), 6.55-6.48 (m, 2H), 6.42 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.33 (d, *J* = 15.1 Hz), 6.15-6.14 (m, 1H), 3.89 (s, 3H), 2.34-2.31, (t, *J* = 7.3 Hz, 2H), 1.39-1.36 (m, 2H), 1.30-1.25 (m, 2H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.5, 163.9, 158.4, 139.2, 137.3, 135.4, 132.2, 131.5, 127.2, 125.7, 123.0, 121.5, 120.7, 113.5, 110.3, 107.1, 96.9, 56.8, 30.9, 23.8, 23.1, 14.1; HRMS (ESI) $[M+Na]^+$: calcd for $C_{22}H_{24}NO_3ClNa$, 408.1342; found 408.1320.

3-benzyl-6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-methoxy-2*H*-pyran-2-one (2-1d). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:8:16) to afford **2-1d** (44.6 mg, 71%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.46 (br, 1H), 7.25-7.19 (m, 4H), 7.15-7.06 (m, 2H), 6.90 (t, *J* = 2.8 Hz, 1H), 6.80-6.70 (m, 3H), 6.63 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.55-6.51 (m, 2H), 6.42 (dd, *J* = 11.4, 13.9 Hz, 1H), 6.34 (d, *J* = 15.2 Hz, 1H), 6.14 (t, *J* = 2.5 Hz, 1H), 3.92 (s, 3H), 3.63 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.4, 163.1, 157.9, 139.9, 138.9, 136.9, 135.1, 131.1, 130.6, 128.1, 128.1, 126.0, 125.8, 124.7, 121.8,

120.8, 120.5, 111.9, 109.1, 104.1, 96.5, 56.9, 28.7; HRMS (EI): calcd for $C_{25}H_{22}NO_3Cl$, 419.1288; found 419.1282.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-3-hexyl-4-methoxy-2*H*-pyran-2-one (2-1e). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:10:20) to afford **2-1e** (43.3 mg, 70%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.06 (dd, *J* = 11.4, 1H), 6.90 (t, *J* = 2.8 Hz, 1H), 6.80-6.70 (m, 2H), 6.63-6.47 (m, 2H), 6.54-6.47 (m, 2H), 6.41 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.32 (d, *J* = 15.2 Hz, 1H), 6.13 (t, *J* = 2.8 Hz, 1H), 3.88 (s, 3H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.38-1.36 (m, 2H), 1.28-1.25 (m, 6H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.9, 163.1, 157.2, 138.5, 136.7, 134.6, 131.1, 130.7, 126.0, 124.7, 121.9, 120.7, 120.4, 111.8, 109.1, 105.4, 96.5, 56.7, 31.0, 28.5, 27.5, 23.0, 22.0, 13.9; HRMS (EI): calcd for $C_{24}H_{28}NO_3Cl$, 413.1739; found 413.1758.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-ethoxy-2*H*-pyran-2-one (2-1f). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:6:12) to afford **2-1f** (38.1 mg, 74%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (br, 1H), 7.04 (dd, *J* = 11.4, 15.2 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.79-6.69 (m, 2H), 6.64-6.37 (m, 4H), 6.28 (d, *J* = 15.1 Hz, 1H), 6.21 (s, 1H), 6.13 (s, 1H), 5.55 (d, *J* = 1.9 Hz, 1H), 4.08 (q, *J* = 6.9 Hz, 2H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.9, 162.6, 158.4, 138.8, 136.8, 135.1, 131.1, 130.5, 126.0, 124.7, 121.6, 120.8, 120.5, 111.9, 109.1, 100.8, 88.7, 64.7, 13.9; HRMS (EI): calcd for $C_{19}H_{18}O_3NCl$, 343.0975; found 343.0969.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-ethoxy-3-methyl-2*H*-pyran-2-one (2-1g). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:6:12) to afford **2-1g** (40.2 mg, 75%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (br, 1H), 7.08 (dd, J = 11.4, 15.2 Hz, 1H), 6.90 (s, 1H), 6.79-6.69 (m, 2H), 6.63-6.58 (m, 2H), 6.54-6.46 (m, 2H), 6.41 (dd, J = 11.4, 14.5 Hz, 1H), 6.31 (d, J = 15.1 Hz, 1H), 6.13 (s, 1H), 4.19 (q, J = 6.9 Hz, 2H), 1.81 (s, 3H), 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.2, 163.4, 156.9, 138.4, 136.6, 134.4, 131.1, 130.7, 126.0, 124.7, 122.0, 120.7, 120.4, 111.8, 109.1, 100.6, 97.0, 64.8, 14.6, 8.8; HRMS (EI): calcd for $C_{20}H_{20}NO_3Cl$, 357.1132; found 357.1132.

3-butyl-6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-ethoxy-2*H*-pyran-2-one (2-1h). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:8:16) to afford **2-1h** (41.9 mg, 70%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (br, 1H), 7.07-7.02 (dd, J = 11.4, 15.1 Hz, 1H), 6.90 (t, J = 2.9 Hz, 1H), 6.80-6.69 (m, 2H), 6.63-6.58 (m, 2H), 6.54-6.46 (m, 2H), 6.41 (dd, J = 11.4, 14. 5Hz, 1H), 6.30 (d, J = 15.2 Hz, 1H), 6.13 (t, J =2.9 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.33 (t, J = 7.3 Hz, 2H), 1.41-1.35 (m, 2H), 1.32-1.22 (m, 5H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.2, 163.1, 157.1, 138.5, 136.6, 134.5, 131.1, 130.7, 126.0, 124.7, 122.0, 120.7, 120.4, 111.8, 109.1, 105.5, 97.1, 64.7, 29.7, 22.7, 21.8, 14.6, 13.7; HRMS (EI): calcd for $C_{23}H_{26}NO_3Cl$, 399.1601; found 399.1591.

6-((2*E*,4*E*,6*E*,8*E*)-9-(3-chloro-1*H*-pyrrol-2-yl)nona-2,4,6,8-tetraen-2-yl)-4-methoxy-2*H*-pyran-2-one (2-1i). The residue was purified using flash

chromatography (acetone:hexane:CH_2Cl_2 = 1:5:10) to afford **2-1i** (39.2 mg, 76%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.03 (d, J = 10.1 Hz, 1H), 6.90-6.89 (m, 1H), 6.80-6.72 (m, 3H), 6.62 (dd, J = 11.4, 15.1 Hz, 1H) 6.55-6.44 (m, 2H), 6.26 (d, J = 1.9 Hz, 1H), 6.13-6.12 (m, 1H), 5.61 (d, J = 1.9 Hz, 1H), 3.83 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 162.6, 160.1, 138.8, 136.4, 131.5, 131.5, 127.7, 126.0, 125.3, 124.8, 120.6, 120.4, 111.8, 109.1, 98.3, 88.2, 56.3, 12.3; HRMS (ESI) [M-H]$^-$: calcd for $C_{19}H_{17}NO_3Cl$, 342.0915; found 342.0913.

12*E*-isorumbrin (2-1j). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:5:10) to afford **2-1j** (38.1 mg, 71%) as a red solid. 1H NMR (500 MHz, DMSO-d_6) δ 11.46 (br, 1H), 7.05 (d, J = 10.1 Hz, 1H), 6.90-6.89 (m, 1H), 6.80-6.72 (m, 3H), 6.61-6.47 (m, 4H), 6.13-6.12 (m, 1H), 3.95 (s, 3H), 2.05 (s, 3H), 1.81 (s, 3H); 13C NMR (125 MHz, DMSO-d_6) δ 166.0, 163.3, 158.8, 138.5, 136.3, 131.6, 131.0, 127.9, 126.0, 125.8, 124.8, 120.5, 120.4, 111.8, 109.1, 100.3, 93.6, 56.7, 12.4, 8.7; HRMS (ESI) [M-H]$^-$: calcd for $C_{20}H_{19}NO_3Cl$, 356.1053; found 356.1043.

6-((3*E*,5*E*,7*E*,9*E*)-10-(3-chloro-1*H*-pyrrol-2-yl)deca-3,5,7,9-tetraen-3-yl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-1k) The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:6:12) to afford **2-1k** (37.9 mg, 68%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.47 (br, 1H), 7.01-6.99 (m, 1H), 6.90-6.89 (m, 1H), 6.80-6.72 (m, 3H), 6.64-6.59 (m, 2H), 6.53-6.48 (m, 2H), 6.13-6.12 (m, 1H), 3.95 (s, 3H), 2.56 (q, J = 7.4 Hz, 2H), 1.81 (s, 3H), 1.07, (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.5, 158.2, 138.8, 136.4, 132.4, 131.6, 130.7, 127.4, 126.0, 124.8, 120.5,

120.4, 111.8, 109.1, 100.2, 93.3, 56.7, 30.6, 14.3, 8.7; HRMS (ESI) $[M-H]^-$: calcd for $C_{21}H_{21}NO_3Cl$, 370.1210; found 370.1202.

3-butyl-6-((2*E*,4*E*,6*E*,8*E*)-9-(3-chloro-1*H*-pyrrol-2-yl)nona-2,4,6,8-tetraen-2-yl)-4-methoxy-2*H*-pyran-2-one (2-1l). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:8:16) to afford **2-1l** (49.2 mg, 82%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.05 (d, J = 10.7 Hz, 1H), 6.90-6.89 (m, 1H), 6.80-6.69 (m, 3H), 6.64-6.44 (m, 4H), 6.13-6.12 (m, 1H), 3.94 (s, 3H), 2.32 (t, J = 7.3 Hz, 2H), 2.05 (s, 3H), 1.40-1.34 (m, 2H), 1.30-1.23 (m, 2H), 0.88 (t, J = 7.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.0, 163.1, 159.0, 138.5, 136.3, 131.6, 131.1, 127.9, 126.0, 125.8, 124.8, 120.5, 120.4, 111.8, 109.1, 105.1, 93.7, 56.7, 29.7, 22.7, 22.0, 13.8, 12.3; HRMS (ESI) $[M+Na]^+$: calcd for $C_{23}H_{26}NO_3ClNa$, 422.1499; found 422.1510.

3-butyl-6-((3*E*,5*E*,7*E*,9*E*)-10-(3-chloro-1*H*-pyrrol-2-yl)deca-3,5,7,9-tetraen-3-yl)-4-methoxy-2*H*-pyran-2-one (2-1m). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:10:20) to afford **2-1m** (42.7 mg, 69%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.01-6.99 (m, 1H), 6.90 (t, J = 2.8 Hz, 1H), 6.80-6.72 (m, 3H), 6.64-6.59 (m, 2H), 6.54-6.50 (m, 2H), 6.13 (t, J = 2.5 Hz, 1H), 3.94 (s, 3H), 2.56 (q, J = 7.4 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 1.40-1.34 (m, 2H), 1.31-1.25 (m, 2H), 1.07 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.1, 163.2, 158.4, 138.8, 136.3, 132.4, 131.5, 130.7, 127.3, 126.0, 124.7, 120.5, 120.3, 111.8, 109.1, 105.1, 93.3, 56.7, 29.7, 22.6, 21.9, 19.2, 14.3, 13.7; HRMS (EI): calcd for $C_{24}H_{28}NO_3Cl$, 413.1749; found 413.1758.

3-benzyl-6-((2*E*,4*E*,6*E*,8*E*)-9-(3-chloro-1*H*-pyrrol-2-yl)nona-2,4,6,8-tetraen-2-yl)-4-methoxy-2*H*-pyran-2-one (2-1n). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:8:16) to afford **2-1n** (47.4 mg, 73%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.46 (br, 1H), 7.25-7.19 (m, 4H), 7.16-7.13 (m, 1H), 7.07 (d, J = 10.1 Hz, 1H), 6.90 (t, J = 2.8 Hz, 1H), 6.81-6.73 (m, 3H), 6.64-6.59 (m, 2H), 6.53-6.45 (m, 2H), 6.14 (t, J = 2.5 Hz, 1H), 3.98 (s, 3H), 3.64 (s, 2H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.4, 163.1, 159.7, 139.9, 138.8, 136.4, 131.6, 131.5, 128.1, 128.1, 127.8, 126.0, 125.8, 125.8, 124.8, 120.6, 120.4, 111.8, 109.1, 104.0, 93.7, 56.9, 28.6, 12.4; HRMS (EI): calcd for $C_{26}H_{24}NO_3Cl$, 433.1445; found 433.1440.

