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Design of marine inspired bioactive compounds: synthesis and lipophilicity assessment

Joana Catarina Gomes da Costa

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Design of marine inspired bioactive compounds: synthesis and lipophilicity assessment

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Work developed under the scientific supervision of Professor Carlos Afonso and Dr Carlos Azevedo.

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RESUMO

A natureza foi desde sempre uma fonte importante de novas substâncias com potenciais efeitos terapêuticos. Entre os diferentes compartimentos ambientais, o mar continua o menos explorado, o mais desconhecido e o mais promissor como fonte de novas substâncias bioativas. Contudo, o mar, dada sua grande diversidade biológica e química, tem tido grande importância na descoberta de novas substâncias bioativas nas últimas décadas. Entre as atividades biológicas encontradas para produtos marinhos, a atividade antimicrobiana é uma das mais relevantes e de maior interesse. A elevada taxa de mortalidade em todo o mundo é causada por doenças infeciosas.

O desenvolvimento de resistências a muitos antibióticos e outros antimicrobianos justificam a importância da descoberta e desenvolvimento de novos antimicrobianos eficazes e seguros.

O núcleo xantónico é considerado uma estrutura privilegiada em Química Farmacêutica que ocorre frequentemente em moléculas de substâncias presentes no ambiente marinho. Entre as várias atividades biológicas encontradas para os derivados xantónicos, uma das mais importantes é a antimicrobiana.

A extração direta da natureza apenas permite obter pequenas quantidades das substâncias ativas, tornando a síntese laboratorial essencial para a obtenção das quantidades necessárias dessas substâncias.

As hicatinas B e C, isoladas do fungo marinho *Aspergillus wentii* são um exemplo de substâncias marinhas com interessante atividade antimicrobiana, cuja síntese total foi anteriormente efetuada pelo nosso grupo de investigação.

Neste trabalho, é explorado o acoplamento carbonilativo de Suzuki para a síntese das hicatinas B e C e alguns análogos. Tendo em vista a otimização multidimensional destas substâncias e a previsão do seu comportamento farmacocinético, foram também determinadas propriedades biofísico-químicas, nomeadamente a lipofilicidade, Log Kp , recorrendo a modelos biomiméticos.

PALAVRAS-CHAVES

Xantonas marinhas; Síntese total; Acoplamento carbonilativo de Suzuki; Hicatinas; Lipofilicidade

ABSTRACT

Nature has always been an important source of new substances with potential therapeutic effects. Among the different environmental compartments, the sea remains the least explored, the most unknown and most promising as a source of new bioactive substances. However, the sea, given its great biological and chemical diversity, has been of great importance in the discovery of new bioactive substances in recent decades. Among the biological activities found for marine products, antimicrobial activity is one of the most relevant and of most interest.

The worldwide high mortality rate caused by infectious diseases and the development of resistance to many antibiotics and other antimicrobials justifies the importance of finding and developing new effective and safe antimicrobials.

The xanthonic nucleus is considered a privileged structure in pharmaceutical chemistry that often occurs in molecules of substances present in the marine environment. Among the various biological activities found for xanthonic derivatives, one of the most important is antimicrobial.

Direct extraction from nature allows only small quantities of active substances to be obtained, making laboratory synthesis essential for obtaining the required quantities of these substances.

Yicathins B and C isolated from the marine fungus *Aspergillus wentii* are an example of marine substances with interesting antimicrobial activity, the total synthesis of which was previously done by our research group.

In this work, Suzuki carbonylative coupling for the synthesis of yicathins B and C and some analogues is explored. In view of the multidimensional optimization of these substances and the prediction of their pharmacokinetic behavior, biophysical-chemical properties were also determined, namely lipophilicity ,Log Kp, using biomimetic models.

