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DESIGN AND SYNTHESIS OF NON-XANTHONE STRUCTURAL ANALOGS OF α-MANGOSTIN

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DESIGN AND SYNTHESIS OF NON-XANTHONE STRUCTURAL ANALOGS OF α-MANGOSTIN

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Dr. S. Yoganathan

ABSTRACT

DESIGN AND SYNTHESIS OF NON-XANTHONE STRUCTURAL ANALOGS OF α-MANGOSTIN

Maryam Foroozmehr

α-Mangostin belongs to a class of polyphenolic compounds called xanthones. The potential pharmacological effects such as anti-bacterial and anti-cancer effects of α-mangostin have made it an important natural product for medicinal chemistry evaluation. During this thesis research, we have designed and synthesized a series of non-xanthone analogs of α-mangostin for medicinal chemistry evaluation. A commercially available starting material, methyl-4-methoxysalicylate was used to synthesize these non-xanthone analogs. The analogs were designed as more flexible derivatives compared to the tricyclic motif within α-mangostin yet retain the hydroxybenzoate scaffold. Through a one-pot chemical synthesis, with relatively high yield (70%), we prepared eight different benzyl-ether analogs. The benzyl-ether scaffolds contained various substituents at the 4-positon of the aryl ring, and we evaluated the effect of these substituents on the antibacterial activity. Moreover, the alkylation chemistry we have utilized is very simple to do and suitable for the large-scale preparation of these analogs. The chemical approach reported here can be extended to incorporate various benzyl and alkyl motifs at the 2-position of the methyl-4-methoxysalicylate core for elaborate medicinal chemistry efforts. Our initial antibacterial activity evaluation of selected derivatives from this series showed no activity at 100 μM concentration against *S. aureus* and *S. epidermidis* strains. Our future plan is to evaluate the antibacterial activity of these analogs against a larger panel of bacteria.

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CHAPTER 1. INTRODUCTION

1.1 Chemistry of xanthones:

Xanthones are an important class of oxygenated heterocycles and are known to exhibit a broad range of biological activities[1]. Many naturally occurring xanthones have been identified and characterized to date[1]. Their structural diversity and pharmacological importance have made xanthones an important class of molecules for drug discovery. As a result, a number of different synthetic xanthone derivatives have been reported in the literature[2]. The xanthone scaffold is made up of a γ-pyran moiety in the middle, fused with two benzene rings[3]. There are different numbering methods for the basic xanthone carbon skeleton in the literature, but the IUPAC provisional recommendations of 2004 for this tricyclic ring is based on a biosynthetic convention in which carbons 1-4 are devoted to ring B (acetate-derived ring) and the carbons 5-8 are assigned to ring A (shikimate-derived), (Figure 1)[4].

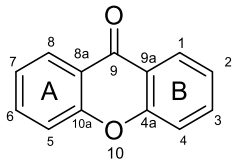

Figure 1. Structure of a xanthone core and IUPAC numbering of the scaffold.

1.2 Classification of xanthones:

Naturally occurring xanthones are classified into six different groups based on their substituents[2]. The most abundant naturally occurring xanthones are prenylated (60%) followed by simple (25%) and glycosylated (11%) xanthones.

1. Simple oxygenated xanthone
2. Xanthone glycosides
3. Prenylated xanthone
4. Bisxanthones
5. Xantholignoids
6. Miscellaneous xanthones

1.2.1 Simple oxygenated xanthone:

The substituents simply include hydroxyl, methoxy or methyl groups which depending on the level of the oxygenation could be subdivided in other groups like mono, di, tri, tetra, penta or hexa oxygenated. As per figure 2, 2-hydroxyxanthone and 2-hydroxy- 1-methoxyxanthone are two examples.

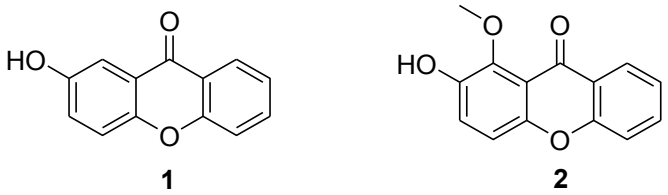

Figure 2. Structures of oxygenated xanthones.

The reported biological activities exclusively related to this group of xanthones include a wide variety of effects. Two of the compounds with their known pharmacological effects are trihydroxy xanthone with antibacterial activity [5] and polyhydroxy[6] and methyl[7] substituent xanthones with antimycobacterial activity, also other pharmacological activities attributed to this group are antimalarial[8], antifungal[5], CNS-depressant[9], anti-convulsant/antiepileptics[10], analgesics[11], antihypertensive[12], anticoagulant[13], anti-asthmatic[14], hepatoprotective[15], antidiabetics[16], anti-inflammatory[17], antiallergics[14] and antianaphylactics[18].

This group of xanthones target a wide variety of enzymes, having very different effects on them, including inhibitory effect on: acetylcholinesterase[19], cyclooxygenases (COXs) through COX-2 gene expression inhibition[20], cyclic AMP-phosphodiesterase [21], cyclic GMP-phosphodiesterase[18], lipoxygenase[20], nitric oxide synthase[22], aspartic[23], topoisomerases I and II[24], competitive reversible selective inhibition of monoamine oxidase A and B[25], competitive inhibition of MMLV[26] and non-competitive inhibition of hypoxantine-xanthine oxidase[27].

Oxygenated xanthones extracted from *Swertia chirata* showed them decreasing the activity of Catalase[28], superoxide dismutase[29] and glutamic acid decarboxylase[9].

Also, this group of xanthones isolated from *Swertia chirata* enhanced the activity of glutathione-S-transferase and glutathione peroxidase[28].

Tetra-oxygenated derivatives isolated from *Tripterospermum lanceolatum* showed them inhibitory activity toward Angiotensin-I-Converting Enzyme[30], phospholipase C [27]and increasing effect on the release of lactate dehydrogenase[31]. Another effect attributed to this group is the activation of protein kinase C[32].

Oxygenated xanthones modulate some other cellular systems as well. For instance, tetraoxygenated xanthones can block the calcium channels[33] and other types of oxygenated xanthones showed complexation with heme in hemoglobin[34], inhibition of proliferation of lymphocytes[35] and inhibition of human complement system[36].

Moreover, oxygenated xanthones are among the naturally occurring xanthones with anti-tumor activity[35]. They do it through six various pathways: DNA binding, DNA synthesis suppression, modulation of protein kinase C, post-replication repair interference,

topoisomerases I and II inhibition. Also, tetraoxygenated xanthones inhibit phospholipase C[37].

1.2.2 Xanthone glycosides:

Xanthone glycosides have a sugar moiety attached to the main tricyclic structure. There are two types of xanthone glycosides: C-glycoside, where the sugar is attached to the main structure by C-C bond, and O-glycoside where its linkage is through C-O-C bond. Most of the xanthone glycosides are O-glycoside type. Examples include mangiferin **(3)** and isomangiferin as the most common C-glycosides, and gentioside **(4)** as O-glycosides.

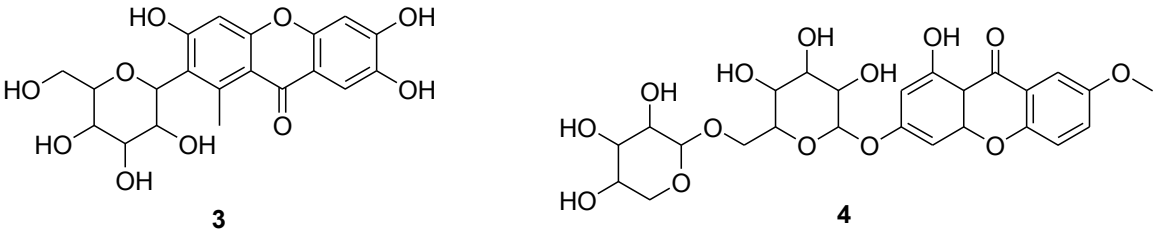

Figure 3. Structures of two representative xanthone glycosides.

The biological activities attributed to this group includes: antiparasitic[38], antiviral[39], antiretroviral[40], CNS-depressant[41], CNS-stimulant[42], analgesics[43], antilipemic[44], antiplatelet-anticoagulants[45], hepatoprotective[46], antidiabetics[47], anti-inflammatory[48], antiallergics[38] and immunomodulator[49].

The enzyme system modulatory effects the xanthone glycosides contain are inhibitory activity toward: Aldose reductase[50], cyclooxygenase[51], α-glucosidase[37], creatine kinase[47a] and competitive inhibition toward isomaltase and sucrase[52], reductase[53] plus competitive reversible selective inhibition toward monoamine oxidase A and B[54], inhibition of gene

expression toward nitric oxide synthase[55], also has decreased the activity of superoxide dismutase[47a].

Xanthones with glycosyl substitution have been shown to affect two different cellular systems. First, activation of proliferation of lymphocytes[56] and second, inhibition of phagocytic activity of macrophages, controlling the expression of genes for primary inflammation mediators[48, 55].

Glycosylated xanthones are among the xanthones with anti-cancer activity[57]. They go through different pathways such as transforming growth factor-β (TGF-β) gene expression, increasing and apoptosis induction via active caspase 3 pathways.

1.2.3 Prenylated xanthone:

In this group of xanthones a 5-carbon unit is attached as substituent to the xanthone core. Allanxanthone-A with two isoprenyl groups in positions 2 and 4 is shown below as an example of this kind (Figure 4).

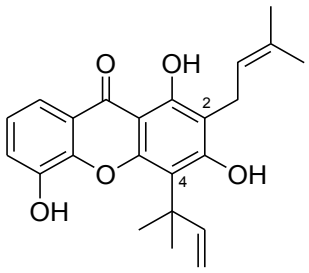

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Figure 4. Structure of prenylated xanthone.

Different biological activities of members in this group have been proven, including: antibacterial[58], antimalarial[59], antifungal[23], antiretroviral[60], CNS- depressant[61], neurological disorders[62], antiplatelet-anticoagulant[63] and anti-inflammatory[61] effects.

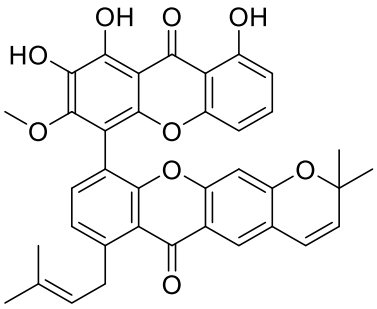
Prenylated xanthones have different effects on a vast number of enzymes. Some good examples are inhibition of acetylcholinesterase[37], cyclooxygenases[64], cyclic-AMP-phosphodiesterases[65], calcium dependent protein kinase[66], myosin light chain kinase[66], Aspartic[23], HIV-1 protease[67], sphingomyelinases[68], topoisomerases I and II[37] and non-competitive inhibition of: calcium ATP-ase[57], cyclic-AMP-binding phosphatase[66], and competitive inhibition of: protein kinase C[66], cyclic AMP dependent protein kinase[66]. This type of xanthone other than inhibitory effect against above-mentioned enzymes can activate caspase-3[69] and caspase-9[70] enzymes.

Prenylated xanthones have modulatory effects on P-glycoprotein[71] and block the prostaglandins D2, E1, E2[64], and act as antagonist toward three different receptors: 5HT 2A[72], histamine H1[73] and platelet activity factor[63].

Prenylated xanthones have anti-cancer activities[74] and do it through seven different pathways: apoptosis induction via active caspase 3 pathways, modulation of protein kinase C and A and mitogen-activated protein kinase, prostaglandin E2 receptors blocking, sphingomyelinases inhibition and topoisomerases I and II inhibition[37].

1.2.4 Bisxanthones:

This group of xanthones have dimeric structures. The first of this kind was extracted from a plant, and a total of 12 different kinds of bisxanthones have been isolated. Globulixanthone E **(6)** and Ploiarixanthone **(7)** are two examples of this kind (Figure 5).



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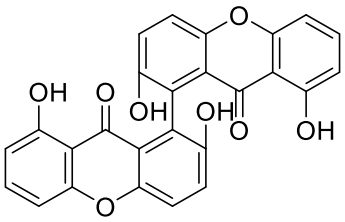

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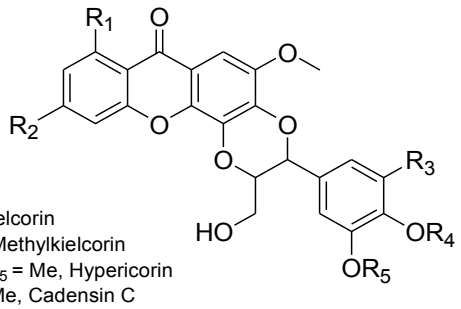
Figure 5. Structures of select bis-xanthones.

The known biological effects of this group of xanthones are antimycobacterial, antimalarial[75], antihypertensive and antiplatelet-anticoagulant activity[76].

The dimers affect different enzymes in different ways including: decreasing the activity of catalase and superoxide dismutase[28] and enhancing the activity of glutathione peroxidase and glutathione-S-transferase[28].

1.2.5 Xantholignoids:

This group makes one of the important types of xanthones and are thought to be biosynthesized by coupling of cinnamoyl alcohol with an O-hydroxyxanthone. Below you can find some examples of this group of xanthones which are named as Kielcorin, 6-methylkielcorin, Hypericorin, and Cadensin C (Figure 6).