6-((2*E*,4*E*,6*E*,8*E*)-9-(3-chloro-1*H*-pyrrol-2-yl)nona-2,4,6,8-tetraen-2-yl)-3-hexyl-4-methoxy-2*H*-pyran-2-one (2-1o). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:10:20) to afford **2-1o** (44.8 mg, 70%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.05 (d, J = 10.1 Hz, 1H); 6.90 (t, J = 2.8 Hz, 1H), 6.80-6.69 (m, 3H), 6.63-6.44 (m, 4H), 6.13 (t, J = 2.5 Hz, 1H), 3.94 (s, 3H), 2.31 (t, J = 7.6 Hz, 2H), 2.04 (s, 3H), 1.38 (m, 2H), 1.25 (m, 6H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.0, 163.0, 159.0, 138.5, 136.3, 131.6, 131.1, 127.9, 126.0, 125.8, 124.8, 120.5, 120.4, 111.8, 109.1, 105.2, 93.7, 56.6, 31.1, 28.5, 27.5, 22.9, 22.0, 13.9, 12.3; HRMS (EI): calcd for $C_{25}H_{30}NO_3Cl$, 427.1914; found 427.1904.

6-((2*E*,4*E*,6*E*,8*E*)-9-(3-chloro-1*H*-pyrrol-2-yl)nona-2,4,6,8-tetraen-2-yl)-4-ethoxy-3-methyl-2*H*-pyran-2-one (2-1p). The residue was purified using

flash chromatography (acetone:hexane:CH_2Cl_2 = 1:6:12) to afford **2-1p** (40.6 mg, 73%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.04 (d, J = 10.1 Hz, 1H), 6.89 (s, 1H), 6.80-6.71 (m, 3H), 6.63-6.58 (m, 1H), 6.53-6.44 (m, 3H), 6.12 (s, 1H), 4.27 (q, J = 6.7 Hz, 2H), 2.03 (s, 3H), 1.82 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.3, 163.4, 158.7, 138.4, 136.2, 131.6, 130.9, 127.9, 126.0, 125.8, 124.8, 120.4, 120.4, 111.7, 109.1, 100.5, 94.2, 64.8, 14.6, 12.4, 8.7; HRMS (EI): calcd for $C_{21}H_{22}NO_3Cl$, 371.1288; found 371.1283.

3-butyl-6-((2*E*,4*E*,6*E*,8*E*)-9-(3-chloro-1*H*-pyrrol-2-yl)nona-2,4,6,8-tetraen-2-yl)-4-ethoxy-2*H*-pyran-2-one (2-1q). The residue was purified using flash chromatography (acetone:hexane:CH_2Cl_2 = 1:10:20) to afford **2-1q** (42.1 mg, 68%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (br, 1H), 7.04 (d, J = 10.7 Hz, 1H), 6.89 (s, 1H), 6.80-6.68 (m, 3H), 6.61 (dd, J = 11.3, 15.1 Hz, 1H), 6.53-6.44 (m, 3H), 6.13 (s, 1H), 4.26 (q, J = 6.9 Hz, 2H), 2.34 (t, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.41-1.35 (m, 2H), 1.33-1.24 (m, 5H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.3, 163.1, 158.9, 138.5, 136.2, 131.6, 131.0, 127.9, 126.0, 125.8, 124.8, 120.4, 120.4, 111.7, 109.1, 105.3, 94.3, 64.7, 29.6, 22.6, 21.8, 14.6, 13.7, 12.3; HRMS (EI): calcd for $C_{24}H_{28}NO_3Cl$, 413.1758; found 413.1751.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-hydroxy-2*H*-pyran-2-one (2-1r). The residue was purified using flash chromatography (MeOH:CH_2Cl_2 = 1:20) to afford **2-1r** (30.8 mg, 65%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.45 (br, 1H), 7.03 (dd, J = 11.4, 15.2 Hz, 1H), 6.90-6.89 (m, 1H), 6.79-6.69 (m, 2H), 6.62 (dd, 11.4, 15.1 Hz,

1H), 6.54-6.44 (m, 2H), 6.40 (dd, *J* = 11.3 Hz, 14.5, 1H), 6.31 (d, *J* = 15.1 Hz, 1H), 6.14-6.13 (m, 1H), 6.11 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.7, 163.0, 159.0, 138.5, 136.6, 134.7, 131.1, 130.6, 126.0, 124.8, 122.1, 120.7, 120.4, 111.8, 109.1, 101.7, 89.4; HRMS (ESI) $[M-H]^-$: calcd for $C_{17}H_{13}NO_3Cl$, 314.0589; found 314.0578.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-hydroxy-3-methyl-2*H*-pyran-2-one (2-1s). The residue was purified using flash chromatography (MeOH:CH_2Cl_2 = 1:20) to afford **2-1s** (34.7 mg, 70%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.44 (br, 1H), 6.97 (dd, *J* = 11.4, 15.1 Hz, 1H), 6.90-6.88 (m, 1H), 6.77 (dd, *J* = 10.8, 15.2 Hz, 1H), 6.69 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.59 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.46 (dd, *J* = 11.4, 14.5 Hz, 1H), 6.39 (dd, *J* = 10.7, 14.5 Hz, 1H), 6.30 (d, *J* = 15.8 Hz, 1H), 6.13-6.12 (m, 2H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.7, 164.0, 155.7, 137.9, 136.3, 133.8, 131.2, 130.7, 126.0, 124.8, 122.1, 120.5, 120.4, 111.7, 109.1, 101.0, 98.5, 8.8; HRMS (ESI) $[M-H]^-$: calcd for $C_{18}H_{15}NO_3Cl$, 328.0740; found 328.0744.

***N*-(3-(6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-2-oxo-2*H*-pyran-4-yloxy)propyl)-5-(dimethylamino)naphthalene-1-sulfonamide (2-1t).** The residue was purified using flash chromatography (acetone:hexane = 1:2) to afford **2-1t** (62.6 mg, 69%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 8.9 Hz, 1H), 8.11 (d, *J* = 7.0 Hz, 1H), 7.98-7.96 (m, 1H), 7.61-7.56 (m, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.03 (dd, *J* = 11.4, 15.1 Hz, 1H), 6.90 (t, *J* = 3.2 Hz, 1H), 6.80-6.70 (m, 2H), 6.63 (dd, *J* = 10.8, 14.5 Hz, 1H), 6.54-6.38 (m,

3H), 6.25 (d, *J* = 15.2 Hz, 1H), 6.14-6.13 (t, *J* = 2.5 Hz, 1H), 6.00 (d, *J* = 2.5 Hz, 1H), 5.26 (d, *J* = 1.9 Hz, 1H), 3.85 (t, *J* = 4.5 Hz, 2H), 2.94-2.90 (m, 2H), 2.81 (s, 6H), 1.76-1.71 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.5, 162.4, 158.2, 151.3, 138.8, 136.8, 135.6, 135.0, 131.1, 130.5, 129.5, 129.0, 129.0, 128.4, 127.8, 126.0, 124.7, 123.4, 121.6, 120.8, 120.4, 118.8, 115.0, 111.8, 109.1, 100.6, 88.5, 65.5, 54.8, 44.9, 28.0; HRMS (EI): calcd for $C_{32}H_{32}N_3O_5ClS$, 605.1751; found 605.1748.

Synthesis of *N*-(3-(2-(6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-2-oxo-2*H*-pyran-4-yloxy)ethoxy)propyl)-5-(dimethylamino)naphthalene-1-sulfonamide (2-1u). Pd_2dba_3 (5.5 mg, 6.0 μmol) and $AsPh_3$ (7.3 mg, 24 μmol) were added to a mixture of compound **2-2u** (0.20 mmol) and 2-**3** (0.169 g, 0.36 mmol) in NMP (1 mL) and allowed to stir at room temperature for 6 h. After which, water was added and the mixture was extracted with Et_2O. The combined organic extract was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated The residue obtained was dissolved in CH_3CN (15 mL) and washed with pentane (15 mL x 5) to remove the tributyltin bromide byproduct. Following that, CH_3CN was removed under reduced pressure and the residue was purified using a short column (*ca.* 5 cm) of silica gel to afford **2-30u** as a orange solid. Pd_2dba_3 (2.7 mg, 3.0 μmol) and $AsPh_3$ (4.6 mg, 15 μmol) was added to THF (1 mL) followed by **4a** (56 mg, 0.195 mmol) and 1.8 M aqueous KOH (0.167 mL, 0.300 mL). Compoun **2-30u** (0.150 mmol) was dissolved in THF (0.5 mL) and added dropwise to the reaction mixture over 5 min with stirring. The reaction mixture was stirred for 20 min at room temperature and quenched with

saturated NH_4Cl. EtOAc was added and the mixture was washed thrice with water followed by saturated NaCl solution. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure and the residue obtained was dissolved in THF (1 mL) and 1 M TBAF in THF (0.300 mL, 0.300 mmol) was added. The mixture was stirred at room temperature for 30 min and thereafter EtOAc was added and the mixture was washed thrice with water followed by saturated NaCl solution. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (acetone:hexane = 1:3) to afford **2-2u** (52.0 mg, 40%) as a red solid. ^{1}H NMR (500 MHz, Acetone-d_6) δ 10.6 (br, 1H), 8.56 (d, J = 8.8 Hz, 1H), 8.39 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 7.0 Hz, 1H), 7.63-7.55 (m, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.09 (dd, J = 11.4, 15.2 Hz, 1H), 6.88 (t, J = 2.9 Hz, 1H), 6.81-6.69 (m, 2H), 6.65-6.60 (m, 3H), 6.46-6.38 (m, 2H), 6.20 (d, J = 15.2 Hz, 1H), 6.13 (d, J = 2.5 Hz, 1H), 6.04 (d, J = 1.9 Hz, 1H), 5.46 (d, J = 1.9 Hz, 1H), 4.09 (t, J = 4.7 Hz, 2H), 3.58 (t, J = 4.7 Hz, 2H), 3.42 (t, J = 6.0 Hz, 2H), 3.03-3.00 (m, 2H), 2.99 (s, 6H), 1.69-1.64 (m, 2H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 169.8, 162.2, 158.6, 151.7, 138.5, 136.5, 135.9, 135.1, 131.2, 130.4, 129.6, 129.5, 129.5, 128.7, 127.6, 126.2, 124.6, 123.1, 121.6, 120.5, 119.7, 119.2, 114.9, 112.5, 109.3, 100.4, 88.5, 68.0 (2 carbons), 67.8, 44.5, 40.3, 29.1; . HRMS (EI): calcd for $C_{34}H_{36}N_3O_6ClS$, 649.2013; found 649.1986.

General Procedure for the Synthesis of 2-1v to 2-1z. Pd_2dba_3 (2.7 mg, 3.0 μmol) and $AsPh_3$ (4.6 mg, 15 μmol) was added to THF (1 mL) followed by the respective compound **2-4** (0.195 mmol) and 1.8 M aqueous KOH (0.167 mL, 0.300 mL). Compound **2-30a or 2-30b** (0.150 mmol) was dissolved in THF

(0.5 mL) and added dropwise to the reaction mixture over 5 min with stirring. The reaction mixture was stirred for 20 min at room temperature and quenched with saturated NH4Cl. EtOAc was added and the mixture was washed with H2O thrice followed by saturated NaCl solution. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chlorothiophen-2-yl)octa-1,3,5,7-tetraenyl)-4-methoxy-2*H*-pyran-2-one (2-1v). The residue was purified using flash chromatography (acetone:CH_2Cl_2 = 1:30) to afford **2-1v** (44.2 mg, 85%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 11.4, 15.2 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 6.89 (d, *J* = 5.7 Hz, 1H), 6.84 (d, *J* = 15.1 Hz, 1H), 6.67 (dd, *J* = 10.8, 15.2 Hz, 1H), 6.59-6.50 (m, 2H), 6.45-6.34 (m, 2H), 6.06 (d, *J* = 15.1 Hz, 1H), 5.84 (d, *J* = 1.9 Hz, 1H), 5.45 (d, *J* = 1.9 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 164.0, 158.7, 138.4, 136.0, 135.7, 135.3, 133.4, 131.6, 129.8, 128.6, 124.5, 123.7, 123.7, 121.9, 101.0, 88.7, 55.9; HRMS (ESI) $[M+Na]^+$: calcd for $C_{18}H_{15}NO_3ClNaS$, 369.0328; found 369.0325.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chlorothiophen-2-yl)octa-1,3,5,7-tetraenyl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-1w). The residue was purified using flash chromatography (acetone:CH_2Cl_2 = 1:30) to afford **2-1w** (43.8 mg, 81%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 11.4, 15.2 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 6.89 (d, *J* = 5.7 Hz, 1H), 6.84 (d, *J* = 15.2 Hz, 1H), 6.67 (dd, *J* = 10.7, 15.1 Hz, 1H), 6.59-6.50 (m, 2H), 6.45-6.34 (m, 2H), 6.08 (d, *J* = 15.2 Hz, 1H), 6.04 (s, 1H), 3.88 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 164.7, 157.4, 138.2, 135.5, 135.4, 135.3, 133.4,

131.7, 129.8, 128.6, 124.5, 123.7, 123.6, 122.2, 103.0, 95.7, 56.2, 8.9; HRMS (ESI) $[2M+Na]^+$: calcd for $C_{38}H_{34}N_2O_6Cl_2NaS$, 743.1072; found 743.1079.