KEY WORDS

Marine xanthones; Total synthesis; Carbonylative Suzuki coupling; Yicathins; Lipophilicity

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FIGURE INDEX

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LIST OF ABBREVIATIONS, ACRONYMS AND SYMBOLS

δ_C	Carbon Chemical shifts in parts per million downfield from tetramethylsilane
δ_H	Proton Chemical shifts in parts per million downfield from tetramethylsilane
^{13}C NMR	Carbon Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
CO	Carbon Monoxide
d	Doublet
dd	Double doublet
DMF	Dimethylformamide
DMG	Direct metalation group
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
DMSO-*d*6	Deuterated dimethylsulfoxide
EIMS	Electron impact mass spectrometry
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GC-MS	Gas chromatography – mass spectrometry
HMBC	Heteronuclear multiple bond correlation
HSQC	Heteronuclear single quantum coherence
HTS	Hight Throughput Screening
IR	Infrared spectroscopy
J	Coupling constant
Log D	Logarithm of the Distribution Coefficient between octanol:buffer at a set pH
Log K_p	Logarithm of membrane-water partition coefficient
Log P	Partition coefficient octanol-water
m	Multiplet
MeCN	Acetonitrile
MeOH	Methanol
MNP	Marine Natural Product
MOM	Methoxymethyl
MOMCl	Methoxymethyl chloride
m.p.	Melting point
MW	Microwave heating

MW	Molecular weight
NMR	Nuclear Magnetic Ressonance
MNP	Marine Natural product
NP	Natural product
PCC	Pyridinium chlorochromate
q	Quadruplet
s	Singlet
t	Triplet
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	Trimethylsilyl
UV/Vis	Ultraviolet/Visible spectrometry

OUTLINE OF THE DISSERTATION

The present dissertation is organized in seven chapters:

A. Introduction

In this chapter the importance of natural products in drug discovery is presented, with a particular interest in marine natural products. The relevance of the xanthonic nucleus and its important activity is showed. Finally, it is also presented Yicathin B and C with potential antimicrobial activity. The assessment of biophysicochemical properties in drug discovery process is presented.

B. Aims

The aims for the work that leaded this dissertation are presented in this chapter.

C. Results and discussion

This chapter is divided into three main sections: I. synthesis of yicathins B and C; II. Exploration of synthesis of analogues by Carbonylative Suzuki Coupling; and III: lipophilicity obtain by biomimetic model of Yicathin B, C and analogues.

The retrosynthetic analysis and the synthesis pathways to yicathins B and C is showed. All synthetic steps are discussed, and structural elucidation is presented and discussed. Lastly, the determination of lipophilicity of the eight compounds is described and discussed.

D. Experimental

All the reagents, the experimental conditions and procedures for the synthesis, the purification steps and the structure elucidation of all synthesized compounds is described in this chapter.

E. Conclusions

In this section, general conclusions of this work are exposed.

F. References

All the literature used as support in this dissertation is listed in this chapter. ACS system for bibliographic references was used.

G. Appendix

In this chapter, the NMR spectra of the new synthetized compound is showed.

A. Introduction

1. Natural products in Drug Discovery

Nature continues to provide a variety of compounds with interesting and important biological activities, which are being used as drugs or as leads in drug discovery and drug design [2]. In fact, in the last three decades up to 65% of new drugs (Fig.1) present in the market were from natural origin or inspired by natural products templates and scaffolds[1].