(a) $R_1 = R_2 = R_3 = R_4 = H$, $R_5 = Me$, Kielcorin
(b) $R_1 = R_3 = R_4 = H$, $R_2 = R_5 = Me$, 6-Methylkielcorin
(c) $R_1 = OH$, $R_2 = R_4 = H$, $R_3 = OMe$, $R_5 = Me$, Hypericorin
(d) $R_1 = R_2 = R_4 = H$, $R_3 = OMe$, $R_5 = Me$, Cadensin C

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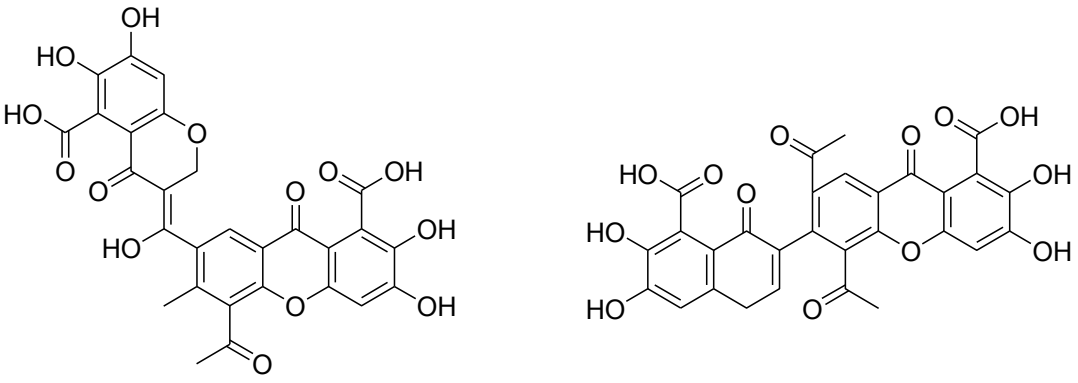
Figure 6. Structures of select xantholignoids.

The reported biological activity related to xantholignoids is just hepatoprotectivity[15]. Also there are two enzymes affected by this group of xanthones in the literature including protein kinase C[77] and topoisomerases I and II[24] which are inhibited by this group and results in its anti-cancer activity[37].

This group of xanthones have shown inhibition of proliferation of lymphocytes[78].

1.2.6 Miscellaneous xanthones:

Other types of xanthones with any substituent other than the above-mentioned substituent is included in this group. There are different examples including: xanthopterin, xantholiptin, and xanthofulvin **(9)** and vinaxanthone **(10)** (Figure 7).



9 **10**

Figure 7. Structures of two different natural xanthones, containing a flavone moiety.

Almost all the above-mentioned biological activities for other groups can be included here for different substituents in miscellaneous group. Some of the most common activities are antiosteoprotics effects for propoxy/ipriflavone analogs[79], antiretroviral effects for flavone-xanthones[67], antiviral[80] and antifungal[81] effects for furano-xanthones.

Xanthone flavones have shown inhibitory activity toward DNA- polymerases[82] and human DNA ligase I[83] and competitive inhibition toward HIV-1[84]. Also furano-xanthones

have shown inhibition of topoisomerases I and II[37]. Xanthone- anthraquinone has shown inhibitory activity toward steroid 11-β-hydroxylase[85] which lead to their anti-cancer activity. On the other hand, xanthones substituted with chloro, bromo and alkyl have shown competitive reversible selective inhibition toward monoamine oxidase A and B[86].

Different xanthones in this group have different effects on cellular systems such as xanthones with carboxy and tetrazole substituents which are binding to albumin[87] or xanthones with nitro substituents which make complexation with heme in hemoglobin[88].

Xanthones in this group with epoxy substituent have shown good anti-cancer activity. They go through different pathways such as DNA synthesis suppression, protein synthesis suppression, RNA synthesis suppression and signal transduction inhibition in Ha-ras oncogene[37].

From a chemical point of view, there are rules for the molecular structure of a compound such as: less than 500 Da of molecular weight, less than 5 and 10 hydrogen bond donors and hydrogen bond acceptors respectively and a less than 5 partition coefficient (log *P*)[89] , which make a compound as a promising drug-candidate. Most xanthones follow all these criteria and frameworks, but exactly how each of these structures produce each specific above-mentioned pharmacological effect is a complex discussion above this study. However, in the following sections (1.4-1.6), the relationship between the chemical structure and two specific attributed pharmacological effects of a particular type of xanthone (α-mangostin) that has been considered in this study will be discussed in detail.

1.2.7 Isolation of xanthones:

The distribution of each class of xanthones in different plants genera is shown in figure 8[1]. As expected, simple xanthones can be found in all important families since they are considered to be the precursor of all other classes of xanthones. The Clusiaceae family (mainly represented by *Garcinia*) is the most important source of prenylated xanthones while xanthone glycosides are mostly found in Gentianaceae family (represented by *Swertia* and *Gentianella* genera).

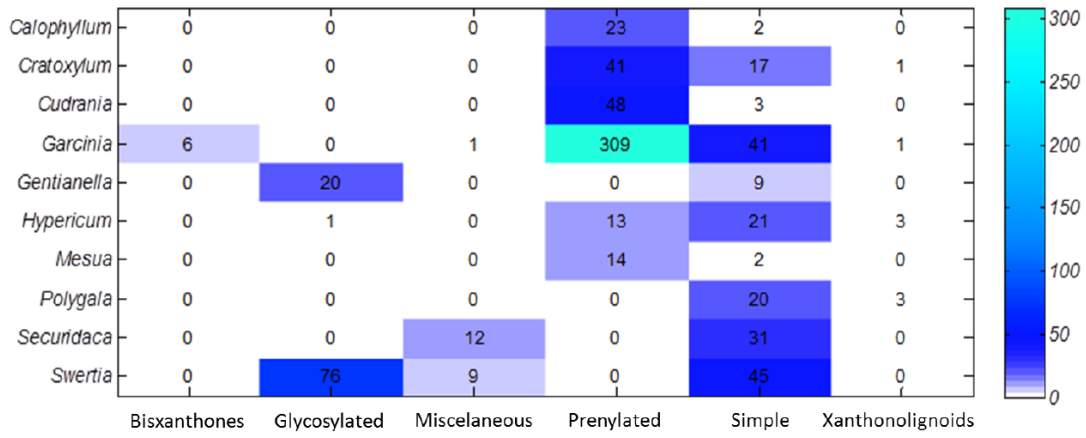


Figure 8. Heatmap for the distribution of different xanthone classes by genera (2012-2019).

[Figure adapted from: Klein-Júnior, L. C.; Campos, A.; Niero, R.; Corrêa, R.; Vander Heyden, Y.; Filho, V. C., Xanthones and Cancer: from Natural Sources to Mechanisms of Action. *Chemistry & biodiversity* **2020,** *17* (2), e1900499.]

Among all the pharmacological properties of xanthones, in this study the anti-bacterial and anti-cancer properties of the synthesized analogs are planned to be surveyed. Consequently, herein we would clarify the relationship between the structure and the biological activity of natural and previously made xanthone compounds specifically in these two medical conditions.

1.3 Natural xanthones from mangosteen fruit:

Mangosteen (Garcinia mangostana) is an evergreen, slow growing tropical tree from the Clusiaceae family, indigenous to southeast Asia but can be found in various tropical regions around the world too. Most of its long-lasting fame is due to its exotic fruit and the variety of medicinal properties it has. The deep purple colored pericarp of mangosteen fruit is the abundant source of a class of polyphenolic compounds called xanthones, largely responsible for its biological activities and health promoting properties[90]. The pharmacological properties of xanthones and their derivatives consist of a diverse range including anti-cancer, anti-oxidant, anti-bacterial, anti-fungal, anti-inflammatory, anti-malarial, anti-HIV and anti-convulsant activities plus inhibitory effect on a wide range of enzymes including acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) which have therapeutic potential in the field of Alzheimer's disease[91], α-glucosidase with the potential of treatment of many diseases including diabetes mellitus type II[92], in addition to inhibitory effect on some other enzymes like topoisomerase, protein kinase and aromatase[3]. Moreover, some benefits of xanthones in cardiovascular diseases have been shown[4]. Between 2012 and 2019 a total number of 1225 xanthones was isolated from different plants, and 48% of those were found in Clusiaceae family[93]. More specifically more than 60 of them have been identified exclusively in mangosteen[94]. To isolate these compounds classical methods like column chromatography has been used and the structure determination has been achieved using MS and NMR methods[93]. The most abundant type of xanthone has been identified in mangosteen fruit is α-mangostin (Figure 9) , which is one the most studied

xanthones with many proved pharmacological efficacies considerably the most cancer-preventive potency among other xanthones[90].

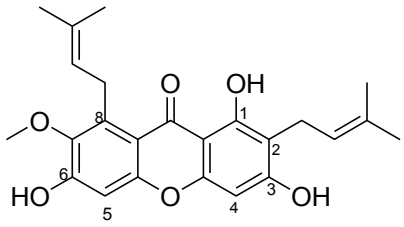


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Figure 9. Structure of α-mangostin.

Isolation of α-mangostin from natural resources is not trivial due to solubility problems and low yield[95]. Hence, there is a limited structure-activity relationship knowledge available in the literature. One of the ways to better understand the biological profiles of α-mangostin is through chemical synthesis of analogs, with simpler structure.

1.4 Anti-cancer activity of α-mangostin:

Today, cancer is the leading cause of death among the societies and more importantly, its main cause is the poor treatment. There are three different cancer treatment approaches: surgery, radiotherapy, and chemotherapy. The anti-cancer drugs have low selectivity and high toxicity which recommend the necessity of production of new chemotherapeutic agents with high selectivity and low toxicity[95]. However, one of the promising ways, is dietary chemoprevention by using naturally occurring phytochemicals like xanthones with proved anti-cancer activity and apparent safety[90]. These secondary metabolites have shown selectivity for cancer cells with minimal damage to normal cells and that is why they have attracted medicinal chemists' attention as candidates for a new and safe anti-cancer drug[93].

α-Mangostin, which is the most potent xanthone against prostate, breast, lung, and colorectal cancer[90] has shown inhibitory activity through various mechanisms of action[96]. The *in-vivo* and *in-vitro* studies have revealed that it acts against cancer cells through inhibition of proliferation, inducing apoptosis and cell cycle arrest, modulating phase I and phase II enzymes, especially downregulation cyclins/cyclin dependent kinases (CDKs) and also has blocking effect on the invasion and metastasis of various cancers which demonstrates its potential as suppressing agent in relation to promotion and progression of cancer i.e. reducing the growth of tumor[93, 97].

Several studies have been reported to describe the medicinal chemistry and different derivatives of α-mangostin for cancer treatment[98]. Due to the low water solubility of α-mangostin, inserting some polar groups to its basic structure can increase its hydrophilicity and anti-cancer properties. Based on the Fei et al. efforts a series of α-mangostin analogs have been synthesized and examined on five human cancer cell lines which several of those showed promising cytotoxicity activities against all the cell lines in μM quantities. Among those the most potent analog with several times more hydrophilicity compared to α-mangostin was the one with chloro group at C4 and phenol groups at C3 and C6 (Figure 10). The structure activity relationship of this compound and the other synthesized compounds showed that the presence of phenol groups on C3 and C6 are critical for inhibition of cancer cells and the C4 modification can increase the activity and drug-like properties. To synthesize analogs in this study α-mangostin has been used as starting material[99].

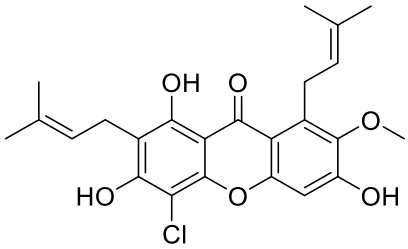

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Figure 10. Substituted α-mangostin.

Some other studies suggested that the hydroxyl groups on isoprenyl side chains can decrease the anti-cancer activity of α-mangostin, while the xanthones containing tetraoxygen groups in their structure in addition to the isoprenyl side chains on ring A and B have the most anti-cancer activity[90, 100].

Yuanita et al. conducted a QSAR study on xanthones to find their active sites and design molecules with highly predicted anti-cancer activity. Based on this research, the most influential positions for anti-cancer activity are C1, C5, C6, C10 and C11 (Figure 11). QSAR equations suggest that the more negative the atomic net charge of C5 and C6, and the more positive the atomic net charge of C1, C10 and C11, the lower log IC_{50} (The half maximal inhibitory concentration) and the higher anti-cancer potency. So to achieve this, C5 and C6 or their neighbors are better to be occupied with electron donating groups like hydroxyl or methoxy to make them more nucleophile groups and other positions including C1, C10 and C11 are better to be occupied with electron withdrawing groups like halogens and nitro group to remove the electron density from the Π-system[95].

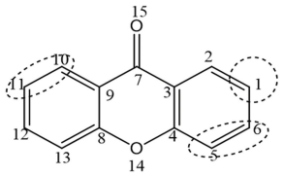

Figure 11. Influential positions for anti-cancer activity.