6-((1*E*,3*E*,5*E*,7*E*)-8-(2-chlorophenyl)octa-1,3,5,7-tetraenyl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-1x). The residue was purified using flash chromatography (acetone:CH_2Cl_2 = 1:40) to afford **2-1x** (44.2 mg, 83%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.57 (m, 1H), 7.36-7.34 (m, 1H), 7.24-7.14 (m, 3H), 7.05 (d, *J* = 15.2 Hz, 1H), 6.85 (dd, *J* = 10.7, 15.2 Hz, 1H), 6.64-6.56 (m, 2H) 6.48-6.35 (m, 2H), 6.08 (d, *J* = 15.2 Hz, 1H), 6.05 (s, 1H), 3.88 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 164.7, 157.4, 138.2, 136.1, 135.4, 135.0, 133.7, 133.4, 131.8, 131.0, 129.9, 129.9, 128.7, 126.8, 126.2, 122.2, 103.0, 95.7, 56.1, 8.9; HRMS (ESI) [2M+Na]+: calcd for $C_{42}H_{38}O_6Cl_2Na$, 731.1943; found 731.1928.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chlorophenyl)octa-1,3,5,7-tetraenyl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-1y). The residue was purified using flash chromatography (acetone:CH_2Cl_2 = 1:40) to afford **2-1y** (42.1 mg, 79%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.28-7.18 (m, 4H), 6.85 (dd, *J* = 10.1, 15.2 Hz, 1H), 6.58-6.50 (m, 3H), 6.47-6.35 (m, 2H), 6.09 (d, *J* = 15.2 Hz, 1H), 6.05 (s, 1H), 3.88 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 164.7, 157.3, 139.0, 138.1, 135.7, 135.4, 134.7, 133.6, 132.6, 131.8, 130.1, 129.9, 127.7, 126.2, 124.8, 122.2, 103.0, 95.8, 56.2, 8.9; HRMS (ESI) $[M+Na]^+$: calcd for $C_{21}H_{19}O_3ClNa$, 377.0920; found 377.0914.

6-((1*E*,3*E*,5*E*,7*E*)-8-(3-chloro-1-(methylsulfonyl)-1*H*-pyrrol-2-yl)octa-1,3,5,7-tetraenyl)-4-methoxy-3-methyl-2*H*-pyran-2-one (2-1z). The residue was purified using flash chromatography (acetone:CH_2Cl_2 = 1:20) to afford **2-**

1z (46.7 mg, 74%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.19 (m, 2H), 7.16 (d, *J* = 3.2 Hz, 1H), 6.94 (d, *J* = 15.8 Hz, 1H), 6.60-6.44 (m, 3H), 6.39 (dd, *J* = 11.4, 13.9 Hz, 1H), 6.31 (d, *J* = 3.2 Hz, 1H), 6.09 (d, *J* = 14.5 Hz, 1H), 6.05 (s, 1H), 3.88 (s, 3H), 3.13 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 164.7, 157.3, 138.0, 136.1, 135.3, 134.2, 133.4, 132.1, 127.4, 122.4, 121.7, 118.6, 117.4, 114.0, 103.1, 95.8, 56.2, 42.5, 8.9; HRMS (ESI) $[M+Na]^+$: calcd for $C_{20}H_{20}NO_5ClNaS$, 444.0648; found 444.0652.

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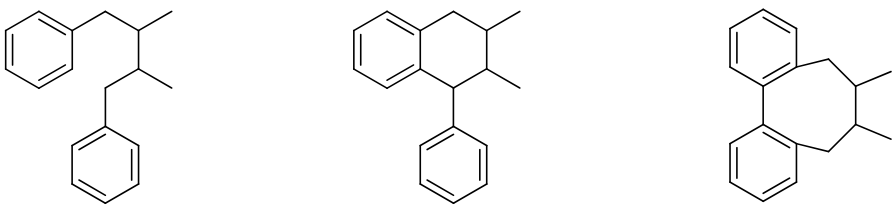
Chapter 3

Synthesis and Biological Evaluation of Lignan Natural Products as Potential Chemotherapeutic Agents

3.1 Introduction

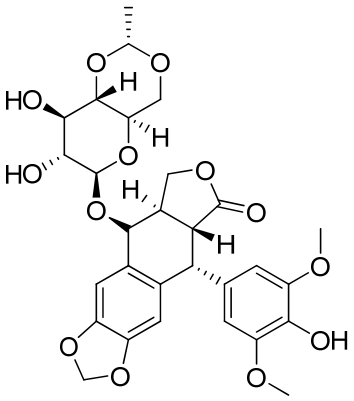
In our continued search for potential antitumor agents from natural products, we were attracted by the numerous biological properties displayed by lignans. Some of these biological effects include antioxidant antitumor, antiviral and antibacterial.[1-7] Lignan is an important class of natural products that is derived from plants. They are secondary plant metabolites produced by the oxidative dimerization of two phenylpropanoid units and are structurally diverse based on the basic scaffold of two phenylpropane units.[8] Typically, lignans are classified into 3 categories based on the types of C-C bond and the oxygen bridge joining the two phenylpropane units.[9] The first class comprises acylic lignan derivatives **3-1** and includes dibenzylbutanes, dibenzyl substituted tetrahydrofuran and dibenzylbutyrolactones (Figure 3.1). The second class consists of cyclohexyl lignan derivatives **3-2** such as podophyllotoxin and the third class is the dibenzocyclooctadienes.



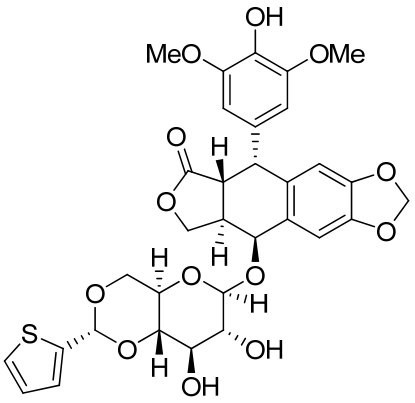
3-1 **3-2** **3-3**

Figure 3.1. Classes of lignan compounds

Among the numerous biological activities displayed by lignans, their antitumor activity is of particular interest to us. Etoposide and teniposide are two clinical drugs that are derived from plant lignans.[8]

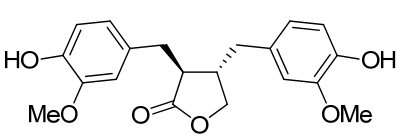


etoposide

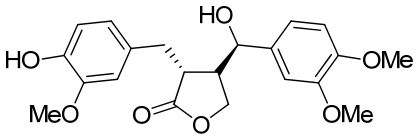


teniposide

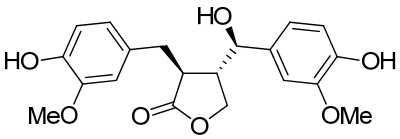
Figure 3.2. Lignan-derived anticancer drugs.



matairesinol



2-hydroxyarctigenin



hydroxymatairesinol

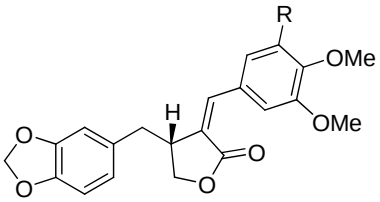
Figure 3.3. Lignans with antitumor properties.

Other examples of anticancer plants lignans include matairesinol and 2-hydroxyarctigenin which were isolated from safflower seeds and found to exhibit potent cytotoxic effects against human promyleocytic leukemia HL-60

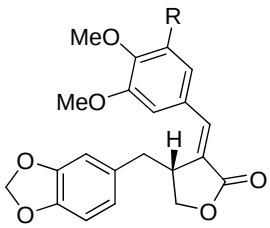
cells (Figure 3.3).[10] Hydroxymatairesinol was able reduce tumor volume in rats and short-term toxicity studies had shown that it is essentially non-toxic to rats.[1,2]

In 2003, Harn and co-workers discovered that the acetone extract of *Bupleurum scorzonerifolium* inhibits the proliferation of A549 human lung cancer cells *in vitro*.[11] *Bupleurum scorzonerifolium*, also known as Nan Chai Hu, is an important Chinese herb that is used in traditional Chinese medicine formulations.[12] In that same year, Lin and co-workers isolated two new lignans, isochaihulactone **3-4a** and chaihunapthone, along with 11 known compounds including nemerosin **3-5a** from the root of *Bupleurum scorzonerifolium* (Figure 3.3).[13] **3-4a** and to a lesser extent, **3-5a** were subsequently found to inhibit proliferation of various human cancer cells.[14,15]

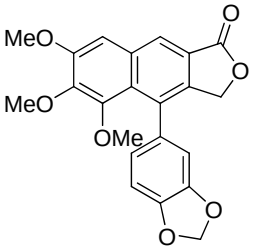
The synthesis of **3-5a** has earlier been reported while the synthesis of **3-4a** has never been reported before. This, together with the cytotoxicity effects of **3-4a** and **3-5a**, prompted us to carry the asymmetric synthesis of **3-4a** and **3-5a** as well as their enanotiomers, sylvestrin **3-4b** and **3-5b**. The synthesis of all 4 stereoisomers is desired as enanotiomers may possess differing biological properties from each other.



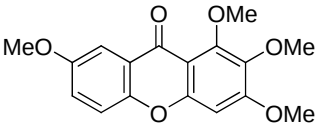
isochaihulactone **3-4a**: R = OMe
isokaerophyllin: R = H



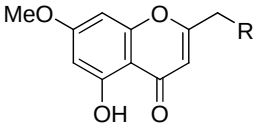
nemerosin **3-5a**: R = OMe
kaerophyllin: R = H



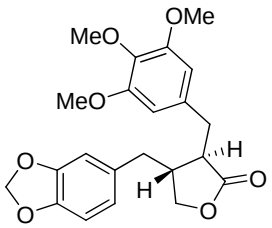
chaihunaphthone



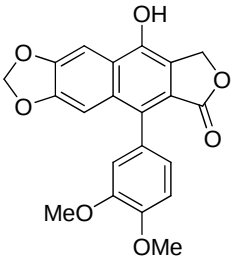
1,2,3,7-tetramethoxyxanthone



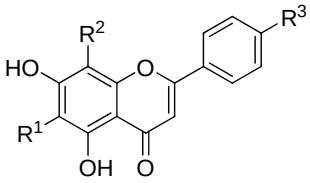
eugenin: R = H
saikochromone A: R = OH



(-)-yatein



chinensinaphthol



isoscutellarein-8-methyl ether: R^1 = H, R^2 = OMe, R^3 = OH
oroxylin: R^1 = OMe, R^2 = H, R^3 = H
wogonin: R^1 = H, R^2 = OMe, R^3 = H

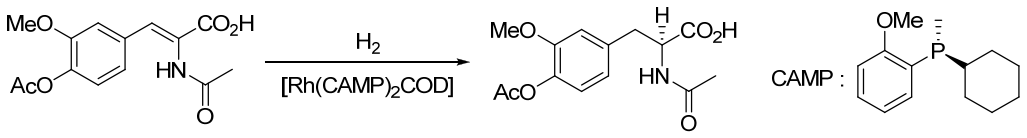
Figure 3.4. Natural products isolated from the root of *Bupleurum scorzonerifolium*.