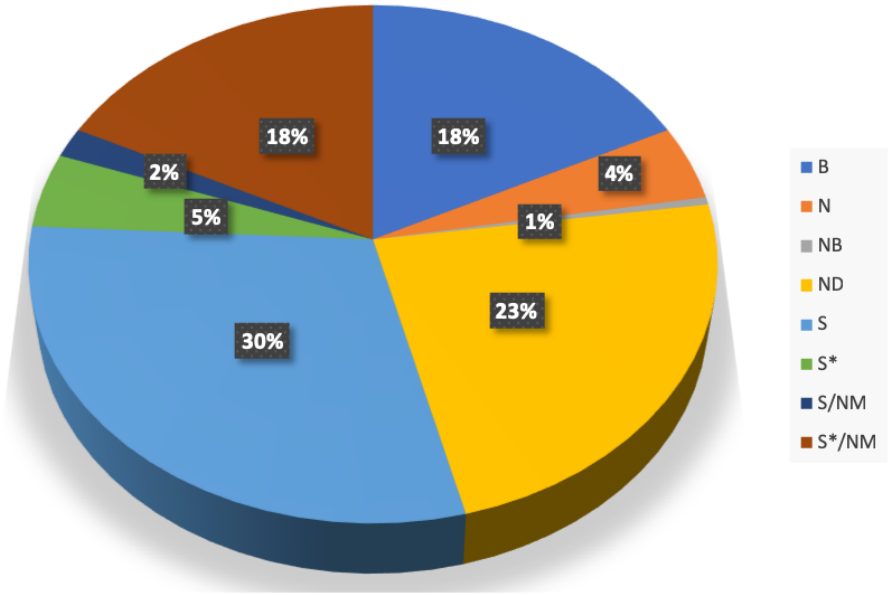


Figure 1-All new Drugs approved in the last three decades (B-Biological macromolecule, N-unaltered natural product, NB-botanical drug, ND-natural product derivative, S-synthetic, S-synthetic (NP pharmacophore), /NM-mimic of natural product) (Adapted from [1])*

Natural products (NPs) present a unique diversity of chemical structures, which are a promising source of new *hits/leads* in drug discovery [3-4]. The discovery of new NPs is a laborious, consuming and hardworking, mainly because the difficulties found in extracting, isolating and identifying new substances and because the substances are normally isolated in small quantities[5]. To overcome these obstacles, the laboratory synthesis or semi-synthesis of identified natural products can be an interesting and often the only solution. Bioactive NPs are normally structurally complex compounds, with an exact spatial

orientation, which is the result of centuries of evolution, adaptation and optimization to a better and more efficient interaction with their biological targets [6]. Furthermore, exploring their synthetic routes can often lead to the discovery of new reactions and new strategies to generate skeletal frameworks and to form new chemical bonds[7]. Also, synthesis provides a way to get structural analogues, which are fundamental in drug design and drug development.

In the search for new biological active compounds, the ocean became a noteworthy source of marine natural products (MNPs) in the last years[8].

2. The marine environment - interest and specificities

The oceans cover more than 70% of the Earth's surface, represent a vast and rich habitat, providing biological and chemical diversity[9]. Only about 5% of the deep sea has been explored and a relatively small portion of the species that live in the sea were identified[10]. This is due to the technical difficulties to achieve the deep sea and the harsh conditions, such as big ranges of temperatures, light, pressure, that do not occur as frequently in other ecosystems[11]. The severe conditions that sea organisms have to face forces them to follow specific biochemical pathways, with a consequent production of a variety of secondary metabolites that cannot be found in the terrestrial environment, which can be useful as *hits* and *leads* in drug discovery[9, 11].

In 2010, the comparison of both natural terrestrial and natural marine scaffolds revealed that about 71% of the skeletal frameworks analyzed were innovative and were found in a marine environment, leading to the conclusion that marine natural products (MNPs) can be a better source of novel scaffolds when compared to terrestrial[12]

Up to 28,500 MNP's had been identified until 2016. In 2017 a total of 1490 new marine natural products were isolated from marine organisms which represents an increase of 17 % when compared to 2016[13]. At the present, six new therapeutic agents that can be considered derivatives of MNP's were approved by regulatory agencies to be used as medicines[14]. In figure 2, four of the six approved drugs are presented (these four are small molecules and the other two are proteins). These facts reinforce the endless possibilities of the marine environment as an important source of new bioactive compounds.

Among all marine organisms, marine microorganisms are relevant and represent a rich source of potentially bioactive secondary metabolites with high chemical and structural diversity and attractive biological features such as antibacterial, antiviral, anticancer, antifouling, anti-inflammatory and anti-mitotic properties[15].