It also has been proven in some other literatures, that xanthones with bromo and chloro substituents were the most potent inhibitors of topoisomerase II, having lower IC_{50} compared to doxorubicin, a commercially available anti-cancer drug[101].

Among all the xanthone derivatives, one of the analogs with much attention as anti-cancer with remarkable effect is 5,6-dimethylxanthone-4-acetic acid (DMXAA) (Figure 12) which is from the carboxyxanthone family and is now in the phase III of clinical trial[102].

The regular synthesis method for DMXAA involves six steps starting with 2,3 dimethylaniline which undergo a heterogeneous reaction to form an isonitrosoacetanilide with an overall 11% yield[103].

Some efforts have been made during these years to find easier ways for this synthesis with higher yield. Yang et al. found a four step method with >50% yield[104].

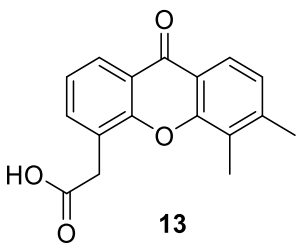

Figure 12. Structure of DMXAA.

1.5 Anti-bacterial activity of α-mangostin:

Antibiotic-resistance is one of the most threatening dangers for human health. There are some reports about the resistance of some Gram-positive bacteria like methicillin-resistant Staphylococcus aureus (MRSA) to different anti-biotics such as β-lactams (oxacillin and ampicillin), vancomycin, fluoroquinolones, linezolid and daptomycin which previously had been treated with these antibiotics. The result is more morbidity and increased cost for healthcare. As a result, there is an urgent need for some new drugs to fight against multi-drug resistant pathogens[105].

α-Mangostin has demonstrated promising anti-bacterial effects. It has been proposed to target the cytoplasmic membrane of Gram-positive bacteria such as MRSA. Also, it has shown some promising advantages like low minimum inhibitory concentration, fast bactericidal effect, and like some other naturally occurring antimicrobial peptides, lower risk of development of resistance[106]. Nevertheless, due to the hydrophobicity it is not selective toward prokaryotic cells. In other words, it cannot differentiate the mammalian cells from bacteria, and it exhibits adverse toxicity. So, there is an interest in developing new α-mangostin analogs with membrane selectivity[105].

Zou et al. worked on some analogs by incorporating cationic substituents with different pK_a on the xanthone scaffold, to make these molecules more amphiphilic and such strategy improved selectivity for bacterial membrane over mammalian cell. The electrostatic interactions cause the attraction between the incorporated cationic groups and the anionic phospholipid head groups in bacterial membrane. Compound AM-0016 (Figure 13) has shown the most potency as bactericidal over a range of Gram-positive bacteria including MRSA with improved selectivity and no antibiotic resistance[105].

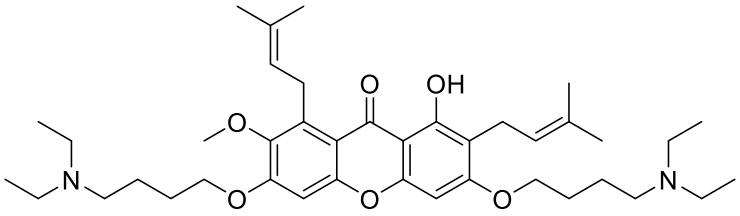

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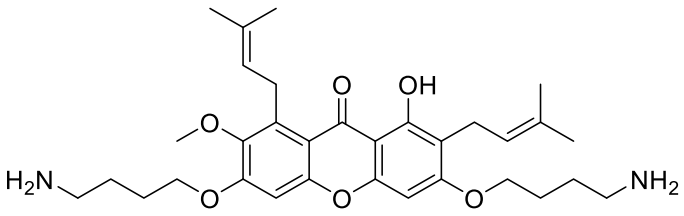
Figure 13. Structure of compound AM-0016.

Due to the disappointing toxicity of the compounds made by Zou et al., more efforts have been focused on the synthesis of new compounds with same potency but reduced toxicity[3]. Among those the most successful examples include two compounds made by Koh et al in 2015. By using the hydrophobic core of α-mangostin and substituting lipophilic chains at C2 and C8, cationic amino acids at C3, produced potent anti-microbials effective against MRSA and VRE, with high selectivity, rapid kill, no antibiotic resistance, and low toxicity. They also distinguished three important structural components. First the need of a bis- or tri-cyclic rigid hydrophobic core. The small size of the molecule and the conformationally constrained structure may enhance the penetration into the Gram-positive membranes. Second, the cationic moieties which afford the electrostatic interactions with bacterial membrane and provide the selectivity over mammalian cells. Third, a lipophilic chain such as isoprenyl group or its reduced form provide the sufficient driving force to penetrate the cytoplasmic membrane of bacteria[107].

Later, the same research group tried to make some more potent analogs with higher selectivity and less hemolytic activity. They designed and synthesized 46 different new compounds inspired by the nonpeptidic xanthone structures, and then divided them into four groups based on spacer length, cationic moieties, lipophilic chains, and tri-arm

functionalization to evaluate their anti-microbial properties. Among those one of them (Figure 14) with two primary amine groups showed the highest potency, acceptable selectivity and less hemolytic activity[108].



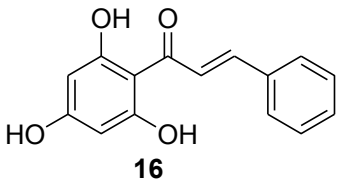
15

Figure 14. Structure of primary amine-conjugated.

Different strategies have been followed in this study to synthesize the compounds. But the starting material in all of them was α-mangostin or using condensation of 2,4-dihydroxylbenzoic acid and phloroglucinol in the presence of Eaton's reagent. The yields vary between 34% to 95%.

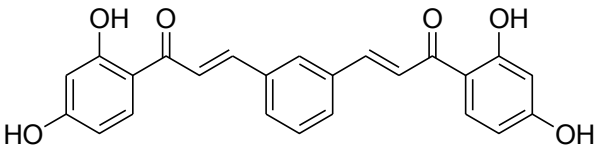
1.6 Chalcones: Structural mimics of xanthones:

In 2016 Cai et al. supported by their previous successful studies on the anti-diabetic and α-glucosidase inhibitory effects of xanthones stated that, the key factors responsible for the inhibitory effects of xanthones are H-bond, extended Π-system, and the flexibility of its structure. Further, they hypothesized that chalcones (Figure 15) as analogs of xanthones can possess better inhibitory effects due to the flexibility of their structural framework. It was proven by making twenty-six chalcones and bis-chalcones which those with hydroxyl substituents showed better inhibitory activity against α-glucosidase enzyme. The structure activity relationship suggests that the number and the place of the hydroxyl groups affect inhibitory activity by acting as hydrogen bonding donor in relation to the enzyme[109].



16

chalcone



17

bis-chalcone

Figure 15. Structure of chalcones and bis-chalcones.

Chalcones also known as α,β-unsaturated ketones are an important naturally occurring compounds belong to the flavonoid family. They exhibit many different pharmacological and beneficial effects including anti-cancer and anti-bacterial effects[109-110]. As it is shown in figure 15, their structure consists of two aromatic rings connected to each other by three-carbon α,β-unsaturated carbonyl bridge. They can be synthesized both naturally in plants and synthetically in the laboratory and are a preferred starting material to synthesize other polycyclic aromatic compounds. That is why methods to synthesize them is among popular research objectives. The most common method used to synthesize them in the lab is aldol condensation of substituted acetophenones with proper substituted benzaldehydes in the presence of a base, mainly sodium or potassium hydroxide. Despite having good efficacy of this method, still there are some drawbacks like the need for the protection of hydroxyl groups before the reaction, the need for analyzing the acidity of the acetophenone hydrogen α, and obtaining biproducts if the bases are good nucleophilic agents. As a result still different research groups are working to find some new ways to synthesize these products to overcome the previous drawbacks[111].

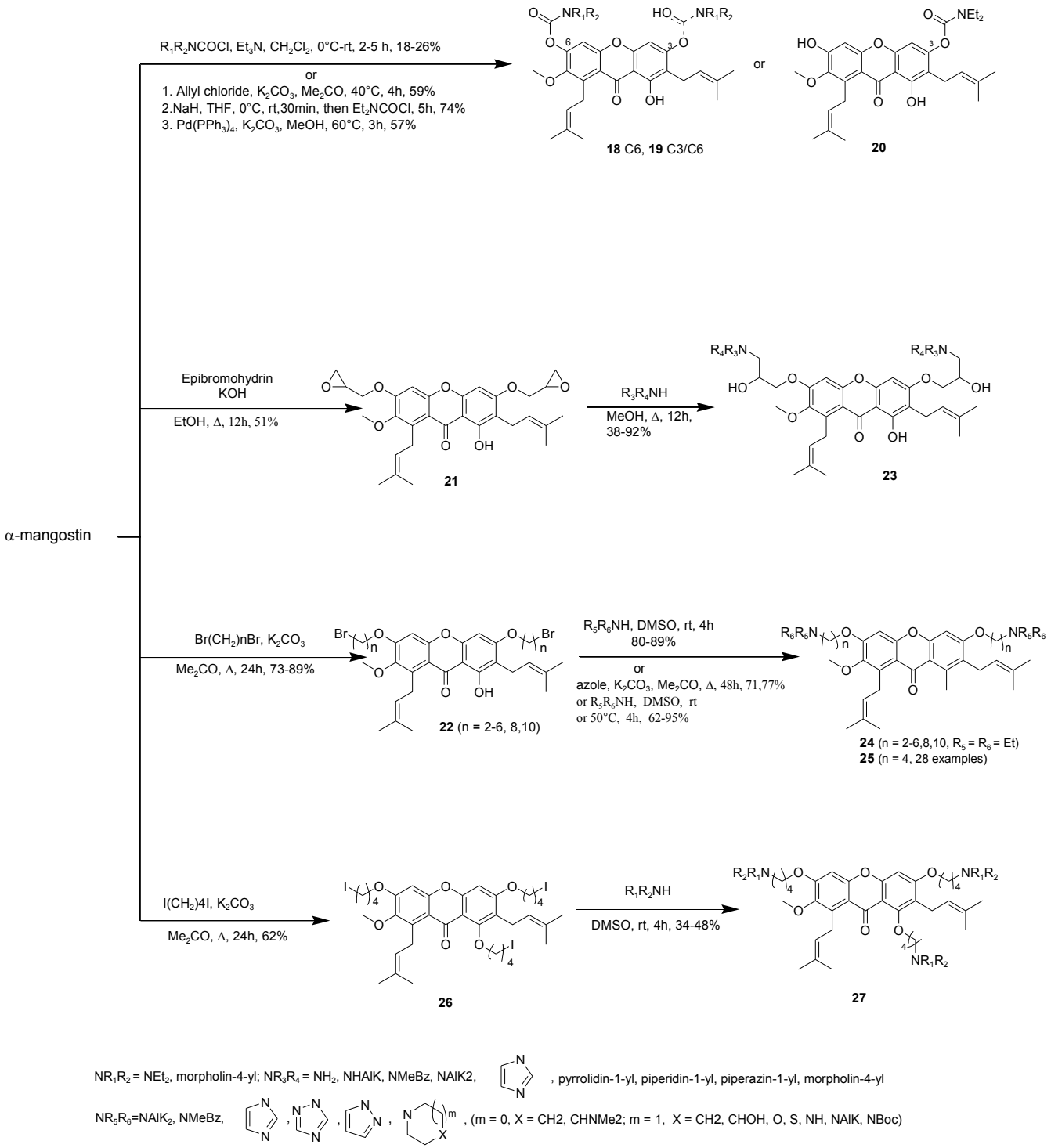
1.7 Chemical synthesis of α-mangostin analogs:

Different synthetic approaches available to make analogs of α-mangostin are driven by three main perspectives aiming to overcome its structural drawbacks which are high

hydrophobicity, low selectivity, and low bioavailability. These three approaches target three different parts of its structure (Figure 9): reactions involving modifications of hydroxy groups (C1, C3 and C6 positions), reactions of aromatic electrophilic substitution (C4 and C5 positions) and modification of prenyl moieties (C2 and C8 positions)[112].

1.7.1 Modifications of hydroxy groups:

This is the most popular way to make α-mangostin analogs. The reactivity of hydroxyl group at C1 position is less than C3 and C6 due to the possible intermolecular hydrogen bond between the OH group at C1 and the carbonyl group at C8. So, by making milder reaction conditions or harsher ones it is possible to control the happening of the reaction at C3 and C6 positions only, or at all C1, C3 and C6 positions. As it is shown on Scheme 1, compounds **18** and **19** are made by reacting the α-mangostin with carbamoyl chlorides. The compound **20** with C3-monoamide is synthesized through the intermediate compound C6-allyl ether which is removed after the reaction with Et_2NCOCl. Also compounds **21** and **22** Show some analogs with ethers at C3 and C6 containing amino groups and heterocyclic fragments. Also, compounds **26** and **27** are examples of tri-ether which are achieved by reacting the α-mangostin with an excess of 1,4-di-iodobutane[113].