Asymmetric synthetic methodologies are gaining in importance as illustrated by the recent trends in the FDA approval of new drug applications. The percentage of chiral drugs approved has increased from 58% in 1992 to 75% in 2006 while achiral drugs approvals had fallen over that same period. In addition, chiral drugs obtained using purely asymmetric synthetic techniques

(excluding the use of chirality pool starting material) has increased from 20% in 1992 to over 50% in 2006.[16]

Of the asymmetric techniques available, asymmetric hydrogenation is by far the most commonly used in academia and the industry. The field of asymmetric hydrogenation began when Wilkinson discovered the ability of Rh-PPh_3 complex to catalyze the hydrogenation of alkenes in solution.[17] This meant that the catalysis and reaction are occurring within the complex and not on the surface of the metal. This allows chemists to synthesize various ligands which can form different complexes with the metal for asymmetric hydrogenation to take place. The earliest industrial application of asymmetric hydrogenation is in the production of the anti-Parkinsonian drug $_L$-3,4-dihydroxyphenylalanine ($_L$-DOPA) at Monsanto in the 1970s.[18] Since then asymmetric hydrogenation has become one of the most important tool for the preparation of optically active compounds. This is due to several advantages of this transformation: high enantioselectivity, low catalyst loading, quantitative yields, perfect atom economy and mild conditions.[19]

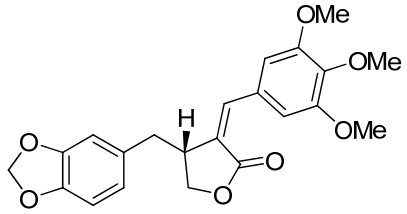
Scheme 3.1. Asymmetric hydrogenation step of the Monsanto $_L$-DOPA process



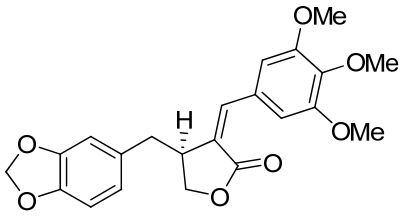
3.2 Results and Discussion

Of the 4 compounds we intend to synthesize, **3-4a** and **3-4b** are natural products which had been isolated previously but never synthesized. **3-5a** is a

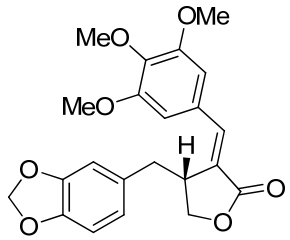
natural product which had previously been synthesized while there are no reports on the isolation or synthesis of **3-5b**.



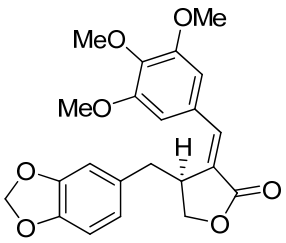
isochaihulactone **3-4a**



slyvestrin **3-4b**



nemerosin **3-5a**

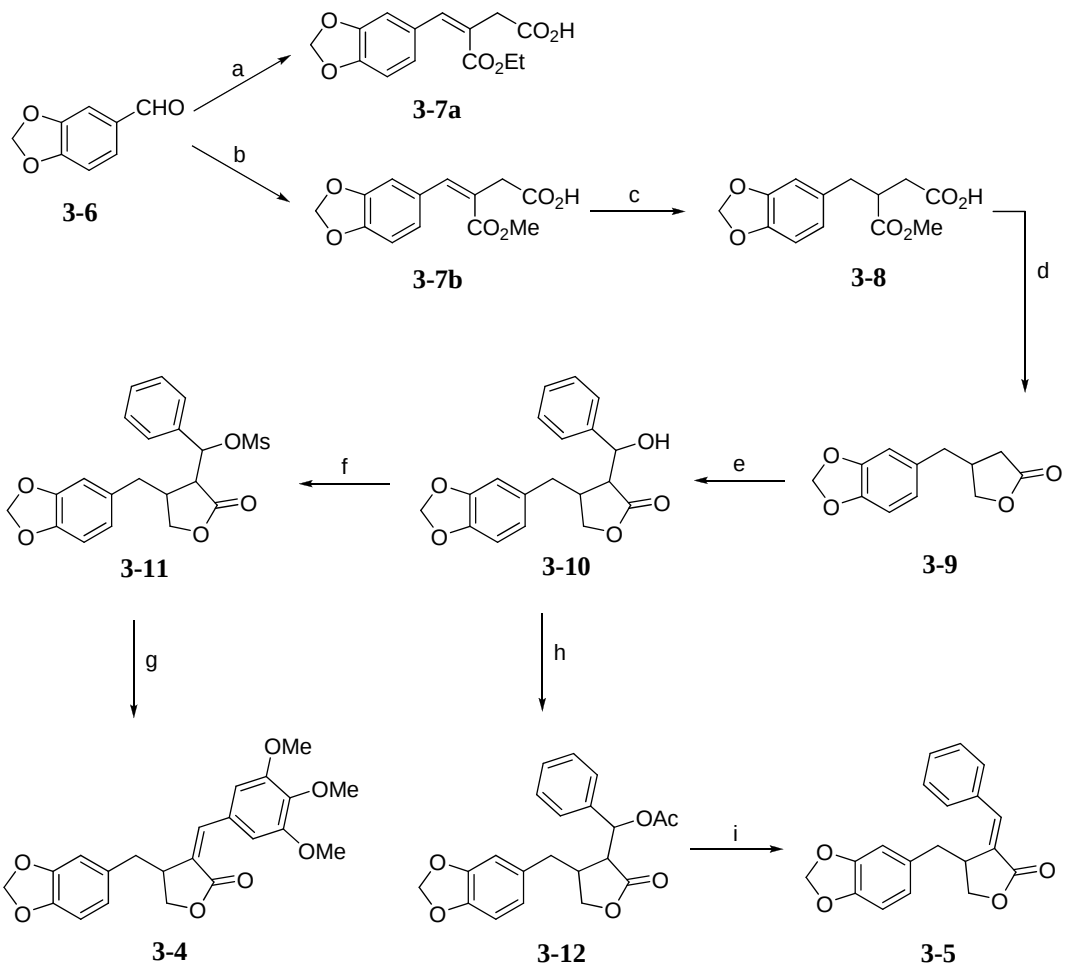


3-5b

Figure 3.5. Compounds synthesized.

Prior to the asymmetric synthesis of the 4 compounds, a synthetic route was developed for the synthesis of the racemic compounds **3-4** and **3-5**. Compound **3-7a** and **3-7b** were readily obtained via Stobbe condensation of piperonal and diethyl succinate. Initially, ethanol and sodium ethoxide were used as the solvent and base respectively which afforded **3-7a** while the use of methanol and sodium methoxide provided **3-7b**. Although both reactions gave comparable yield, the latter reaction was preferred as **3-7b** is a solid and can be purified via recrystallization unlike **3-7a** which requires chromatographic methods as it exists as a sticky liquid. This allows the synthesis of **3-7b** in large quantity as its starting materials are inexpensive as well.

Scheme 3.2. Preparation of **3-4** and **3-5**[a]



[a]Reagents and conditions: : (a) diethyl succinate, EtONa, EtOH, 70 °C; (b) diethyl succinate, MeONa, MeOH, reflux; (c) 10% Pd/C, H_2, MeOH, rt; (d) (i) KOH, $CaCl_2$, EtOH, 0 °C; (ii) $NaBH_4$, rt; (iii) 3 M HCl, rt; (e) LDA, 3,4,5-trimethoxybenzaldehyde, THF, -78 °C, (f) MsCl, TEA, CH_2Cl_2, 0 °C; (g) DBU, CH_3CN, rt; (h) Ac_2O, TEA, DMAP, CH_2Cl_2, rt; (i) DBU, $PhCH_3$, 80 °C.

Subsequent hydrogenation of **3-7b** afforded **3-8** in excellent yield and the chemoselective reduction of the potassium salts of **3-8** with $CaCl_2/NaBH_4$ in ethanol gave the desired lactone **3-9**. Aldol condensation of **3-9** with 3,4,5-trimethoxybenzaldehyde gave alcohol **3-10** which was treated with either

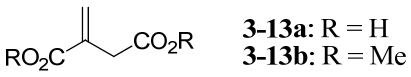
methanesulfonyl chloride or acetic anhydride to afford the corresponding meslyate **3-11** or acetate **3-12** respectively. Base promoted elimination of the formed acetate afforded **3-5** exclusively but elimination of the mesylate intermediate to afford **3-4** proved less selective. Varying the reaction conditions failed to increase the ratio of **3-4** to **3-5** beyond 3:1. The ratio of **3-4** and **3-5** were determined by ^{1}H NMR.

Table 3.1. Optimization of the synthesis of **3-4**.

Solvent	Base	Temp. (°C)	**3-4 : 3-5**
CH_3CN	DBU	rt	3:1
CH_3CN	DBU	-40	3:1
DMF	DBU	rt	3:1
DMF	DBU	0	3:1
DMF	KOH	rt	3:1
Toluene	DBU	rt	1:2
EtOH	KOH	rt	3:1
EtOH	DBU	rt	3:1

With the racemic synthesis of **3-4** and **3-5** achieved, we proceeded with the asymmetric hydrogenation of **3-7b**. Although there are many chiral ligands available for the successful asymmetric hydrogenation of itaconic acid and its

dimethyl ester derivatives **3-13a** and **3-13b**, there have been far fewer reports on the successful asymmetric hydrogenation of *β*-substituted itaconic acid derivatives.[20-24] Ligands which afforded high enantioselectivity for the hydrogenation are MOD-DIOP[25,26], Et-DuPhos[27], TangPhos[28] and catASium M[29].