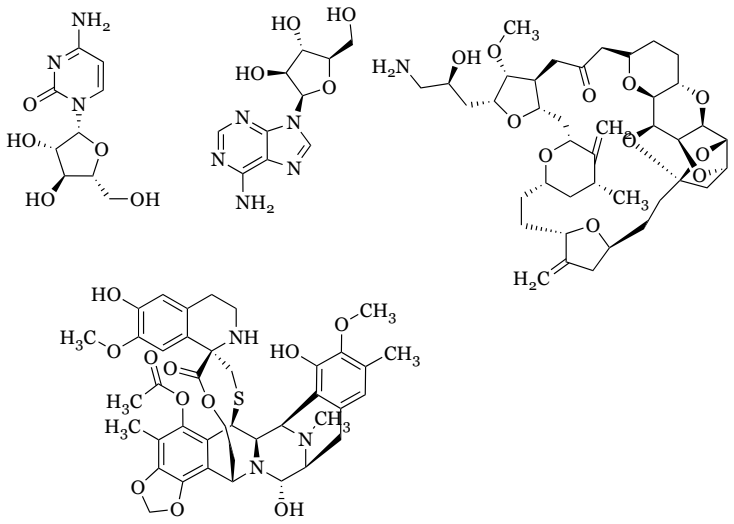


Figure 2- Drugs approved as therapeutic agents

3. Xanthones: chemistry and antimicrobial activity

Xanthones (Figure 3) are a class of oxygen-containing heterocycles with a γ-pyrone moiety condensed with two benzene rings. Xanthones appear in nature as secondary metabolites, normally occurring in higher plants families, fungi and lichen. They are broadly dispersed in nature and gather significantly attention due to their remarkable and varied biological activities, being considered as "privileged structures" in Medicinal Chemistry [16]. Several bioactive xanthones were already synthesized in the laboratory [17-19].

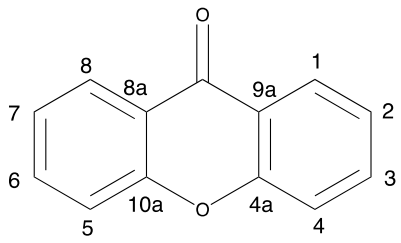


Figure 3- Xanthone Scaffold

Among the variety of pharmacological activities that xanthones can exhibit, such as antitumoral, anti-inflammatory and others, antimicrobial activity is a relevant activity. A recent review reported that, in the last three decades, 53 new marine xanthones were isolated and possessed anti-infective activity[17]. Some of these anti-infective xanthone derivatives are presented in figure 4.