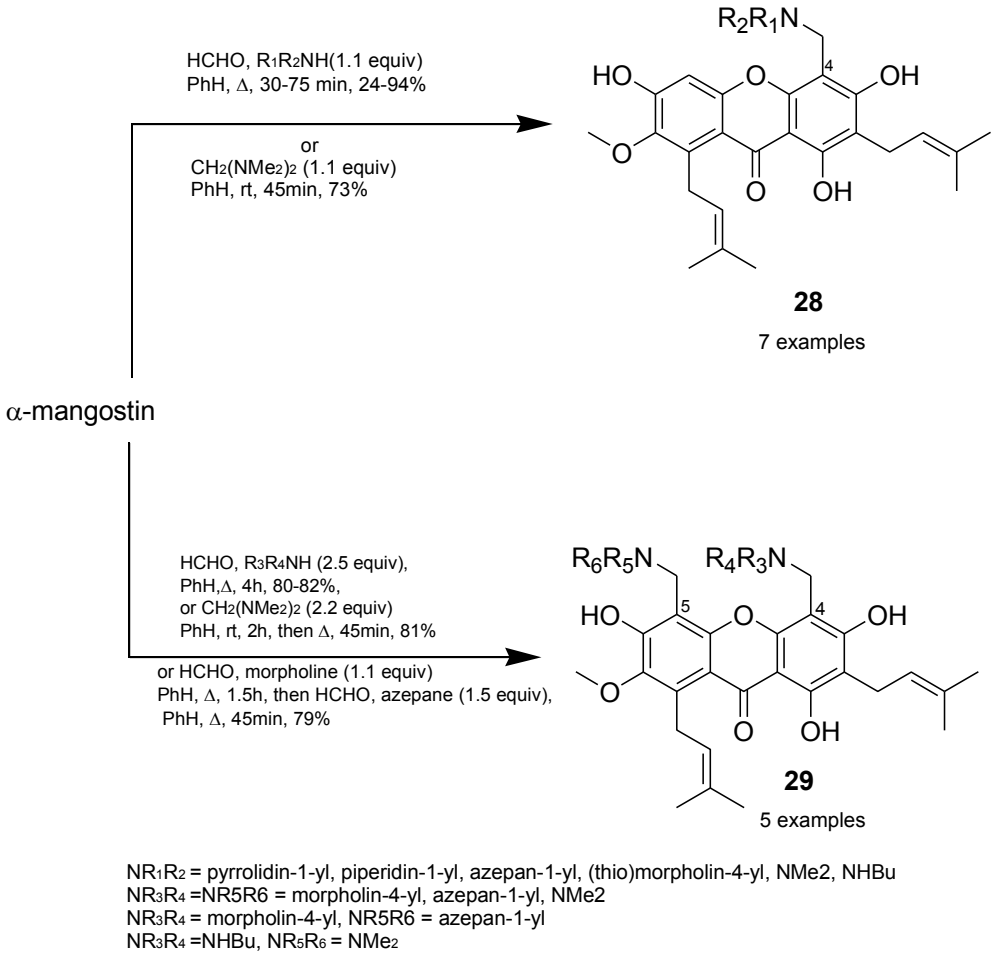


Scheme 1. Modifications of hydroxy groups of α-mangostin.

[Scheme adapted from: Buravlev, E. V., Synthesis of new derivatives of α-mangostin (micro review). *Chemistry of Heterocyclic Compounds* **2019**.]

1.7.2. Reactions of aromatic electrophilic substitution:

One of the common reactions in this group is S_EAr reactions which substitute a halogen atom at C4 position by using N-Bromosuccinimide or NBS and NCS[99] or N-Chlorosuccinimide (Not shown in scheme 2). More recent studies suggested a Mannich reaction in which aminomethyl groups, including heterocyclic fragments, are introduced at C4 and then at C5 positions[113-114](Scheme 2).

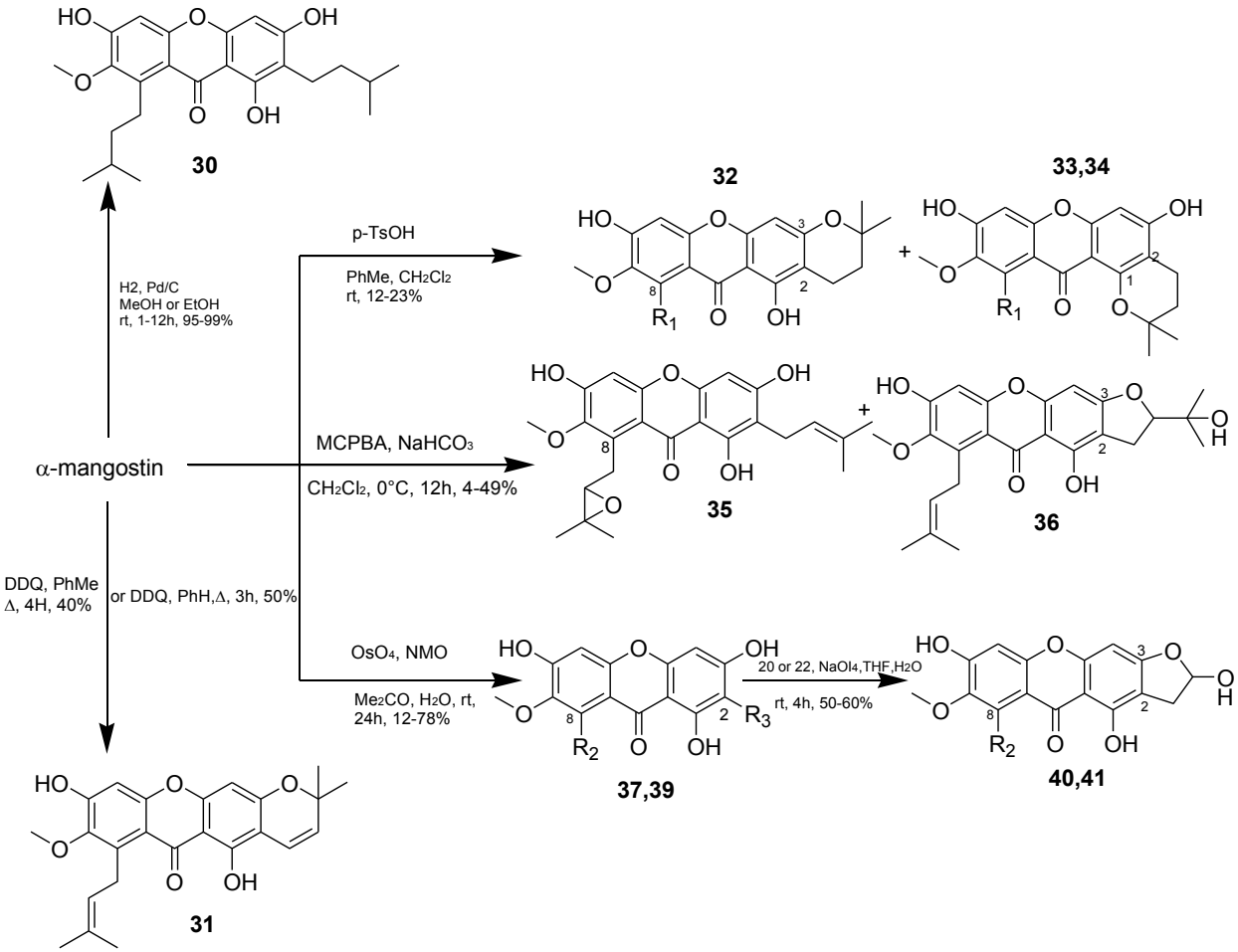


Scheme 2. Reactions of aromatic electrophilic substitution on α-mangostin.

[Scheme adapted from: Buravlev, E. V., Synthesis of new derivatives of α-mangostin (micro review). *Chemistry of Heterocyclic Compounds* **2019**.]

1.7.3 Modification of prenyl moieties:

A common reaction in this group is hydrogenation of the double bonds of the prenyl groups at C2 and C8 positions by using Pd/C as a catalyst and other conditions slightly different in different studies, yielding a molecule with isopentyl substituents **(30)**[99, 108, 112]. Compounds **(31-36)** are afforded through oxidation reactions; depending on the oxidizing agent, different cyclic compounds are made (Scheme 3) [112-113, 115].



32,33 R_1 = $(CH_2)_2CMe_2OH$, **34** R_1 = prenyl; **37** R_2 = prenyl, R_3 = $CH_2CH(OH)CMe_2OH$;

38 R_2 = $CH_2CH(OH)CMe_2OH$,R_3 = prenyl **39** R_2 = R_3 = $CH_2CH(OH)CMe_2OH$; **40** R_2 = prenyl; **41** R_2 = $CH_2CH(OH)CMe_2OH$

Scheme 3. Modification of prenyl moieties on α-mangostin.

[Scheme adapted from Buravlev, E. V., Synthesis of new derivatives of α-mangostin (micro review). *Chemistry of Heterocyclic Compounds* **2019**.]

CHAPTER 2. HYPOTHESIS AND DESIGN RATIONALE

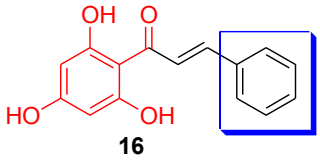
Chemical synthesis of α-mangostin analogs that contain a poly-oxygenated xanthone core is not trivial due to the complexity of structure. Hence, we hypothesized that structurally simpler, non-xanthone compounds that contain part of the α-mangostin scaffold is a useful approach to study the SAR (structure-activity relationship) of α-mangostin. Such an approach provides a simple and economical entry to this pharmacologically important class of natural products. Additionally, such structurally flexible analogs of α-mangostin have not been synthesized to date to explore their pharmacological potential.

α-Mangostin (Figure 9), similar to other xanthones, has a tricyclic planar structure and is considered a very hydrophobic compound. Its high hydrophobicity is linked to low solubility in aqueous medium and low selectivity in terms of adverse effects. As it has been discussed earlier α-mangostin has a broad range of biological activities and possibly many different targets.

Chalcones (Figure 15) as structural mimics of xanthones, although still preserve planar structure as xanthone, demonstrated that a tricyclic core is not necessary for pharmacological activity.

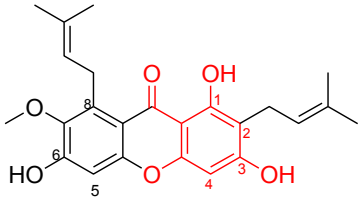
Based on this observation, we planned to develop simple chemical methods to generate non-xanthone analogs of α-mangostin, where the oxygenated benzoyl motif is preserved, and new functional motifs are introduced at the 2-position of the benzoyl motif (Figure 16).

- Pharmacologically effective molecules:



16

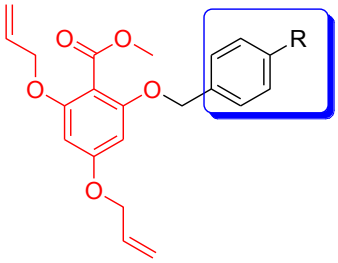
chalcone



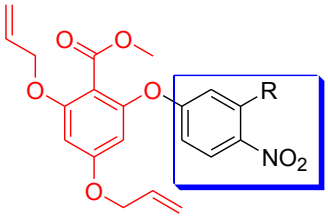
11

α−mangostin

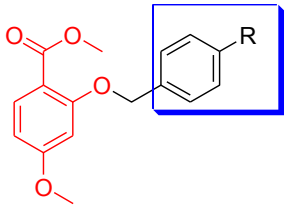
- Designed molecules in this study:



(50)



(49)



compounds **(57-62)**

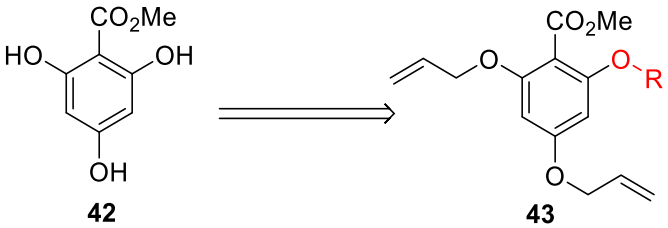
Figure 16. Key structural motifs.

Figure 16, highlights the structural motifs we proposed to include in our design of new analogs based on the pharmacophore of α-mangostin and chalcones. By keeping the two aryl rings and multiple hydroxyl groups that are important for the inherent pharmacological activity of mangostins, we hope that the new analogs will retain a reasonable bioactivity.

Moreover, having 'non-xanthone' core provides more flexibility, instead of rigidity, which is known to improve a compound's physiochemical properties and likely the ability to bind to a desirable target. In addition, incorporation of substituted aryl rings to the 'benzoyl core' enables us to build a structurally diverse library of analogs and evaluate the SAR for the non-xanthone derivative of mangostins.

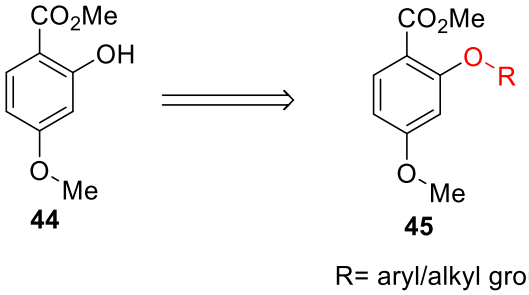
To investigate this hypothesis, we proposed two different approaches.

First, we envisioned using a commercially available polyphenol (2,4,6-trihydroxybenzoic acid) **(42)** as starting material and performing structure diversification to generate a library of synthetic analogs of α-mangostin (Scheme 4).