3-13a: R = H
3-13b: R = Me

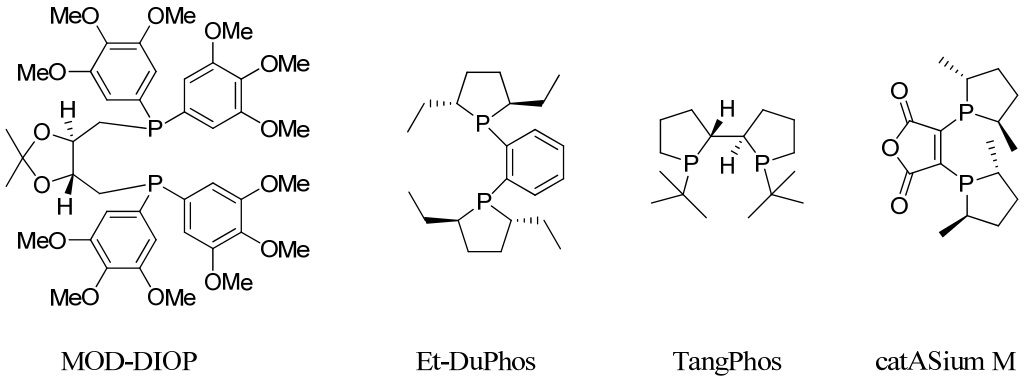
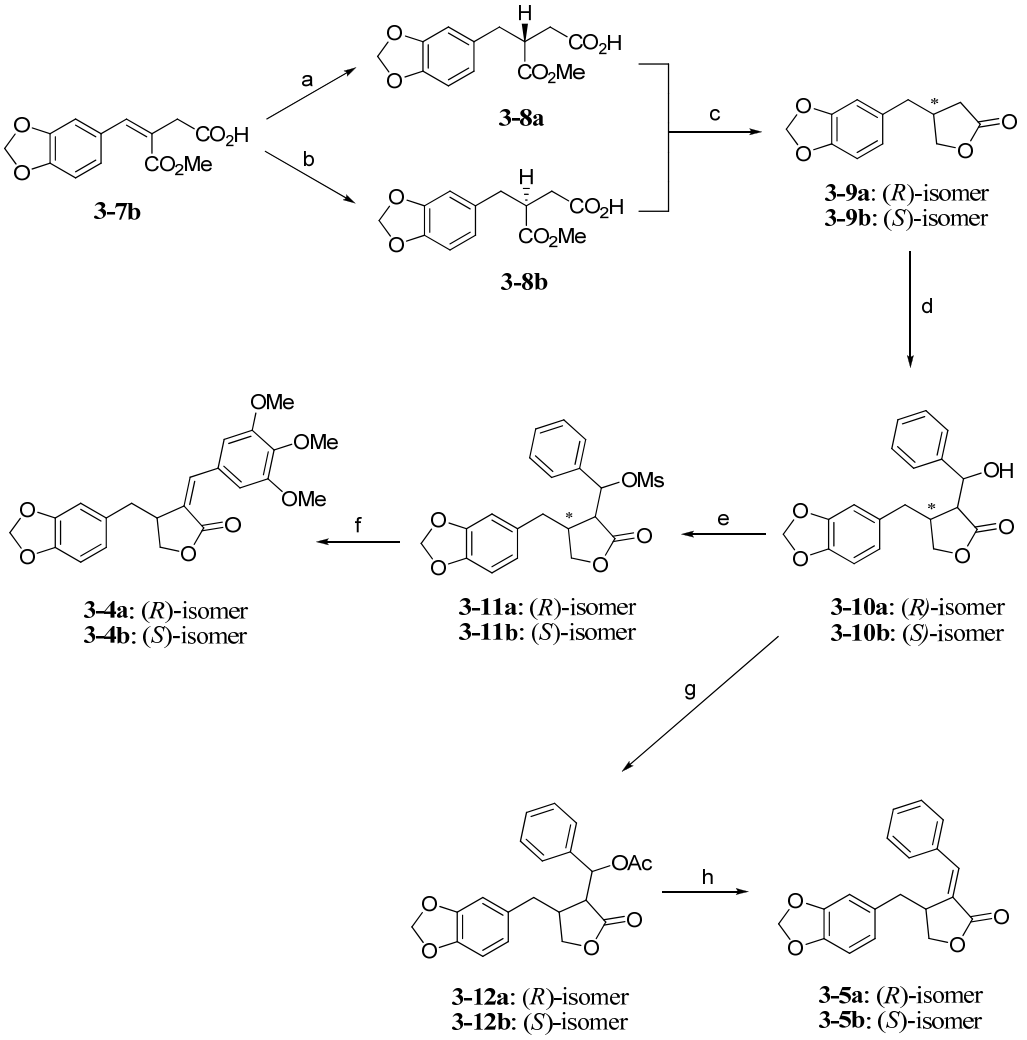


Figure 3.6. Structure of itaconic acid **3-13a**, its dimethyl derivative **3-13b** and ligands used for asymmetric hydrogenation.

Initial attempts at asymmetric hydrogenation of **3-7b** began with the use of commercially available catASium M. To our disappointment, the reaction failed to proceed and the starting material **3-7b** was recovered. Despite the meticulous degassing of solvent and increasing the pressure of H_2, there was no improvement. We eventually tried (*S*)-Et-DuPhos and gratifying, the hydrogenation of **3-7b** proceeded readily to furnish **3-8a** in 97% enantiomeric excess (ee). To obtain the other enantiomer, (*R*)-Et-DuPhos was used and **3-8b** was obtained in 90% ee. The enantio enrichment of **3-8a** and **3-8b** was carried out by washing the crude products **3-8a** and **3-8b** with Et_2O which improved

the ee of the two products to at least 98%. The ee of the compounds were determined by HPLC after converting **3-8a** and **3-8b** to their dimethyl ester derivatives. This simple enantio enrichment method, coupled with the readily available starting material **3-7b** prompted us to adopt commercially available Et-DuPhos as the chiral ligand for the hydrogenation of **3-7b**.

Scheme 3.3. Asymmetric synthesis of **3-4** and **3-5**[a]



[a]Reagents and conditions: (a) [{(*S*,*S*)-(Et-DuPhos)}Rh(COD)]BF_4, MeONa, 8 bar H_2, MeOH, rt; (b) [{(*R*,*R*)-(Et-DuPhos)}Rh(COD)]BF_4, MeONa, 8 bar H_2, MeOH, rt; (c) (i) KOH, $CaCl_2$, EtOH, 0 °C; (ii) $NaBH_4$, rt; (iii) 3 M HCl, rt; (d)

LDA, 3,4,5-trimethoxybenzaldehyde, THF, -78 °C, (e) MsCl, TEA, CH_2Cl_2, 0 °C; (f) DBU, CH_3CN, rt; (g) Ac_2O, TEA, DMAP, CH_2Cl_2, rt; (h) DBU, $PhCH_3$, 80 °C.

With both **3-8a** and **3-8b** in hand, we proceeded with the synthesis based on the synthetic route of the racemic **3-4** and **3-5** (Scheme 3.3) to afford the 4 final compounds, **3-4a**, **3-4b**, **3-5a** and **3-5b**.

3.3 Biological Results[a]

[a]All the biological results were obtained as a result of a collaboration with another research group.

Table 3.2. Cytotoxicity of synthesized compounds against various cancer cells[a]

		IC_{50} (μM)			
Cell line	Origin	**3-4a**	**3-4b**	**3-5a**	**3-5b**
PC3	Androgen-independent prostate adenocarcinoma	7.2	1.1	13.5	8.7
LNCaP	Androgen-dependent prostate adenocarcinoma	6.5	0.96	12.5	13.8
J5	Hepatocarcinoma	Not attempted	Not attempeted	5.3	5.3
OECM-1	Oral squamous cell carcinoma	7.3	0.40	9.1	12.1

[a]The viability of the cells after treatment with various chemicals was evaluated using an MTT assay preformed in triplicate after 48 h of incubation.

The cytotoxicities of the 4 compounds against various cancer cells are shown in Table 3.2. As illustrated, the *Z*-isomers **3-4a** and **3-4b** displayed more potent cytotoxicities against all the classes of cancer cells tested compared to the *E*-isomers **3-5a** and **3-5b**. Comparing between **3-5a** and **3-5b**, it appears that there is little difference between the cytotoxicities of the two enanotiomers. However comparison of the 2 *Z*-isomers **3-4a** and **3-4b** showed that the S-enantiomer **3-4b** is significantly more potent than its mirror image **3-4a**. This is especially so against OECM-1 cancer cells where **3-4b** is 18-fold more potent than **3-4a**.

3.4 Conclusion

Earlier in Chapter 2, we described the synthesis of a class of polyenylpyyrole natural products and their analogs which displayed excellent cytotoxicity against A549 human lung cancer cells. In continuing our efforts to develop natural product-based antitumor agents, we have herein provided the synthesis of isochaihulactone **3-4a** and nemerosin **3-5a** as well as their enantiomers slyvestrin **3-4b** and **3-5b**. This represents the first reported synthesis of **3-4a**, **3-4b** and **3-5b**. The *Z*-isomers of these 4 compounds showed higher cytotoxicity against the cancer cells tested compared to the *E*-isomers. In particular **3-4b** displayed excellent activity against OECM-1 oral cancer cells with an IC_{50} of 0.40 μM.

3.5 Experimental Section

General Procedures. All chemical reagents and solvents were obtained from Sigma Aldrich, Merck, Alfa Aesar, or Fluka and were used without further purification. Analytical TLC was carried out on precoated silica plates (Merck silica gel 60, F254) and visualized with UV light or stained with phosphomolybdic acid (PMA) stain. Flash column chromatography was performed with silica (Merck, 70-230 mesh). The ee of the dimethyl esters of **3-8a**, **3-8b**, **3-4a**, **3-4b**, **3-5a** and **3-5b** were determined via HPLC using a CHIRALPAK IB analytical column. The purities of the compounds were determined via HPLC using a Shimadzhu LCMS-IT-TOF system with a Phenomenex Luma C18 column. Compounds used in the biological assays have purities of at least 95%. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker ACF 300 or AMX 500 Fourier transform spectrometer. Chemical shifts were reported in parts per million (δ) relative to the internal standard of tetramethylsilane (TMS). The signals observed were described as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet). The number of protons (n) for a given resonance was indicated as nH. Mass spectra were performed on a Finnigan/MAT LCQ mass spectrometer under electron spray ionization (ESI) or electron impact (EI) techniques.

4-(benzo[*d*][1,3]dioxol-5-yl)-3-(ethoxycarbonyl)but-3-enoic acid (3-7a). 21% sodium ethoxide solution (9.0 mL, 24.0 mmol) was added to a mixture of piperonal (3.0 g, 20.0 mmol) and diethyl succinate (5.2 g, 30.0 mmol) in ethanol (30 mL) and stirred at 70 °C for 1 h. The reaction mixture was cooled to room temperature before adding 3 N HCl until pH 2~3 was achieved. The

mixture was extracted with Et_2O and the combined organic extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified using flash chromatography (MeOH:CH_2Cl_2 = 1:30) to afford **3** (4.60 g, 82%) as a pale yellow, viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 6.89-6.83 (m, 3H), 5.99 (s, 2H), 4.28 (q, *J* = 6.9 Hz, 2H), 3.58 (s, 2H), 1.33 (t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 167.5, 148.4, 147.9, 142.0, 128.7, 124.0, 123.9, 109.1, 108.6, 101.4, 61.3, 33.6, 14.1; HRMS (ESI) $[M+Na]^+$: calcd for $C_{14}H_{14}O_6Na$ 301.0688, found 301.0686.

4-(benzo[*d*][1,3]dioxol-5-yl)-3-(methoxycarbonyl)but-3-enoic acid (3-7b). MeONa (1.30 g, 24.0 mmol) was added to a mixture of piperonal (3.0 g, 20.0 mmol) and diethyl succinate (5.2 g, 30.0 mmol) in methanol (30 mL) and refluxed for 1 h. After which, the solvent was removed under reduced pressure before adding 3 N HCl until pH 2~3 was achieved. The mixture was extracted with Et_2O and the combined organic extracts was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was washed with Et_2O to afford **3-7b** (4.12 g, 78%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.5 (s, 1H), 7.68 (s, 1H), 7.00-6.94 (m, 3H), 6.07 (s, 2H), 3.73 (s, 3H), 3.43 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.0, 167.5, 148.1, 147.6, 140.5, 128.4, 124.6, 124.1, 108.9, 108.6, 101.5, 52.0, 33.5; HRMS (EI): calcd for $C_{13}H_{12}O_6$ 264.0634, found 264.0626.

3-(benzo[*d*][1,3]dioxol-5-ylmethyl)-4-ethoxy-4-oxobutanoic acid (3-8). A mixture of 10% Pd/C (300 mg) and **3-7a** (3.96 g, 15.0 mmol) was dissolved in MeOH (30 mL) and stirred under a hydrogen atmosphere for 12 h. The reaction mixture was filtered and the filtrate concentrated to give **3-8** (3.83 g,

96%) as a colorless, viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 1.1 Hz, 1H), 6.60-6.58 (m, 1H), 5.93 (s, 2H), 3.68 (s, 3H), 3.08-2.95 (m, 2H), 2.72-2.67 (m, 2H), 2.47-2.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 174.4, 147.8, 146.4, 131.6, 122.1, 109.2, 108.3, 100.9, 52.0, 42.9, 37.3, 34.5; HRMS (ESI) $[M-H]^-$: calcd for $C_{13}H_{14}O_6$ 266.0790, found 266.0793.

(*R*)-3-(benzo[*d*][1,3]dioxol-5-ylmethyl)-4-methoxy-4-oxobutanoic acid (3-8a). Compound **3-7b** (2.64 g, 10.0 mmol), MeONa (54 mg, 1.00 mmol) and [{(*S*,*S*)-(Et-DuPhos)}Rh(COD)]BF_4 (6.6 mg, 0.01 mmol) was added to degassed MeOH in a 100 mL hydrogenation vessel. The reaction vessel was stirred at room temperature under a hydrogen atmosphere (8 bar) for 48 h. Subsequently, the solvent was removed under reduced pressure and the residue was acidified with 1M HCl and extracted with EtOAc. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was washed with Et_2O twice to afford **3-8a** (2.00 g, 75%, 99% ee) as a pale yellow solid. $[\alpha]^{25}$ +14.1° (*c* 1.0, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR matches that of **3-8**.