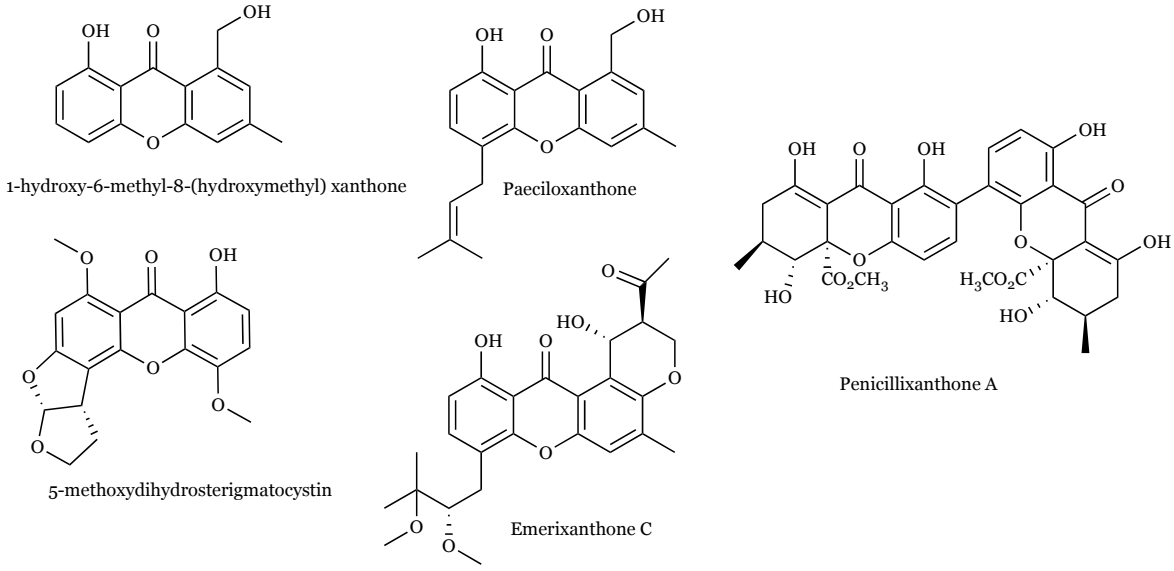


Figure 4- Anti-infective xanthones

Infectious diseases are one of the main causes of morbidity and mortality across the world[20]. As presented in figure 5, they are amongst the top 15 causes of death in 2017. Tuberculosis, diarrheal diseases and respiratory infections, among others, accounted for nearly 14 % of global deaths [21]. The problem aggravates with the growing development of "drug resistant microorganisms", with many antibiotics and other antimicrobials losing their effectiveness. Antimicrobial resistance is the capacity of microorganisms, such as bacteria, viruses, parasites, or fungi, to grow even when in the presence of a drug that normally would kill it or stop its growth, and it constitutes a global burden, being one of the major threats to public health[22]. This fact justifies the high importance of finding new, effective and safe antimicrobials.

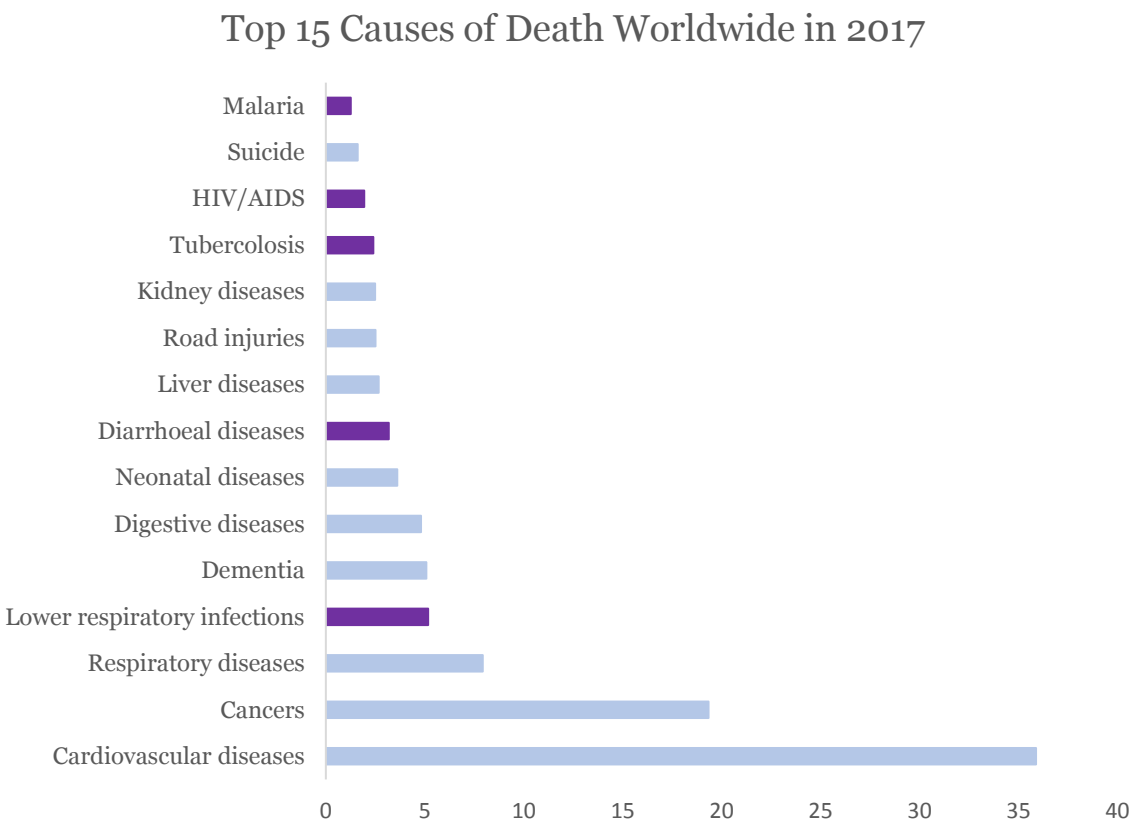
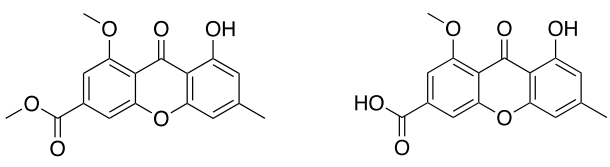