Scheme 4. Synthetic plan for α-mangostin analogs using 2,4,6-trihydroxybenzoate as precursor.

A second approach was designed to synthesize α-mangostin analogs using a commercially available methyl-4-methoxysalicylate **(44)** as a precursor. The plan is to develop a simple chemical approach to alkylate compound **44** to generate a series of analogs and explore the antibacterial activity potential.



Scheme 5. Synthetic plan for α-mangostin analogs using 4-methoxysalicylate as precursor.

We wanted to explore the effect of structural flexibility on the bioactivity profile and physiochemical properties of α-mangostin. Additionally, the phenyl ring of the benzyl

ether motif (R group in compound **45**) allows us to include different functional groups such as polar and non-polar motifs that may further improve the bioactivity profile.

CHAPTER 3. EXPERIMENTAL

3.1 Chemistry

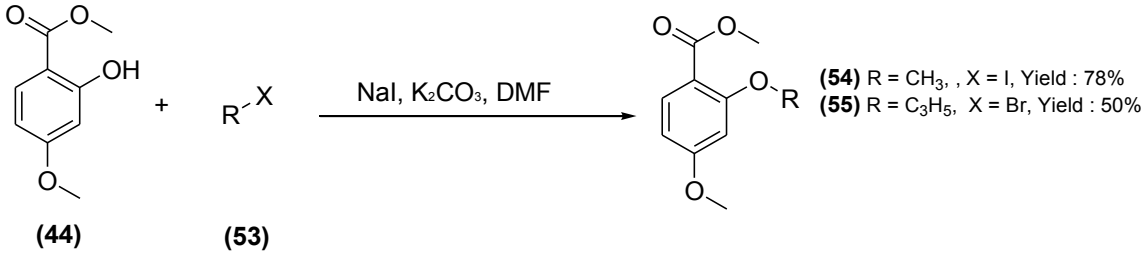
3.1.1 Materials and Instrumentation:

All chemicals were procured from VWR International (Radnor, PA), Fisher Scientific (Hampton, NH), AK Scientific, Inc. (CA), Acros Organics (Geel, Belgium), Aldrich Chemical Co. (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Arkpharm, Inc. (Arlington Heights, IL), Chem-Impex Int. Inc. (Wood Dale, IL), and were used without additional purification. Qualitative analysis of reactions was performed by thin layer chromatography (TLC) with silica gel G as the adsorbent (250 microns) on aluminum backed plates (Agela Technologies) and Ultraviolet (UV) light at 254 nm or 365 nm for visualization purposes. 1H NMR experiments were performed using a Bruker 400 UltrashieldTM spectrometer (at 400 MHz) equipped with a *z*-axis gradient probe. 1H NMR chemical shifts were reported in parts per million (δ / ppm) for majority of the intermediates and all the target compounds. The 1H NMR data are depicted as: chemical shift multiplicity s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), tt (triplet of triplets), m (multiplet), H (number of protons) and J (coupling constant). Column chromatography purifications were performed using silica gel (40-63 μm) purchased from Silicycle Inc. (Quebec City, CANADA). LR-LC/MS analyses were performed on single quadrupole, Agilent Technologies 1260 infinity series LC.

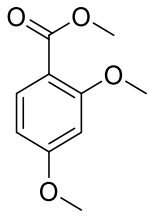
3.1.2 General procedure for the alkylation reaction:

Methyl 4-methoxysalicylate (200 mg, 1 equiv.),K_2CO_3 (3 equiv) and NaI (0.3 equiv) were mixed in dimethylformamide (DMF, 25 mL) and allowed to stir at room temperature. After 20 minutes of stirring, either alkyl halide derivative (1.5 equiv) or the benzyl bromide derivative (1.5 equiv.) was added to the suspension at room temperature and continued to stir for 14 hours. TLC analysis after 14 hours showed complete consumption of methyl-4-methoxysalicylate. At that point, the crude reaction mixture was diluted with water (150 mL). The aqueous layer extracted with ethyl acetate (4 x 50mL). Combined organic layers were washed with water (3 x 50 mL), 10% $NaHCO_3$ (50 mL), water (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide a pale-yellow oily material. The crude product was dissolved in minimal amount of ethyl acetate and purified using flash column chromatography (silica gel column, 0 to 20% EtOAc in hexanes linear gradient). The appropriate fractions were collected and concentrated *in vacuo* providing the desired product as a colorless oil.

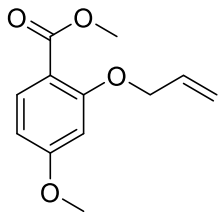
3.1.3 Representative procedure for the synthesis of Alkyl halide derivatives (Scheme 8):



3.1.4 Characterization data for compounds 54 and 55:

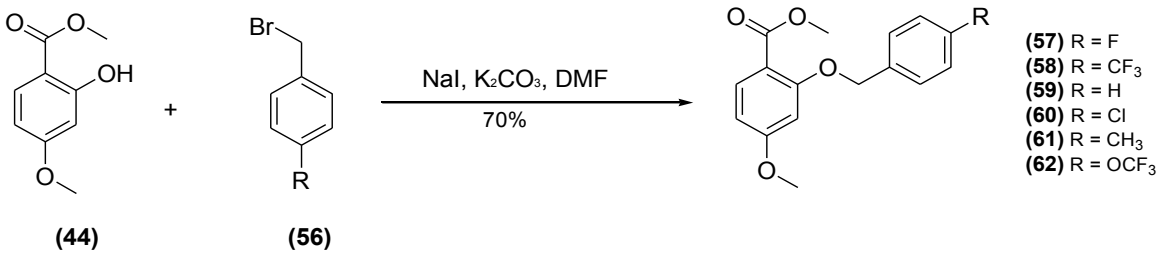


Methyl 2,4-dimethoxy benzoate (54): colorless oil, 78%; $\mathbf{R_f}$**:** 0.55 (20% EtOAc/hexanes). $^{\mathbf{1}}$**H NMR:** (400MHz, CD_3OD): δ 3.80 (3H, s), 3.87 (3H, s), 3.92 (3H, s), 6.61 (1H, dd, J = 1.5, 0.5 Hz), 6.82 (1H, dd, J = 7.6, 1.5 Hz), 7.80 (1H, dd, J = 7.6, 0.5 Hz); $^{\mathbf{13}}$**CNMR**: (100 MHz, CD_3OD): δ 55.9, 161.3, 55.5, 52.3, 98.8, 112.1, 133.8, 166.5, 163.2, 105.9; **LC-MS:** (ESI, $[M+H]^+$) calculated for $[C_{10}H_{12}O_4 + H^+]$ 196.07 observed 196.0.



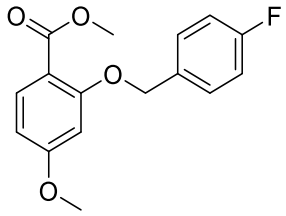
2-[(Allyl) oxy]-4-methoxy-methylsalicylate (55): colorless oil, 50%; $\mathbf{R_f}$**:** 0.60 (20% EtOAc/hexanes). $^{\mathbf{1}}$**H NMR:** (400MHz, CD_3OD): δ 3.80 (3H, s), 3.88 (3H, s), 4.62 (2H, d, J = 8.6 Hz), 4.95-5.08 (2H, dd, J = 16.5, 1.3 Hz), 5.04 (dd, J = 10.7, 1.3 Hz), 6.00 (1H, ddt, J = 16.5, 10.7, 8.6 Hz), 6.59 (1H, dd, J = 1.5, 0.5 Hz), 6.83 (1H, dd, J = 7.6, 1.5 Hz), 7.80 (1H, dd, J = 7.6, 0.5 Hz); $^{\mathbf{13}}$**CNMR**: (100 MHz, CD_3OD): δ 132.9, 52.3, 55.5, 118.1, 163.2, 159.6, 105.9, 101.4, 166.5; **LC-MS:** (ESI, $[M+H]^+$) calculated for $[C_{12}H_{14}O_4 + H^+]$ 222.09 observed 222.1.

3.1.5 Representative procedure for the synthesis of Benzyl bromide derivatives (Scheme 9):

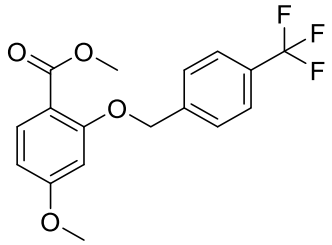


(44) **(56)**

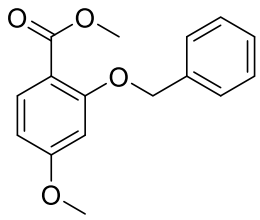
3.1.6 Characterization data for compounds 57_62:



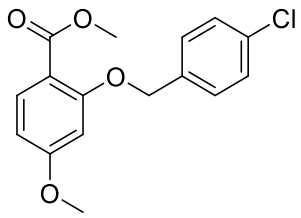
2-[(4-Fluorobenzyl) oxy]-4-methoxy-methylsalicylate (57): pale yellow oil, 70%; **R_f:** 0.45 (20% EtOAc/hexanes). **^{1}H NMR:** (400 MHz,CD_3OD): δ 7.81 (1H, dd, J = 7.61, 0.47 Hz), 7.56 -7.53 (2H, ddd, J = 8.4 1.14 0.55 Hz), 7.1 (2H, ddd, J = 8.4, 1.13, 0.55 Hz), 6.65 (1H, dd, J = 1.47, 0.47 Hz), 6.59-6.57 (1H, dd, J = 7.61, 1.47 Hz), 5.1 (2H, s), 3.8 (6H, s); **^{13}C NMR:** (100 MHz, CD_3OD): δ 164.6, 160.2, 133.3, 128.7, 114.8, 105.4, 100.2, 69.4, 54.6, 50.7; **LC-MS:** (ESI, $[M+H]^+$) calculated for $[C_{16}H_{15}FO_4 + H^+]$ 290.10 observed 290.1.



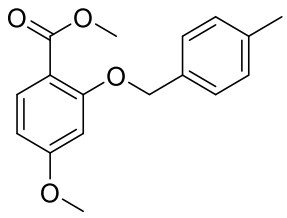
2-[(4-Trifluoromethyl) benzyl oxy]-4-methoxy-methylsalicylate (58): colorless oil, 70%; **R_f:** 0.32 (20% EtOAc/hexanes). **^{1}H NMR:** (400 MHz,CD_3OD): δ 3.83 (3H, s), 3.88 (3H, s), 5.20 (2H, s), 6.49 (1H, dd, J = 1.5, 0.5 Hz), 6.55 (1H, dd, J = 7.6, 1.5 Hz), 7.66 (4H, s), 7.90 (1H, dd, J = 7.6, 0.5 Hz).**^{13}C NMR:** (100 MHz, CD_3OD): δ 165.95, 164.17, 159.89, 140.7, 134.1, 130.1, 126.8, 125.5, 122.78, 112.86, 105.28, 100.63, 69.68, 55.52, 51.7; **LC-MS:** (ESI, $[M+H]^+$) calculated for $[C_{17}H_{15}F_3O_4 + H^+]$ 340.09 observed 340.1.



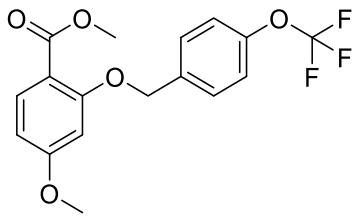
2-benzyloxy-4-methoxy-methylsalicylate (59): colorless oil, 70%; **R_f:** 0.67 (20% EtOAc/hexanes). **^{1}H NMR:** (400 MHz,CD_3OD): δ 3.80 (3H, s), 3.87 (3H, s), 5.16 (2H, s), 6.50 (1H, dd, J = 1.5, 0.5 Hz), 6.52 (1H, s), 7.25-7.38 (3H, tt), 7.40 (2H, dd, J = 7.8, 1.3 Hz), 7.87 (1H, dd, J = 7.6, 0.5 Hz). **^{13}C NMR:** (100 MHz, CD_3OD): δ 166.2, 164.1, 160.2, 136.6, 133.9, 128.55, 127.7, 126.8, 112.95, 112.9, 105.1, 100.6, 77.0, 70.58, 55.4, 51.7; **LC-MS**: (ESI, $[M+H]^+$) calculated for $[C_{16}H_{16}O_4 + H^+]$ 272.10 observed 272.1.



2-[(4-Chlorobenzyl) oxy]-4-methoxy-methylsalicylate (60): colorless oil,70%; $\mathbf{R_f}$**:** 0.40 (20% EtOAc/hexanes). $^{\mathbf{1}}$**H NMR:** (400 MHz, CD_3OD): δ 3.81(3H, s), 3.86 (3H, s), 5.10 (2H, s), 6.48 (1H, dd, J = 1.5, 0.5 Hz), 6.84 (1H, dd, J = 7.5, 1.5 Hz), 7.36 (2H, ddd, J = 8.3, 1.1, 0.5 Hz), 7.44 (2H, ddd, J = 8.3, 1.4, 0.5 Hz), 7.87 (1H, dd, J = 7.6, 0.5 Hz); $^{\mathbf{13}}$**C NMR:** (100 MHz, CD_3OD): δ166.0, 164.12, 160.0, 135.18, 134.01, 133.5, 128.73, 128.17, 112.89, 105.24, 100.68, 77.0, 76.7, 69.81, 55.5, 51.7; ; **LC-MS:** (ESI, $[M+H]^+$) calculated for $[C_{16}H_{15}ClO_4 + H^+]$ 306.07 observed 306.0.