(*S*)-3-(benzo[*d*][1,3]dioxol-5-ylmethyl)-4-methoxy-4-oxobutanoic acid (3-8b). Compound **3-7b** (2.64 g, 10.0 mmol), MeONa (54 mg, 1.00 mmol) and [{(*R*,*R*)-(Et-DuPhos)}Rh(COD)]BF_4 (6.6 mg, 0.01 mmol) were added to degassed MeOH in a 100 mL hydrogenation vessel. The reaction vessel was stirred at room temperature under a hydrogen atmosphere (8 bar) for 48 h. Subsequently, the solvent was removed under reduced pressure and the residue was acidified with 1M HCl and extracted with EtOAc. The combined organic

extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was washed with Et_2O twice to afford **3-8b** (2.00 g, 71%, 98% ee) as a pale yellow solid. $[\alpha]^{25}$ -13.8° (*c* 1.0, CH_2Cl_2). ^1H NMR and ^{13}C NMR matches that of **3-8**.

General procedure for the esterification of 3-8a and 3-8b. To **3-8a** or **3-8b** (53.2 mg, 0.20 mmol) in MeOH (2 mL) was added TMSCl (86.9 mg, 0.80 mmol) and stirred at 40 °C for 30 min. After which, H_2O was added and the reaction mixture was extracted with EtOAc. The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated to afford the methyl ester derivatives of **3-8a** and **3-8b** in essentially quantitative yield.

General procedure for the synthesis of 4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-dihydrofuran-2(3H)-one (3-9). KOH (85%, 1.04 g, 15.7 mmol) and $CaCl_2$ (1.84 g 16.6 mmol) were successively added to **3-8** (4.40 g, 15.7 mmol) in EtOH (40 mL) at 0 °C and stirred for 5 min. Thereafter, $NaBH_4$ (1.30 g, 34.4 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 4 h. After which, 3 M HCl was added until the reaction mixture achieved pH 0-1. The reaction mixture was then stirred for an additional 1 h. After evaporation of the solvent, water was added to the mixture and extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried over $MgSO_4$, concentrated and the residue obtained was purified using flash chromatography (EtOAc:hexane = 1:4).

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-dihydrofuran-2(3H)-one (3-9). 3-9 (2.82 g, 82%) was obtained as a colorless viscous oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.3 Hz, 1H), 6.63-6.58 (m, 2H), 5.94 (s, 2H), 4.32 (t, *J* =

8.2 Hz, 1H), 4.03-3.99 (m, 1H), 2.82-2.72 (m, 1H), 2.69-2.64 (m, 2H), 2.59 (dd, *J* = 8.2, 17.8 Hz, 1H), 2.27 (dd, *J* = 7.0, 17.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 148.0, 146.4, 131.9, 121.6, 108.8, 108.4, 101.0, 72.5, 38.6, 37.3, 34.1; HRMS (EI): calcd for $C_{12}H_{12}O_4$ 220.0736, found 220.0737.

(*R*)-4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-dihydrofuran-2(3H)-one (3-9a). **3-9a** (2.82 g, 82%) was obtained as a colorless viscous oil. $[\alpha]^{25}$ +4.2° (*c* 1.0, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR matches that of **3-8**.

(*S*)-4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-dihydrofuran-2(3H)-one (3-9b). **3-9b** (2.54 g, 75%) was obtained as a colorless viscous oil. $[\alpha]^{25}$ -3.8° (*c* 1.0, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR matches that of **3-9**.

General procedure for the synthesis of (*Z*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(3,4,5-trimethoxybenzylidene)dihydrofuran-2(3H)-one (3-4). A solution of 2 M lithium diisopropylamine in THF (6.5 mL) was added dropwise to a solution of **3-9** (2.20 g, 10.0 mmol) in THF (30 mL) at -78 °C and stirred for 45 min. Subsequently, a solution of 3,4,5-trimethoxybenzaldehyde (2.55 g, 13.0 mmol) in THF (7 mL) was added to the reaction mixture and stirred at -78 °C for 10 min. The mixture was quenched using saturated NH_4Cl solution and allowed to warm to room temperature before extracting with CH_2Cl_2. The combined organic extract was dried over $MgSO_4$, concentrated and the residue obtained was purified using flash chromatography (EtOAc:hexane = 2:3) to obtain a pale yellow viscous oil **3-10**. Triethylamine (3.63 g, 35.9 mmol) was added to the oil in CH_2Cl_2 (25 mL) and cooled to 0 °C. Methanesulfonyl chloride (3.39 g, 29.6 mmol) was then added at 0 °C and stirred for 15 min. The reaction mixture was quenched with water

and extracted with Et_2O. The combined organic extract was washed with brine, dried over $MgSO_4$, concentrated to afford a yellow viscous oil **3-11**. **3-11** was dissolved in CH_3CN (15 mL) with DBU (1.52 g, 10.0 mmol) added. The reaction mixture was stirred for 15 min, before water was added and extracted with EtOAc. The combined organic extract was washed with brine, dried over $MgSO_4$, concentrated and the residue obtained was purified using flash chromatography (EtOAc:Hexane = 1:3).

(*Z*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(3,4,5-trimethoxybenzylidene)dihydrofuran-2(3H)-one (3-4). 3-4 (2.71 g, 68%) was obtained as white powder. ^{1}H NMR (500 MHz, $CDCl_3$) of **2** δ 7.25 (s, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 1.3 Hz, 1H), 6.63-6.61 (m, 2H), 5.94 (d, *J* = 3.2 Hz), 4.32 (dd, *J* = 7.5, 9.5 Hz, 1H), 4.10 (dd, *J* = 3.8, 9.5 Hz, 1H), 3.80 (s, 6H), 3.80 (s, 3H), 3.31-3.28 (m, 1H), 2.93 (dd, *J* = 6.3, 13.3 Hz, 1H), 2.79 (dd, *J* = 8.8, 13.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 152.6, 147.9, 146.4, 140.5, 139.6, 131.3, 128.8, 126.3, 122.2, 109.2, 108.6, 108.3, 101.0, 69.8, 60.8, 56.1, 44.3, 40.6; HRMS (ESI) $[M+Na]^+$: calcd for $C_{22}H_{22}O_7Na$ 421.1263, found 421.1252.

Isochaihulactone (3-4a). **3-4a** (2.75 g, 69%) was obtained as a white powder. $[\alpha]^{25}$ -68.5° (*c* 1.0, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR matches that of **3-4**.

Slyvestrin (3-4b). **3-4b** (2.63 g, 66%) was obtained as a white powder. $[\alpha]^{25}$ +75.2° (*c* 1.0, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR matches that of **3-4**.

General procedure for the synthesis of (*E*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(3,4,5-trimethoxybenzylidene)dihydrofuran-2(3H)-one (3-5). A solution of 2 M lithium diisopropylamine in THF (6.5 mL) was added dropwise to a solution of **3-9** (2.20 g, 10.0 mmol) in THF (30 mL) at -78 °C and stirred for 45 min. Subsequently, a solution of 3,4,5-trimethoxybenzaldehyde (2.55 g, 13.0 mmol) in THF (7 mL) was added to the reaction mixture and stirred at -78 °C for 10 min. The mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature before extracting with CH_2Cl_2. The combined organic extract was dried over $MgSO_4$, concentrated and the residue obtained was purified using flash chromatography (EtOAc:hexane = 2:3) to yield a pale yellow viscous oil **3-10**. To the oil was added CH_2Cl_2 (10 mL), Ac_2O (1.30 g, 12.7 mmol), triethylamine (1.30 g, 12.9 mmol), DMAP (30 mg, 0.25 mmol) and stirred for 20 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with 1.5 M HCl, water and saturated $NaHCO_3$ solution. The organic extract was dried over $MgSO_4$ and then concentrated to provide **3-12** as a yellow oil. **3-12** and DBU (1.1 mL, 7.4 mmol) were dissolved in toluene (20 mL) and stirred at 80 °C for 1 h. After evaporation of the solvent, the residue was purified by flash chromatography (EtOAc:Hexane = 1:3)

(*E*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(3,4,5-trimethoxybenzylidene)dihydrofuran-2(3H)-one (3-5). 3-5 (1.81 g, 91%) was obtained as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.76 (s, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.60-6.57 (m, 2H), 5.91 (d, J = 5.1 Hz), 4.30-4.23 (m, 2H), 3.88 (s, 3H), 3.87 (s, 6H), 3.85-3.81 (m, 1H), 3.01 (dd, J =

5.0, 14.5 Hz, 1H), 2.65 (dd, J = 10.1, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 153.3, 147.9, 146.5, 139.8, 137.6, 131.2, 129.4, 127.0, 121.8, 109.0, 108.4, 107.3, 101.0, 69.6, 60.9, 56.2, 39.4, 37.7; HRMS (ESI) $[M+Na]^+$: calcd for $C_{22}H_{22}O_7Na$ 421.1263, found 421.1248.

Nemerosin (3-5a). **3-5a** (1.77 g, 89%) was obtained as a white powder. $[\alpha]^{25}$ -18.6° (*c* 1.0, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR matches that of **3-5**.

(*S*,*Z*)-4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3-(3,4,5-trimethoxybenzylidene)dihydrofuran-2(3H)-one (3-5b). **3-5b** (1.73 g, 87%) was obtained as a white powder. $[\alpha]^{25}$ +22.5° (*c* 1.0, CH_2Cl_2). ^{1}H NMR and ^{13}C NMR matches that of **3-5**.

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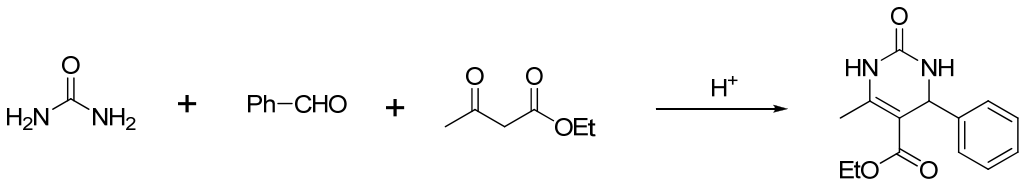
Chapter 4:

A Rapid and Convenient Synthesis of 5-Unsubstituted 3,4-Dihydropyrimidin-2-ones and thiones

4.1 Introduction

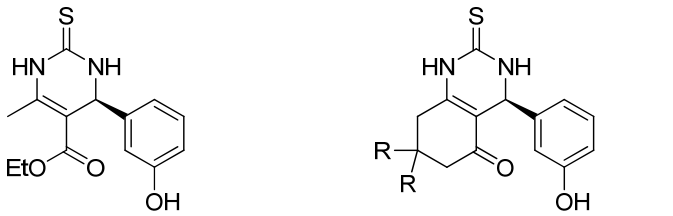
It has been more than 100 years since Pietro Biginelli discovered a multicomponent reaction that formed the 3,4-dihydropyrimidin-2-one compound **4-1** in 1893.[1] It involves a one-pot reaction between urea, benzaldehyde and ethyl acetoacetate (Scheme 4.1). However this reaction was largely ignored in the decades that followed until 1980s when interest in this efficient reaction picked up significantly. This is due to the discovery of 3,4-dihydropyrimidine-2-ones/thiones as useful targets in chemical synthesis because they have been associated with a diverse range of therapeutic and medicinal properties.[2-11] The dihydropyrimidinone scaffold is also found in various marine alkaloids which have been shown to possess antiviral, antibacterial and anti-inflammatory activities.[12] Moreover the batzelladine alkaloids are known to be potent HIV gp-120-CD4 inhibitors.[13]

Scheme 4.1. The Biginelli reaction



4-1

In particular, monastrol and their analogs have been found to inhibit human kinesin Eg5, which plays an essential role in mitosis (Figure 4.1).[14,15] Because compounds that cause mitotic arrests have been known to possess anticancer activity, we were interested in synthesizing a small library of monastrol analogs. In addition, our group had earlier explored the sodium channel blockade activities of pyrimidin-2-ones and pyrimidi-2-thiones and identified two compounds, **4-2** and **4-3** which possess neuronal sodium channel blockade activities (Figure 4.2).[16] In continuing our interest in the investigation of pyrimidin-2-ones and pyrimidi-2-thiones for their sodium channel blockade and anti-tumor activities, the synthesis of these compounds carrying different substituents from **4-2** and **4-3** was explored.