2-[(4-Methylbenzyl) oxy]-4-methoxy-methylsalicylate (61): colorless oil, 70%; $\mathbf{R_f}$**:** 0.58 (20% EtOAc/hexanes). $^{\mathbf{1}}$**H NMR:** (400 MHz,CD_3OD): δ 2.34 (3H, s), 3.80 (3H, s), 3.86 (3H, s), 5.11 (2H, s), 6.50 (2H, dd, J = 7.6, 1.5 Hz), 7.19 (2H, dd, J = 7.5, 0.5 Hz), 7.39 (2H, J = 7.5, 0.5 Hz), 7.87 (1H, dd, J = 7.6, 0.5 Hz); $^{\mathbf{13}}$**C NMR:** (100 MHz, CD_3OD): δ 166.28, 164.0, 160.3, 137.47, 133.88, 133.63, 129.22, 126.91, 112.98, 105.13, 100.69, 77.37, 77.05, 76.7, 55.46, 51.69, 21.20; **LC-MS:** (ESI, $[M+H]^+$) calculated for $[C_{17}H_{18}O_4 + H^+]$ 286.12 observed 286.1.



2-[(4-Trifluoromethoxy) benzyl oxy]-4-methoxy-methylsalicylate (62): colorless oil, 70%; **R_f:** 0.36 (20% EtOAc/hexanes). **^{1}H NMR:** (400 MHz,CD_3OD): δ 3.83 (3H, s), 3.87 (3H, s), 5.1 (2H, s), 6.50 (1H, dd, J = 1.5, 0.5), 6.54 (1H, dd, H = 7.5, 1.5 Hz), 7.23 (2H, dd, J = 7.9, 1.3), 7.58 (2H, dd, J = 7.9, 1.2), 7.91 (1H, dd, J = 7.6, 0.5 Hz); **^{13}C NMR:** (100 MHz, CD_3OD): δ 165.97, 164.16, 160.02, 148.73, 135.39, 134.04, 128.20, 121.09, 112.89, 105.28, 100.70, 77.34, 77.02, 76.7, 55.51, 51.71; **LC-MS:** (ESI, $[M+H]^+$) calculated for $[C_{17}H_{15}F_3O_5 + H^+]$ 356.09 observed 356.1.

3.2 Antibacterial activity evaluation:

Bacterial strain of choice was first inoculated in 10 mL of LB broth for 16 hours in shaker at 37 ˚C. The following day, 100 µL of the inoculum was transferred to a test tube with fresh media to obtain an inoculum with an optical density at 600 nm (OD_{600}) of 0.2. All compounds were dissolved in DMSO to prepare samples for testing. Drugs were prepared as serially diluted concentration of 100, 50, 25, 12.5 and 6.25 µg/mL and 100 µL was transferred into a 96-well plate. Then 100 µL of inoculum (with OD_{600} = 0.2) was transferred into each well with the test drug. The plate was then incubated at 37 °C for 14 hours. The OD_{600} was recorded using microplate reader (ELx808). MICs (Minimum inhibitory concentration) are reported as the lowest concentration at which no bacterial growth was observed.

CHAPTER 4. RESULTS AND DISCUSSION

4.1. Synthesis of α-mangostin analogs based on 2,4,6-trihydroxybenzoic acid:

Our synthetic approach began with the conversion of 2,4,6- trihydroxybenzoic acid **(42)** to the corresponding acetonide **(46)** to protect the carboxylic acid and the adjacent hydroxyl. The plan is to selectively protect the hydroxyls at 4- and 6-positions with a removable protecting group. To achieve this, first the carboxylic acid and the hydroxyl at 2-position are tied together in one step via an acetonide ring formation. It is well known that an acetonide that connects a carboxyl group and a phenol can be converted into the methyl ester readily. Based on literature protocol, we examined two different reaction conditions to install the acetonide protecting group. One of the methods involved the use of acetone and catalytic amount of 4-dimethylaminopyridine (DMAP) and resulted in a slow, low yielding reaction[116]. Therefore, we shifted to the second approach where trifluoroacetic anhydride (TFAA), trifluoroacetic acid (TFA) and acetone [117]. The acetonide **(46)** was obtained with an unsatisfactory yield of 39%. Based on TLC analysis, we observed that the reaction did not go to completion and unreacted starting material remained in the reaction mixture. Then, we increased the equivalences of TFA and TFAA from 7.77 and 2.85 to 22 and 8.6, respectively. In addition, the reaction was performed at 30 ˚C to assess the effect of temperature. The optimized condition provided an improved yield to 57% (Scheme 6).

With the available material, we moved forward to protect the two OH groups in compound **46**, as either benzyl ether or allyl ether[118]. Benzylation reaction did not provide the desired product in good yield. We faced difficulties separating the benzyl alcohol byproduct from the desired product. The benzyl alcohol was generated when the

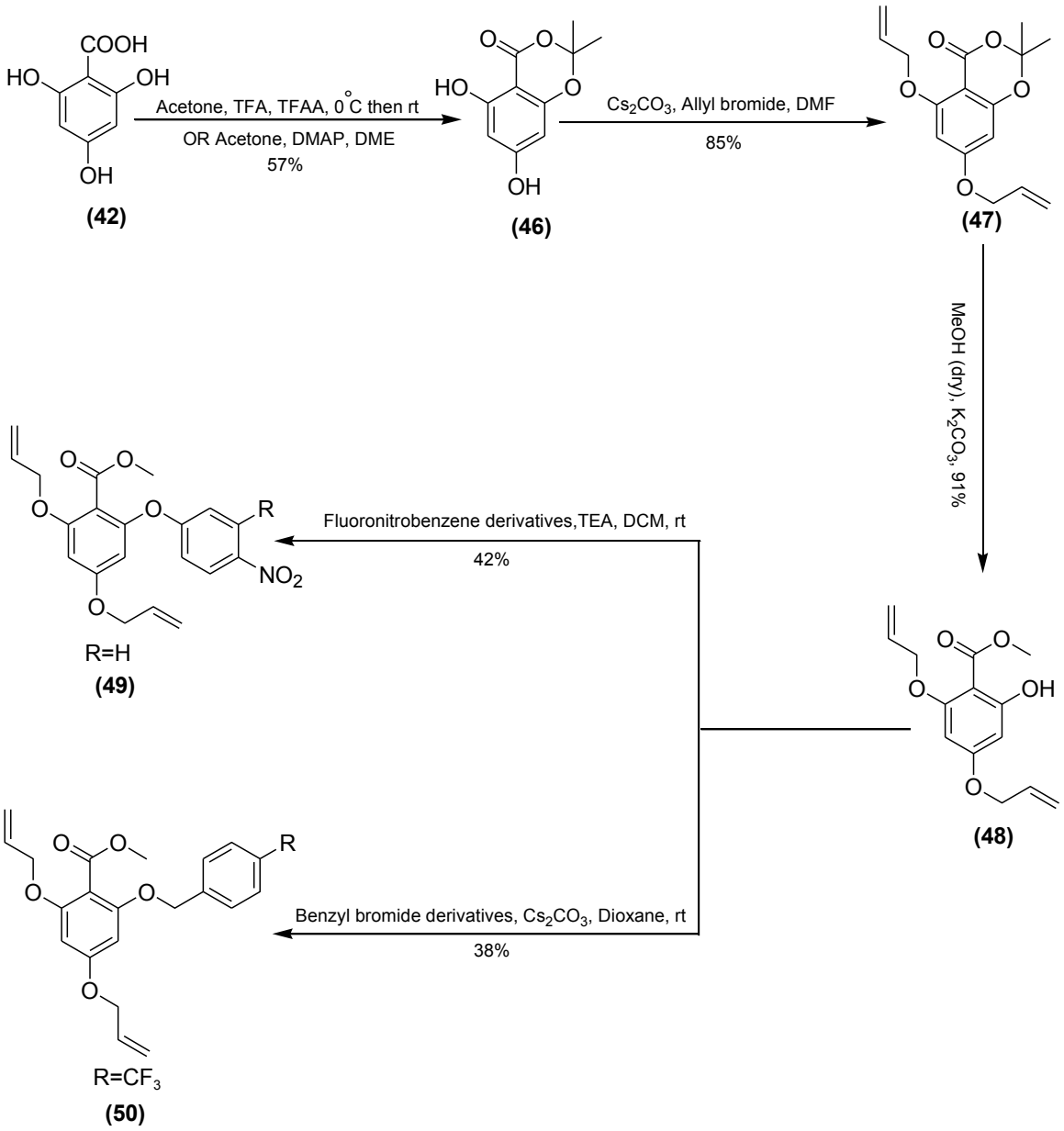
benzyl bromide reacted with residual water as the reaction mixture was not completely anhydrous. On the other hand, allylation was successful and yielded the product in good yield (Scheme 6). The suggested mechanism for this reaction involves deprotonation of (OH) groups by the base (Cs_2CO_3) and allylation of the phenoxide motif in the presence of allyl bromide.

Following the allylation, deprotection or methanolysis of compound **47** gave compound **48** (Scheme 6). The reaction proceeded well in the presence of methanol and potassium carbonate, where *in situ* generated methoxide assisted in the ring opening of acetonide, and subsequent conversion of acetonide into the methyl ester derivative **48**. Compound **48** serves as a common precursor for further derivatization at the phenolic oxygen via alkylation. The reason for installing the allyl ethers is that after the structure diversification of phenolic hydroxyl at 2-position, the allyl ethers can be selectively deprotected.

To make the proposed analogs from compound **48**, two different approaches were examined. In one approach compound **48** was reacted with 1-fluoro-2,4-dinitrobenzene, in the presence of triethylamine (TEA) at room temperature. The goal is to synthesize a selection of 'biaryl-ethers' via this approach. The deprotonated phenoxide group reacted with the fluoro-dintrobenzene via a nucleophilic aromatic substitution reaction. During the reaction, a typical Meisenheimer complex is formed, and the fluorine is lost to generate the desired 'biaryl-ether' product.

In the second approach, compound **48** was reacted with 4-(trifluoromethyl)benzyl bromide in the presence of Cs_2CO_3 at room temperature. Both of these approaches gave the desired products with low yield (< 50%), and we had difficult time isolating the final

products in high purity (Scheme 6). The reaction yielded a complex mixture of products that were difficult to separate and characterize. We suspect that under the reaction condition, the allyl groups may be migrating within compound **48**, providing a mixture of compounds. Also, the fluoro-dintrobenzene reagent may be rapidly decomposing to form the corresponding phenol-byproduct. Our attempts to change solvents and reaction temperature also failed to improve the yield and purity of the product. Since we had another key step involved in the synthetic scheme, we were not satisfied with the outcome of these two approaches. We also noticed that the yield we obtained for this approach is not reproducible. We abandoned our strategy that involved 2,4,6-trihydroxybenzoic acid as the precursor for the analog synthesis, and decided to move to a simpler polyphenol precursor to generate the proposed analogs.

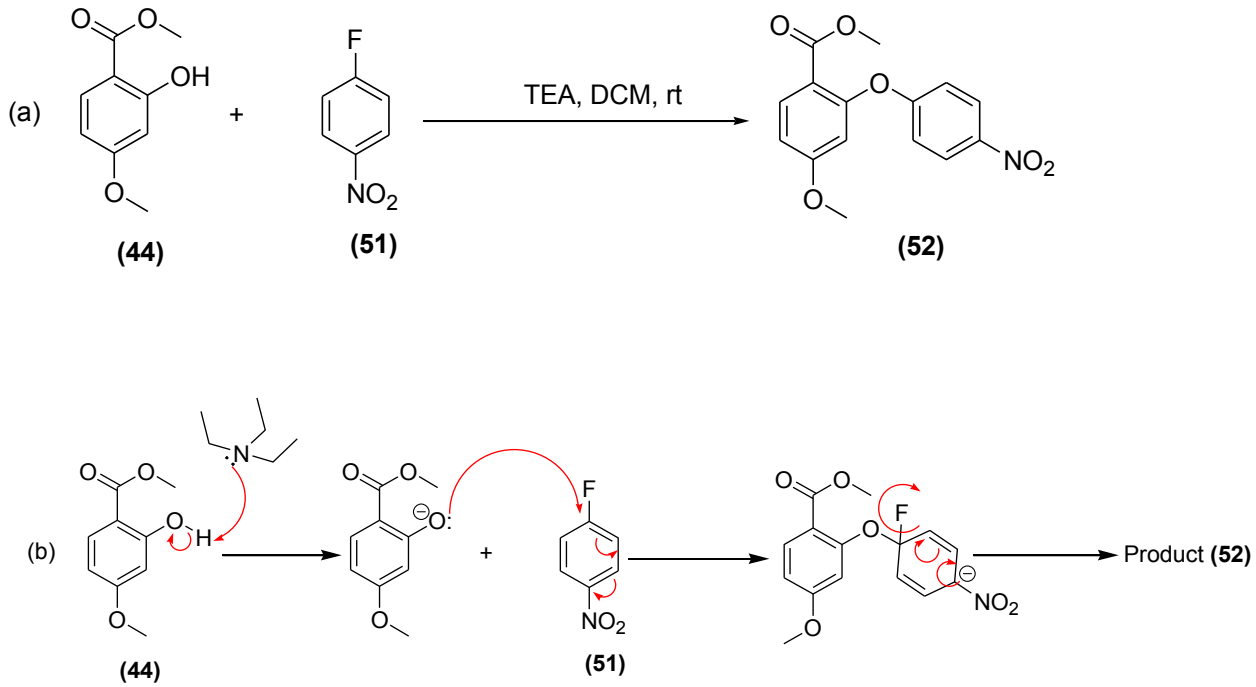


Scheme 6. Synthesis of α-mangostin analogs via 2,4,6-Trihydroxybenzoic acid route.

The reason to abandon our initial approach also relates to the need for excessive amount of TFA and TFAA. These reagents are corrosive, and not easy to handle in large quantities for large scale synthesis to obtain a reasonable amount of substrate for structure diversification.

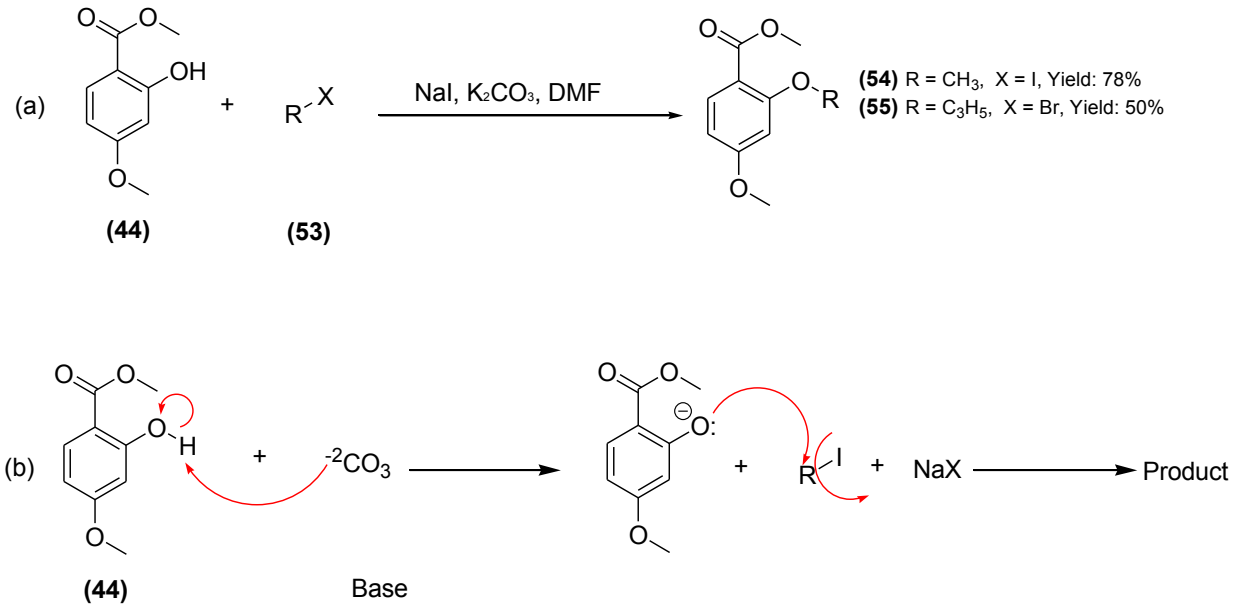
Therefore, we shifted our focus to an alternate approach to make simplified analogs of α-mangostin using commercially available methyl-4-methoxysalicylate as a precursor **(44)**. While compound **44** has structural similarities with α-mangostin, it is structurally simpler, and no protecting group manipulation is needed to generate the proposed analogs. In this method, we envisioned derivatizing compound **44** using (1) 1-fluoro-2,4-dinitrobenzenes, (2) alkyl bromides, and (3) benzyl bromides.

As shown in scheme 7a, we attempted the reaction between 1-fluoro-2,4-dinitrobenzene **(51)** and the phenol precursor **(44)** to generate a biaryl-ether analog. It was expected that this reaction works through a nucleophilic aromatic substitution reaction (Scheme 7b) and results in the formation of the desired product. However, the reaction did not proceed as expected. Analysis of the reaction by TLC indicated the presence of unreacted phenol precursor **(44)**. We suspect that the phenol motif is not accessible due to steric reason and perhaps not reactive under the condition tested. Another factor to note is that 1-fluoro-2,4-dinitrobenzene is not stable under the reaction condition and decomposed to the corresponding phenol-derivative as the reaction condition is not 100% anhydrous. Due to time constrains we had for this project, we did not further explore other methods to generate biaryl-ethers or optimize the reaction condition. We believe that the reaction condition may be optimized by using fresh reagents and maintaining an anhydrous reaction environment for this type of chemistry. Moreover, elevated temperatures may be investigated to force the reaction to go to completion.



Scheme 7. (a) Reaction of methyl-4-methoxysalicylate and 1,4-fluoro nitro benzene derivatives (b) Proposed mechanism.

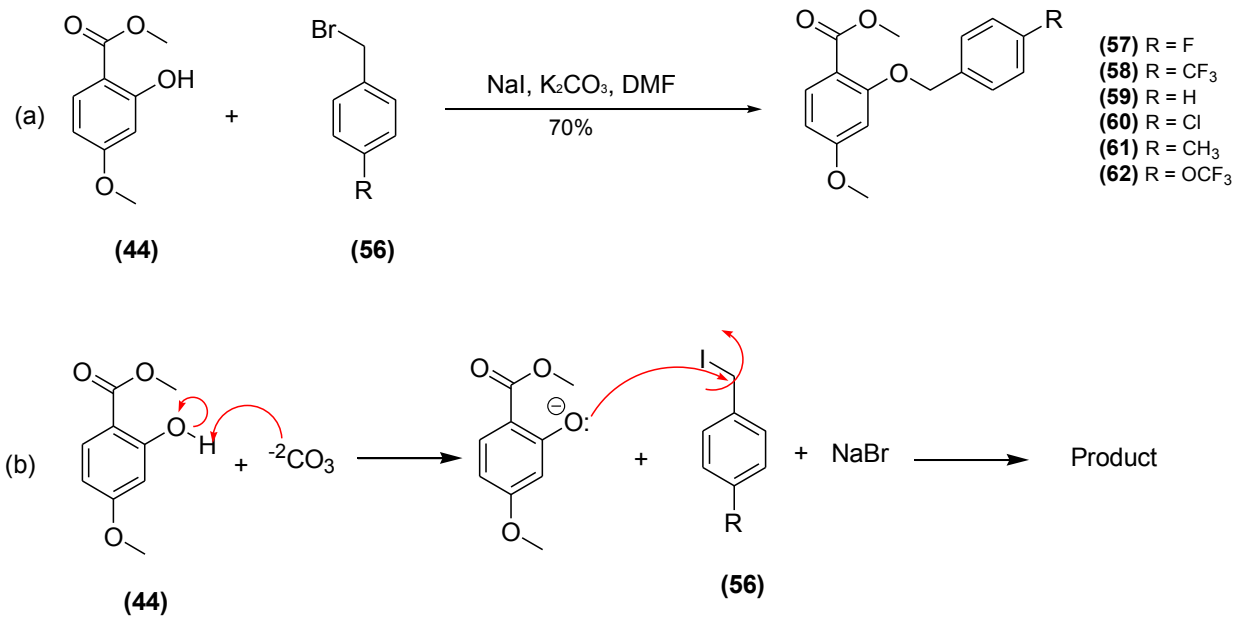
As another direction, we also tried to alkylate the common precursor **(44)** with different alkyl halides through a nucleophilic substitution reaction (SN_2). The methylation reaction, using methyl iodide worked well to generate the corresponding methyl ether product. Also, the reaction using allyl bromide yielded the product in acceptable yield. However, the other alkyl bromides, such as propyl bromide and butyl bromide did not provide the desired products, perhaps due to low reactivity of alkyl bromides under the tested conditions. Due to limited scope for this reaction, we did not pursue our interest in alkyl halides for the generation of this class of methyl-4-methoxysalicylate analogs (Scheme 8).



Scheme 8. (a) Reaction between methyl-4-methoxysalicylate and alkyl halides (b) Proposed mechanism.

Then, as shown in Scheme 9, we tried the reactivity of phenol precursor **(44)** with benzyl bromide derivatives **(56).** This approach worked well as one-step process going through SN_2 mechanism, with good yield at room temperature. The conversion of the precursor to the desired products **(57-62)** occurred in less than 4 hours, with 70-85% yield. Since benzyl bromides are more reactive compared to alkyl bromides, the benzylation occurred smoothly. Using this strategy, we proceeded to synthesize a series of benzyl-ethers using five different benzyl bromides. The benzyl groups contain different substitutions at the 4-postion of aryl ring (F, CF_3, Cl, CH_3 and OCF_3). The substituents are polar or non-polar groups and allow us to study a preliminary structure activity relationship at 4-position. Moreover, such substitutions are useful for altering the physicochemical property of a molecule. Moreover, by including electron donating or electron withdrawing groups, hydrogen bond donors or acceptors, the analogs may exhibit different biological

properties. All these compounds were purified using silica column chromatography and fully characterized using NMR and LCMS techniques to confirm the structure.



Scheme 9. (a) Reaction between methyl-4-methoxysalicylate and benzyl bromide derivatives (b) Proposed mechanism.

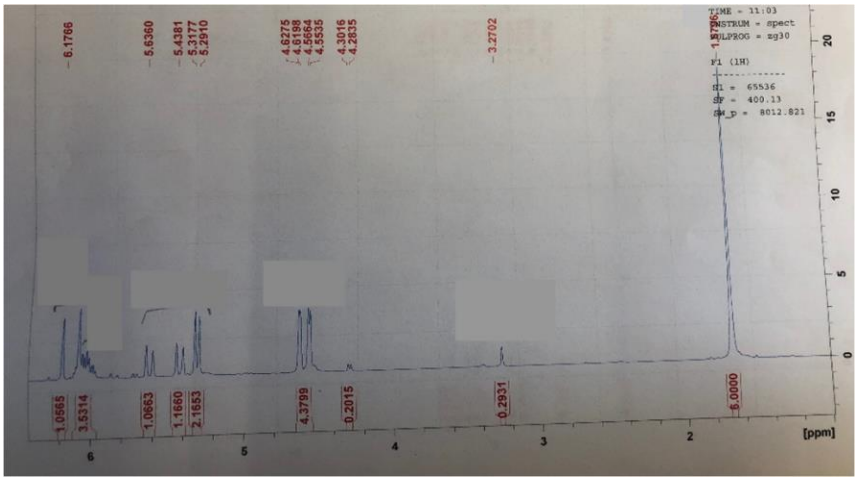
Following the successful synthesis of benzyl-ether analogs of methyl-4-methoxysalicylate, we went ahead and performed a preliminary antibacterial evaluation of two of the analogs against both Gram-positive and Gram-negative bacteria.

4.2 Characterization for compounds 47 and 61:

4.2.1 Nuclear Magnetic Resonance (NMR):

4.2.1.1 H-NMR for compound 47:

(a)



(b)

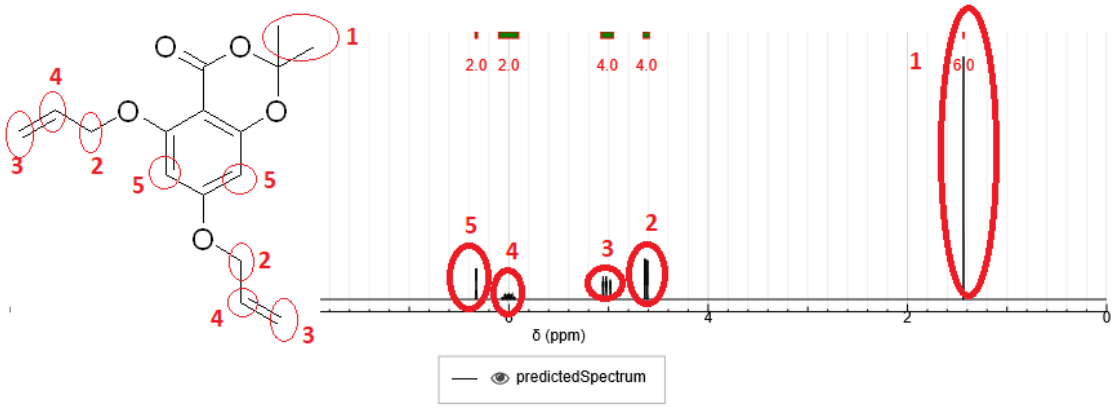
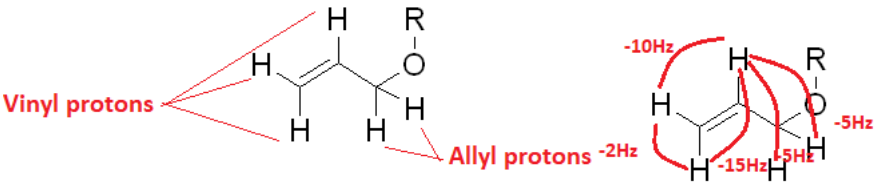


Figure 17. (a) Actual H-NMR for compound 47; (b) Predicted H-NMR for compound 47.