(S)-monastrol

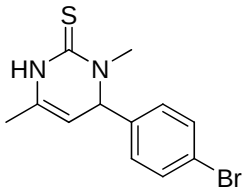
R = H: (S)-enastron
R = Me: (S)-dimethylenastron

Figure 4.1. Structures of (S)-monastrol and its analogs as inhibitors of kinase Eg5.

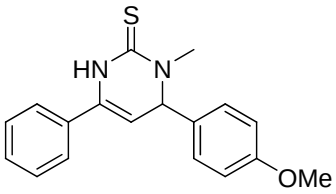
4.2 Results and Discussion

Typically, dihydropyrimidinones obtained via Biginelli reaction would house an ester at the C5 position.[17] However Bussolari and co-worker had demonstrated that replacing alkyl acetoacetate with oxalacetic acid **4-6** as a substrate for the Biginelli reaction led to the formation of 5-unsubstituted 3,4-dihydropyrimidin-2-ones due to in-situ decarboxylation after cyclization.[18]

These compounds are of interest to us as they bear resemblance to monastrol and compounds **4-2** and **4-3**. Moreover, there already exists in the literature a large library of dihydropyrimidinones with an ester at the C5 position. As such, we decided to explore the synthesis of the more novel 5-unsubstituted 3,4-dihydropyrimidin-2-ones/thiones.



4-2

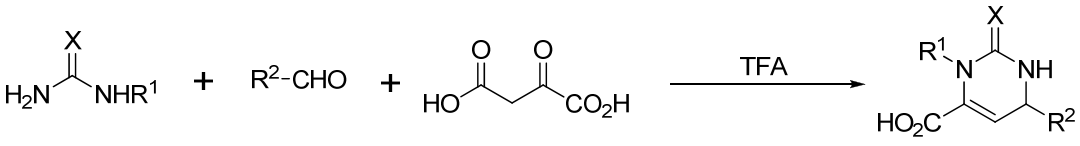


4-3

Figure 4.2. Pyrimidi-2-thione **4-2** and pyrimidin-2-one **4-3** with sodium channel blockage ability.

One of the major drawbacks to the reaction reported by Bussolari and co-worker is the long reaction time (12 h). For library preparation, it would be desirable if the reaction could be (i) conducted expeditiously with good yield and (ii) applied to a variety of reagents. To achieve this, we explored the use of microwave irradiation and also expanded the diversity by applying thiourea and substituted urea/thiourea to the reaction (Scheme 4.2).

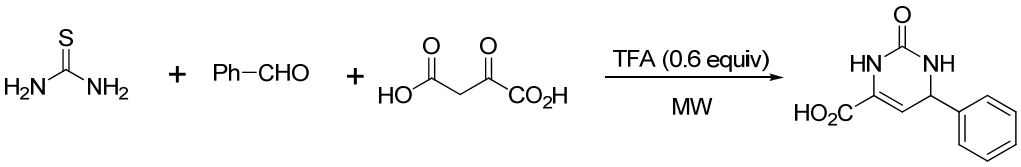
Scheme 4.2. Modified Biginelli reaction.



4-4 **4-5** **4-6** **4-7**

According to Bussolari and co-worker, 5-unsubstituted 3,4-dihydropyrimidin-2-ones could be effectively synthesized from oxalacetic acid, urea and aldehyde when TFA was used as a catalyst and dichloroethane as the solvent. In our initial synthesis of 6-phenyl-2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid **4-7a**, we adopted Bussolari's procedure but replaced urea with thiourea and obtained the compound in 64% yield. This result was encouraging as it demonstrated the first synthesis of 2-thioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid. To optimize the reaction, we explored microwave irradiation under different reaction conditions (Table 4.1) and found that **4-7a** was obtained in good yields when the reaction was performed in solvents like CH_2Cl_2, THF or dichloroethane (entries ii, viii and x, Table 1). To demonstrate the versatility of these reaction conditions for the synthesis of **4-7**, we carried out the reaction with different aldehydes.

Table 4.1. Optimization of the synthesis of **4-7a**.



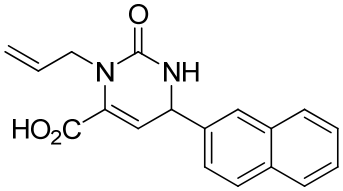
4-4a **4-5a** **4-6** **4-7a**

Entry	**4-4a** (equiv)	**4-5a** (equiv)	**4-6** (equiv)	Solvent	Time (min)	Temp (°C)	Yield (%)
i	1.5	1.2	1	EtOH	10	120	60
ii	1.3	1.2	1	CH_2Cl_2	10	90	79
iii	1.3	1.2	1	CH_2Cl_2	15	90	74

iv	1.3	1.2	1	Toluene	10	90	-
v	1.3	1.2	1	THF	10	90	61
vi	1.3	1.2	1	THF	15	90	69
vii	1.3	1.2	1	THF	15	100	76
viii	1.2	1	1.2	THF	20	100	82
ix	1.3	1.2	1	$ClCH_2CH_2Cl$	10	90	78
x	1.2	1	1.2	$ClCH_2CH_2Cl$	10	90	84

However further experimentation showed that when CH_2Cl_2 and dichloroethane were used in the synthesis of certain analogs, in particular **4-7b** and **4-7c**, the desired product was not obtained and instead a black tar-like substance was found coated to the sides of the microwave vessel. A possible reason is that the product is less soluble in CH_2Cl_2 and dicholoroethane and precipitated on the sides of the microwave vessel during the reaction. The intense heat from the microwave radiation subsequently caused the decomposition of the product into the tar-like substance. Consequently, the reaction condition shown in entry viii of Table 1 was used as the general procedure for our synthesis and a diverse set of **4-7** was prepared in good yields with both electron-withdrawing and electron-donating aldehydes (Table 4.1). For reactions with substituted thiourea/urea, the reaction was observed to proceed chemoselectively to provide only the N3-substituted 3,4-

dihydropyrimidin-2-ones/thiones (determined by X-ray structure of **4-7w** and 1D NoE of **4-7p** and **4-7r**).



4-7w

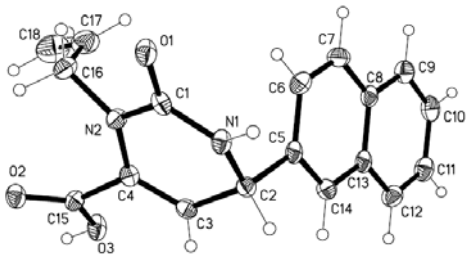
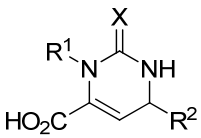


Figure 4.3. X-ray crystal structure of 4-7w

4.3 Conclusion

In summary, we have demonstrated an expeditious and high yielding synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-thiones and 5-unsubstituted 3,4-dihydropyrimidin-2-ones (Table 4.2). We have shown that under microwave irradiation, the reaction time was shortened from 12 h to 15 min. These results further demonstrate the value of microwave-assisted synthesis in increasing yield, shortening reaction time and streamlining high throughput synthesis.

Table 4.2 List of compounds synthesized.



4-7

Compound	X	R^1	R^2	Yield (%)[a]
4-7a	S	H	C_6H_5	82 (64[b])
4-7b	S	H	4-FC_6H_4	83

4-7c	S	H	2,4-$(MeO)_2C_6H_3$	83
4-7d	S	H	2-furyl	93
4-7e	S	H	2-thienyl	76
4-7f	S	H	2-naphthyl	82
4-7g	O	H	C_6H_5	94 (88[c])
4-7h	O	H	4-FC_6H_4	73
4-7i	O	H	2,4-$(MeO)_2C_6H_3$	91
4-7j	O	H	2-furyl	83
4-7k	O	H	2-thienyl	71 (72[c])
4-7l	O	H	2-naphthyl	89
4-7m	S	CH_3	C_6H_5	89
4-7n	S	CH_3	4-FC_6H_4	84
4-7o	S	allyl	C_6H_5	78
4-7p	S	allyl	3-ClC_6H_4	75
4-7q	S	allyl	2-naphthyl	79
4-7r	O	CH_3	C_6H_5	84
4-7s	O	CH_3	4-FC_6H_4	83
4-7t	O	CH_3	2,4-$(MeO)_2C_6H_3$	76
4-7u	O	allyl	C_6H_5	83
4-7v	O	allyl	3,5-$Br_2C_6H_3$	77
4-7w	O	allyl	2-naphthyl	81

[a] isolated yield

[b] using the conventional heating method as reported by Bussolari et al (ref 6)

[c] yield reported in ref 18

4.4 Experimental Section

General Procedures. All chemical reagents and solvents were obtained from Sigma Aldrich, Merck, Alfa Aesar, or Fluka and were used without further purification. The microwave-assisted reactions were performed using the Biotage Initiator microwave synthesizer. Analytical TLC was carried out on precoated silica plates (Merck silica gel 60, F254) and visualized with UV light. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker ACF 300 or AMX 500 Fourier transform spectrometer. Chemical shifts were reported in parts per million (δ) relative to the internal standard of tetramethylsilane (TMS). The signals observed were described as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet). The number of protons (n) for a given resonance was indicated as nH. Mass spectra were performed on a Finnigan/MAT LCQ mass spectrometer under electron spray ionization (ESI) or electron impact (EI) techniques.

General Procedure for the Synthesis of 4-7a to 4-7l. To a mixture of oxalacetic acid (2.6 mmol), aldehyde (2.0 mmol) and urea/thiourea (2.6 mmol) in THF (3 mL) was added TFA (0.10 mL). The mixture was heated at 95 °C for 15 min using microwave irradiation in a sealed tube. Thereafter, the mixture was cooled and the solvent was removed under reduced pressure. The residue obtained was washed with Et_2O and dried under vacuum to afford the final product.

6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7a: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.47 (s, 1H), 7.43-7.27 (m, 5H), 6.05 (d, J = 4.8 Hz, 1H), 5.18 (dd, J = 2.4, 4.8 Hz, 1H); ^{13}C NMR (75 MHz,

DMSO-d_6) δ 174.4, 162.3, 142.6, 128.8, 127.9, 126.3, 125.8, 110.8, 54.6; HRMS (ESI) $[M-H]^-$: calcd for $C_{11}H_9N_2O_2S$, 233.0379; found 233.0383.

6-(4-fluorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7b: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.50 (s, 1H), 7.33-7.30 (m, 2H), 7.26-7.22 (m, 2H), 6.04 (dd, J = 1.3, 3.2 Hz, 1H), 5.20 (dd, J = 2.5, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.3, 163.3, 162.3, 160.1, 138.9, 138.8, 128.5, 128.4, 126.0, 115.8, 115.5, 110.6, 53.9; HRMS (EI): calcd for $C_{11}H_9FN_2O_2S$, 252.0369; found 252.0363.

6-(2,4-dimethoxyphenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7c: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.38 (s, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.60-6.58 (m, 2H), 5.95-5.94 (m, 1H), 5.29 (dd, J = 2.5, 4.4 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.9, 162.4, 160.4, 156.3, 127.5, 125.6, 122.5, 110.2, 105.1, 98.6, 55.7, 55.3, 49.6; ; HRMS (ESI) $[M+H]^+$: calcd for $C_{13}H_{15}N_2O_4S$, 295.0747; found 295.0753.

6-(furan-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7d: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.56 (s, 1H), 7.67 (s, 1H), 6.46 (dd, J = 1.9, 3.2 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 5.97-5.96 (m, 1H), 5.26 (dd, J = 2.6, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 162.2, 153.4, 143.2, 127.3, 110.7, 107.6, 107.2, 48.2; HRMS (EI): calcd for $C_9H_8N_2O_3S$, 224.0256; found 224.0250.

6-(thiophen-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7e: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.61 (s, 1H), 7.51

(dd, J = 1.9, 3.8 Hz, 1H), 7.03-7.01 (m, 2H) 6.08-6.07 (m, 1H), 5.46 (dd, J = 2.6, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.0, 162.2, 146.2, 127.1, 126.3, 126.2, 125.0, 110.0, 49.8; HRMS (ESI) $[M-H]^-$: calcd for $C_9H_7N_2O_2S_2$, 238.9943; found 238.9944.