Since NMR plays an important role in structure determination, we selected two compounds we have synthesized to illustrate the process involved in characterization of

chemical structure. For compound **47**, the expected number of H-NMR signals regardless of multiplicity, can be divided into five different groups (Figure 17). Compound **47** does not have an element of symmetry; hence, we expect all protons to have distinct chemical shift values.

Group 1: A singlet at 1.7 ppm is observed, representing 6 protons, which represent the two methyl groups connected to the same carbon on the acetonide ring. As these two methyl groups are not distinguishable at the NMR timescale, they appear one singlet peak on proton NMR spectrum. The chemical shift at 1.7 ppm matches the expected value for an aliphatic methyl proton.



(a) (b)

Figure 18. (a) Allyl ether different protons; (b) Allyl ether coupling constants.

Group 2: There are 2 allyl ethers in this molecule and with four distinct types of protons (Figure 18a). Each pair of protons in two allyl ether groups are different from each other. The allyl protons in each allyl ether group cannot be identical and each of which is coupled with the interior vinyl proton resulting in a doublet. The presented peaks in the actual NMR spectrum at 4.5 and 4.6 ppm match with 4 allyl protons in the two allyl ether groups. It is possible the more downfield peak at 4.6 ppm be related to the more deshielded allyl ether group closer to the electronegative oxygen atom.

Group 3: These are two terminal vinyl protons of allyl ether group directly connected to the sp^2 carbon. Due to the lack of rotation around the Π-bond these two protons in each allyl ether group couple with each other. As they are magnetically different, they have different chemical shift values. Also, each of these terminal vinyl protons couple with the interior vinyl proton with a different coupling constant (Figure 18b). So, as each one is coupled with 2 other protons what we can predict about the multiplicity is a doublet of doublet. In the actual NMR spectrum, the group 3 peaks at 5.6 to 5.2 ppm can be attributed to these terminal vinyl protons. The coupling constant between the two germinal protons is around 2 Hz and the coupling constant between the interior vinyl proton and the trans alkene proton is around 15 Hz. The cis alkene proton has a coupling constant value of 10 Hz. Based on the coupling constant values, it is possible that two of the middle peaks would have been very close to each other which are not possible to be distinguished from each other and that is the reason in the presented NMR spectrum, 6 peaks are seen instead of 8 peaks within the expected region.

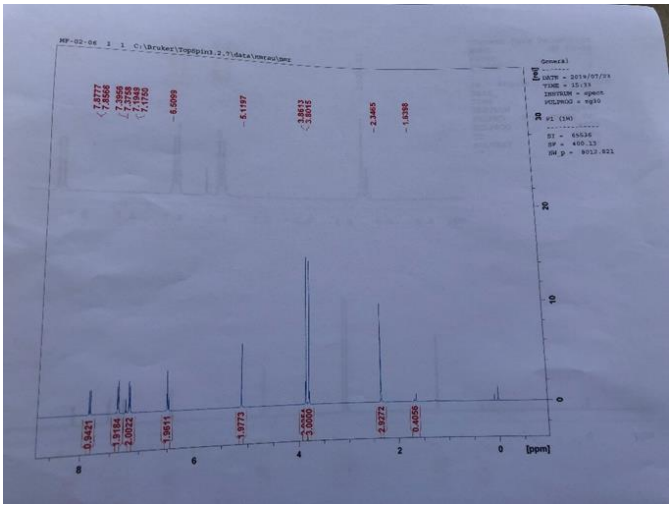
Group 4: This group can perfectly be attributed to the interior vinyl hydrogen in allyl ether group which has a particularly interesting resonance. This hydrogen couples to other four hydrogens in the allyl ether group with three different coupling constants (Figure 18b) and makes a very distinct multiplicity. As these interior vinyl hydrogens in each of the two allyl ether groups are in the same environment their chemical shifts are at around 5.6 ppm.

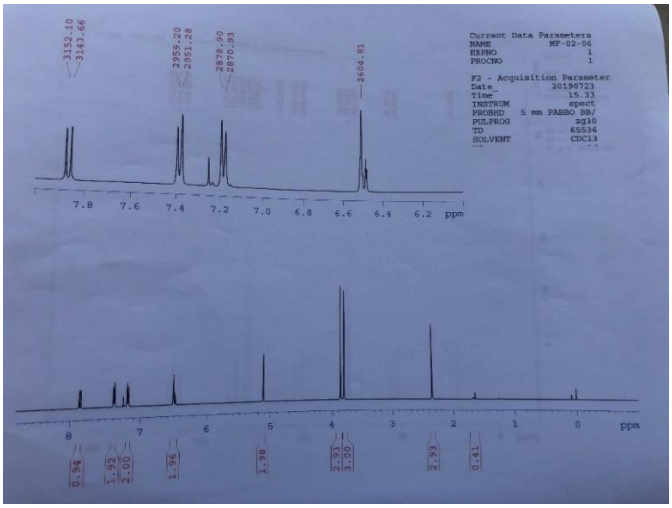
Group 5: This group represents the aromatic protons on benzene ring. On the NMR spectrum, the aromatic peaks are at around 6.2 ppm, which are in the lower ppm region of the spectrum within the aromatic region. Since the aryl ring has electron donating

groups, the electronic of the ring gives these aryl protons a chemical shift around 6 ppm. In other words, the lone pair of electrons of oxygens on the aryl ring push the electron density into the ring via resonance, making the aryl proton peaks appear more upfield. Also, as there is no symmetry in this molecule and each of the two aromatic hydrogens are in different chemical environments, the two protons have distinct chemical shifts. Moreover, lack of neighboring protons to couple, the peaks appear as singlet.

4.2.1.2 H-NMR for compound 61:

(a)





(b)

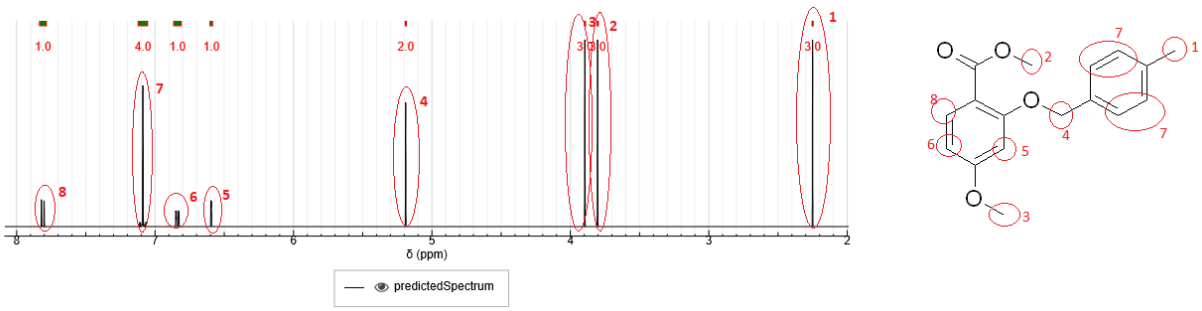


Figure 19. (a) Actual H-NMR for compound 61; (b) Predicted H-NMR for compound 61.

Group 1: The methyl group on the 4-position of the benzyl unit is similar to the methyl group on toluene, which based on data in the Spectral Database for Organic Compounds maintained by the Japanese AIST, has the chemical shift of 2.34 ppm in $CDCl_3$. The chemical shift for this peak in our actual NMR spectrum (Figure 19a) is exactly at 2.34 ppm, confirming its assignment.

Group 2: This methyl group is part of the ester functional group where the methyl group is connected to oxygen atom. It makes this methyl group more deshielded than an aliphatic methyl group, and that is why the peak appears more downfield at 3.8 ppm in the NMR spectrum. As the three hydrogens on the methyl group are chemically and magnetically equivalent, it appears as a singlet.

Group3: This methyl group is directly connected to the oxygen atom on an aryl ring. Hence, it is deshielded and shows up more downfield at 3.86 ppm. Like other methyl groups, it also shows up as a singlet on the NMR spectrum.

Group 4: This peak represents the benzylic protons. Since the $-CH_2-$ group is connected to an aryl ring and an oxygen atom, the signal for these protons is shifted downfield to 5.1 ppm.

Group 5: The proton in this group is on the benzene ring and expected to be seen at around 6.5 – 8.0 ppm range. As there are two electron donating groups next to this hydrogen (-OR), the protons on the ring are more shielded and show up more upfield. The signal for these protons is observed near 6.5 ppm. Figure 19a shows two peaks next to each other at 6.5 ppm, as a singlet and a doublet. The singlet peak at this chemical shift represents the proton in this group with no neighboring proton to couple.

Group 6: This is another hydrogen on the aromatic ring next to an electron donating group (-OR) and another hydrogen. As there is an electron donating group next to it, it is not surprising to see the peak more upfield and near 6.5 ppm. Also, as it is shown in Figure 18a There are two peaks at 6.5 ppm next to each other, a singlet and a doublet, which the doublet one is attributed to this hydrogen. This proton couple with the adjacent hydrogen on the aryl ring and appears as a doublet.

Group 7: In the proton NMR (Figure 19a), there is a symmetrical doublet-doublet pattern at 7.2 ppm and 7.4 ppm which is extremely a strong evidence for para-substituted benzene. These two doublets represent the four protons on the aryl ring of the benzyl group. Each two protons opposite each other on the benzene ring can be assumed to be in the same chemical and magnetic environment. So, each set is represented in one peak and appears as doublet due to coupling with adjacent aryl proton.

Group 8: This is the most downfield peak at 7.8 ppm which stands for the hydrogen on the benzene ring next to a carbonyl group. As the carbonyl group is an electron withdrawing group, it is expected the adjacent hydrogen would be less shielded and shows up more downfield. Figure 18a shows the chemical shift and the splitting pattern for this peak.

4.3 Antibacterial evaluation of selected methyl-4-methoxysalicylate analogs:

Since α-mangostin is known to exhibit antibacterial activity against a broad range of bacteria, we investigated the antibacterial activity of the synthetic analogs we have generated. As a first step, we selected two benzyl-ether analogs (**58** and **60**) for the antibacterial evaluation. The studies were done using standard Gram-positive strains (two different *S. aureus*, and a *S. epidermidis)* that show greater sensitivity to antibiotics and α-mangostin. Since these Gram-positive bacteria are relatively easy to cultivate in the laboratory, and commonly used for antibiotic discovery efforts, we selected these bacteria for our evaluation. Additionally, these bacteria are also associated with various types of infections in clinical setting. The data are shown in Table 1 below. The minimum inhibitory concentration (MIC) value determination was done by a Ph.D. student, Nikita Acharekar in the Yoganathan lab. Ciprofloxacin and α-mangostin were used as positive control and exhibited potent MIC values in the range of 0.01 – 0.6 µg/mL. We found that the synthetic analogs **58** and **60** showed no antibacterial activity even at 100 µg/mL. Although the biological data is not promising at this stage, our plan is to continue to test the remaining analogs against a panel of bacteria. In addition, as anti-cancer property of this group of compounds is an interest to us, we may be exploring the anti-cancer activity of these analogs in the future.

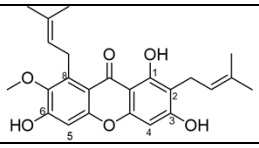
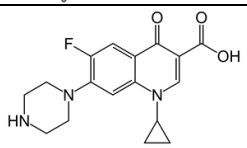
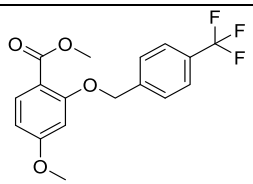
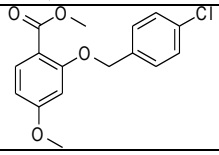
Compound name or #	Compound Structure	MIC values (μg/mL)		
		S. aureus (ATCC 29213)	*S. aureus* (ATCC 12600)	*S. epidermidis* (ATCC 12228)
α-mangostin		0.01	0.6	0.6
ciprofloxacin		0.3	0.3	0.3
58		>100	>100	>100
60		>100	>100	>100

Table 1. Antibacterial activity of selected methyl-4-methoxysalicylate analogs.

CHAPTER 5. CONCLUSION

Herein, we report a direct and efficient approach to access several non-xanthone α-mangostin analogs. Currently reported methods in the literature are using commercially available α-mangostin to make new analogs with improved efficacy and less toxicity[99, 103, 105, 108, 119]. But our approach utilizes a simple commercially available phenolic acid substrate to prepare a series of 'non-xanthone' derivatives for medicinal chemistry evaluation. We have developed a synthetic method to make α-mangostin analogs by using the commercially available methyl-4-methoxysalicylate as the precursor, and selectively modified the phenol motif in a one-step process. Our approach generated a series of benzyl ether analogs via one-step synthesis. Since there is a large array of benzyl halides available commercially, one can use our method to generate an extensive library of analogs for medicinal chemistry studies. Although our initial antibacterial study did not provide any potent analogs, we believe that using the chemistry we developed, more analogs can be synthesized to identify potential antibacterial compounds of this nature. Additionally, these analogs we have generated can be tested against other pathogenic bacteria and likely for cytotoxicity against cancer cell lines.

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