6-(naphthalen-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7f: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.56 (s, 1H), 7.97-7.90 (m, 3H), 7.76 (s, 1H), 7.53-7.47 (m, 3H), 6.14 (d, J = 4.5 Hz, 1H), 5.39 (dd, J = 2.5, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 162.3, 140.0, 132.8, 132.6, 128.8, 127.9, 127.6, 126.6, 126.3, 126.0, 124.9, 124.6, 110.6, 54.9; HRMS (EI): calcd for $C_{15}H_{12}N_2O_2S$, 284.0619; found 284.0612.

2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7g. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.76 (s, 1H), 7.39-7.28 (m, 5H), 5.79 (d, J = 4.4 Hz, 1H), 5.16 (dd, J = 1.9, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.0, 152.4, 143.8, 128.7, 127.7, 127.6, 126.1, 109.0, 54.7; HRMS (EI): calcd for $C_{11}H_{10}N_2O_3$, 218.0691; found 218.0696.

6-(4-fluorophenyl)-2-oxo-1,2,3,6-tetrahydro pyrimidine-4-carboxylic acid 4-7h: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.35-7.32 (m, 2H), 7.22-7.19 (m, 2H), 5.78-5.77 (m, 1H), 5.18 (dd, J = 1.9, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.9, 162.5, 160.6, 152.3, 140.0, 140.0, 128.2, 128.2, 127.8, 115.5, 115.4, 108.7, 54.0; HRMS (EI): calcd for $C_{11}H_9FN_2O_3$, 236.0597; found 236.0594.

6-(2,4-dimethoxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7i: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63 (s, 1H), 7.10 (d, J

= 8.2 Hz, 1H), 7.02 (s, 1H), 6.58-6.55 (m, 2H), 5.75 (d, *J* = 4.4 Hz, 1H), 5.31 (dd, *J* = 1.9, 4.4 Hz, 1H), 3.81 (s, 3H), 3.76 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.0, 160.0, 156.3, 152.9, 127.5, 127.0, 123.4, 108.2, 104.9, 98.5, 55.6, 55.3, 49.2; HRMS (EI): calcd for $C_{13}H_{14}N_2O_5$, 278.0903; found 279.0913.

6-(furan-2-yl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7j: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.62, (s, 1H), 7.34 (s, 1H), 6.42-6.41 (m, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 5.75 (dd, *J* = 1.9, 3.2 Hz, 1H), 5.21 (dd, *J* = 2.5, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.8, 154.7, 152.3, 142.8, 129.3, 110.5, 106.1, 105.5, 48.5; HRMS (EI): calcd for $C_9H_8N_2O_4$, 208.0484; found 208.0479.

2-oxo-6-(thiophen-2-yl)-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7k. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.49 (s, 1H), 7.47-7.46 (m, 1H), 7.01-6.99 (m, 2H), 5.83-5.82 (m, 1H), 5.46 (dd, *J* = 2.5, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.9, 151.9, 148.0, 128.1, 127.0, 125.5, 124.0, 108.2, 50.1; HRMS (EI): calcd for $C_9H_8N_2O_3S$, 224.0256; found 224.0255.

6-(naphthalen-2-yl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7l: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91-7.90 (m, 3H), 7.80 (s, 1H), 7.77 (s, 1H), 7.53-7.49 (m, 3H), 7.43 (s, 1H), 5.87 (d, *J* = 4.4 Hz, 1H), 5.35 (dd, *J* = 1.9, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.0, 152.5, 141.1, 132.9, 132.5, 128.6, 128.0, 127.8, 127.6, 126.4, 126.1, 124.7, 124.3, 108.6, 55.0; HRMS (EI): calcd for $C_{15}H_{12}N_2O_3$, 268.0848; found 268.0838.

General Procedure for the Synthesis of 4-7m-4-7w. To a mixture of oxalacetic acid (2.6 mmol), aldehyde (2.0 mmol) and *N*-substituted urea/thiourea (2.6 mmol) in THF (3 mL) was added TFA (0.10 mL). The mixture was heated at 95 °C for 15 min using microwave irradiation in a sealed tube. Thereafter, the mixture was cooled and the solvent was removed under reduced pressure. 0.5 M NaOH (20 mL) was then added to the residue and the resulting solution was extracted with EtOAc (3 x 15 mL). Subsequently, the aqueous phase was acidified using conc. HCl and extracted with 10 % *i*PrOH in CH_2Cl_2 (3 x 15 mL). The combined organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was washed with Et_2O and dried under vacuum to afford the final product.

3-methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7m: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.41-7.26 (m, 5H), 6.22 (d, J = 5.7 Hz, 1H), 5.00 (dd, J = 3.2, 6.3 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.3, 163.5, 141.9, 131.9, 128.8, 127.8, 126.0, 115.5, 52.6, 38.1; HRMS (EI): calcd for $C_{12}H_{12}N_2O_2S$, 248.0619; found 248.0622.

6-(4-fluorophenyl)-3-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7n: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.32-7.39 (m, 2H), 7.24-7.21 (m, 2H), 6.21 (d, J = 5.1 Hz, 1H), 5.02 (dd, J = 3.2, 5.7 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.2, 163.5, 162.7, 160.7, 138.1, 138.1, 132.1, 128.2, 128.2, 115.7, 115.5, 115.2, 51.9, 38.1; HRMS (EI): calcd for $C_{12}H_{11}FN_2O_2S$, 266.0525; found 266.0518.

3-allyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7o: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 1H), 6.97-6.94 (m, 2H),

6.88-6.62 (m, 3H), 5.78 (dd, J = 1.3, 5.7 Hz, 1H), 5.26-5.18 (m, 1H), 5.07-5.03 (m, 1H), 4.62-4.60 (m, 2H), 4.54-4.50 (m, 1H), 4.19 (dd, J = 7.0, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.9, 163.5, 141.8, 133.8, 130.5, 128.7, 127.8, 126.0, 117.3, 116.5, 52.6, 49.6; HRMS (EI): calcd for $C_{14}H_{14}N_2O_2S$, 274.0776; found 274.0770.

3-allyl-6-(3-chlorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7p: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.5 (br, 1H), 9.35 (s, 1H), 7.46-7.24 (m, 4H), 6.26 (d, J = 5.1 Hz, 1H), 5.66 (dd, J = 5.0, 10.7 Hz, 1H), 5.49 (d, J = 15.8 Hz, 1H), 5.08-5.06 (m, 2H), 4.96 (d, J = 17.0 Hz, 1H), 4.64 (dd, J = 5.7, 15.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.1, 163.5, 144.2, 133.7, 133.4, 131.1, 130.8, 127.7, 126.0, 124.6, 117.4, 115.8, 52.0, 49.6; HRMS (EI): calcd for $C_{14}H_{13}ClN_2O_2S$, 308.0386; found 308.0372.

3-allyl-6-(naphthalen-2-yl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7q: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.98-7.87 (m, 3H), 7.74 (s, 1H), 7.54-7.47 (m, 3H), 6.33 (d, J = 5.1 Hz, 1H), 5.76-5.68 (m, 1H), 5.52 (dd, J = 4.5, 15.8 Hz, 1H), 5.25-5.24 (m, 1H), 5.08-5.00 (m, 2H), 4.71 (dd, J = 6.3, 15.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.0, 163.6, 139.2, 133.8, 132.7, 132.4, 130.8, 128.7, 127.7, 127.6, 126.6, 126.3, 124.6, 124.3, 117.5, 116.4, 52.9, 49.7; HRMS (EI): calcd for $C_{18}H_{16}N_2O_2S$, 324.0932; found 324.0918.

3-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7r: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.41-7.28 (m, 5H), 5.89-5.88 (m, 1H), 5.05-5.04 (m, 1H), 3.07 (s, 3H); ^{13}C NMR (125 MHz,

DMSO-d_6) δ 163.9, 154.2, 143.2, 132.5, 128.7, 127.5, 126.0, 112.3, 53.2, 31.5; HRMS (EI): calcd for $C_{12}H_{12}N_2O_3$, 232.0848; found 232.0841.

6-(4-fluorophenyl)-3-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7s: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44 (s, 1H), 7.35-7.32 (m, 2H), 7.23-7.19 (m, 2H), 5.88 (d, J = 4.5 Hz, 1H), 5.07 (d, J = 3.2 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 162.5, 160.6, 154.2, 139.5, 139.4, 132.7, 128.2, 128.1, 115.6, 115.4, 112.0, 52.5, 31.5; HRMS (EI): calcd for $C_{12}H_{11}FN_2O_3$, 250.0754; found 250.0746.

6-(2,4-dimethoxyphenyl)-3-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7t: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.10 (s, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.58-6.55 (m, 2H), 5.84 (d, J = 4.4 Hz, 1H), 5.16 (d, J = 3.2 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.0, 160.1, 156.6, 154.9, 132.5, 126.9, 122.9, 111.9, 104.8, 98.6, 55.6, 55.3, 48.2, 31.6; HRMS (EI): calcd for $C_{14}H_{16}N_2O_5$, 292.1059; found 292.1071.

3-allyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7u: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.2 (s, 1H), 7.52 (s, 1H), 7.41-7.38 (m, 2H), 7.31-7.28 (m, 3H), 5.91 (d, J = 4.4 Hz, 1H), 5.77-5.69 (m, 1H), 5.10 (d, J = 5.0 Hz, 1H), 5.06-4.98 (m, 2H), 4.58 (dd, J = 3.8, 16.4 Hz, 1H), 4.33 (dd, J = 6.3, 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 153.7, 143.1, 135.2, 131.4, 128.7, 127.6, 126.0, 116.3, 113.2, 53.3, 43.8; HRMS (EI): calcd for $C_{14}H_{14}N_2O_3$, 258.1004; found 258.0996.

3-allyl-6-(3,5-dibromophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7v: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.3 (s, 1H), 7.77 (s,

1H), 7.62 (s, 1H), 7.50 (s, 2H), 5.96-5.95 (m, 1H), 5.73-5.67 (m, 1H), 5.14-5.13 (m, 1H), 5.07-4.96 (m, 2H), 4.56 (dd, J = 2.5, 16.4 Hz, 1H), 4.31 (dd, J = 5.7, 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 153.5, 147.5, 134.9, 132.5, 132.3, 128.1, 122.8, 116.4, 111.8, 52.1, 43.8; HRMS (EI): calcd for $C_{14}H_{12}Br_2N_2O_3$, 413.9215; found 413.9201.

3-allyl-6-(naphthalen-2-yl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid 4-7w: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96-7.89 (m, 3H), 7.78 (s, 1H), 7.65 (s, 1H), 7.53-7.50 (m, 3H), 6.00 (dd, J = 1.3, 5.1 Hz, 1H), 5.82-5.74 (m, 1H), 5.30 (dd, J = 1.9, 5.0 Hz, 1H), 5.08-5.03 (m, 2H), 4.64-4.60 (m, 1H), 4.39 (dd, J = 5.7, 16.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.9, 153.7, 140.5, 135.2, 132.9, 132.5, 131.6, 128.6, 127.8, 127.6, 126.5, 126.1, 124.5, 124.3, 116.3, 113.0, 53.5, 43.9; HRMS (EI): calcd for $C_{18}H_{16}N_2O_3$, 308.1161; found 308.1154.

X-ray crystal data of 4-7w

Identification code	yl217	
Empirical formula	C39 H38 N4 O7	
Formula weight	674.73	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.7733(11) Å	α= 90°.
	b = 21.947(2) Å	β= 110.448(2)°.
	c = 15.1328(16) Å	γ = 90°.
Volume	3352.6(6) $Å^3$	
Z	4	
Density (calculated)	1.337 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	1424	
Crystal size	0.24 x 0.16 x 0.08 mm^3	
Theta range for data collection	2.22 to 27.50°.	
Index ranges	-6<=h<=13, -28<=k<=28, -19<=l<=19	
Reflections collected	23436	
Independent reflections	7675 [R(int) = 0.0739]	
Completeness to theta = 27.50°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9926 and 0.9781	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7675 / 0 / 463	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0631, wR2 = 0.1392	
R indices (all data)	R1 = 0.1267, wR2 = 0.1623	
Largest diff. peak and hole	0.566 and -0.265 $e.Å^{-3}$	

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