Figure 5-Top 15 causes of Death Worldwide (Adapted from[21])

4. Yicathins B and C

Marine environment can be a natural solution to minimize this huge healthy problem, since it can provide novel and very active antimicrobial substances. Recently, two xanthones, yicathin B **(12)** and yicathin C **(11)**, were isolated from a extract of a *Aspergillus* fungus, obtained from the inner tissue of the marine red alga *Gymnogongrus flabelliformis*. These yicathins showed relevant antimicrobial activity[23].



12 **11**

*Figure 6-Yicathin B **(12)** and C **(11)***

Yicathin B (12) showed antibacterial activity against *Escherichia coli* and **yicathin C (11)** showed antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Colletotrichum lagenarium* [23].

B. Aims

These yicathins can just be extracted only in small amounts directly from nature and its extraction implies technical equipment and, eventually, seasonable issues. So, the synthesis of yicathins B and C is significant. These substances can be used as hits of new antimicrobial drug candidates. Yicathins were isolated from marine organisms but have never been synthetized in the laboratory. The total synthesis of these marine derived xanthones and new analogues was achieved for the first time by our group. However, small amounts of desired compounds were obtained.

Taking into account the synthetic path that was already used and in order to better master the reactions involved, and also to get more quantities of these yicathins, its synthesis was performed again. During these synthetic pathways, six analogues were additionally obtained, which can be explored as new hits and leads. Furthermore, new synthetic methodologies, such as the carbonylative Sukuzi coupling, were explored to achieve key intermediates in a reduced number of steps, reducing the overall original synthetic plan. Finally, the determination of biophysicochemical parameters, namely the lipophilicity of the yicathins and analogues was also performed. Lipophilicity is an important property that conditions the pharmacokinetic behavior of drugs. Based on these main goals, the aims of the developed work were:

i. Synthesis of all the building blocks needed to the synthesis of yicathins B and C and analogues;
ii. Synthesis of yicathins B and C and analogues, as well as their intermediates, in more quantities;
iii. Purification of the compounds and elucidation of their structures;
iv. Exploring the Carbonylative Sukuzi Coupling to obtain key intermediates of yicathins and analogues;
v. Predicting biophysicochemical properties of the new compounds, using micelles as a biomimetic model to evaluate the lipophilicity.

C. Results and Discussion

C.1. Synthesis of Yicathins B and C

1. Retrosynthesis of Yicathins B and C

The retrosynthesis of yicathins B and C was previously planned, and the total synthesis of yicathin B and C and analogues was already been achieved in our group. In order to synthesize yicathins, the chosen pathway was through a benzophenone intermediate. Accordingly to the retrosynthetic plan (Figure 7), yicathin C can be obtained in seven steps and yicathin B is obtained with an additional step. Firstly, two key building blocks are prepared andthe condensation of these two building blocks by an halogen-lithium exchange, followed by an oxidation gives the benzophenone. The xanthone nucleus is obtained by a deprotection followed by an intramolecular nucleophilic aromatic substitution to yield a benzyl alcohol. yicathin C is obtained by the oxidation of the benzylic alcohol to carboxylic acid, and yicathin B is obtained by a Fischer esterification of yicathin C.

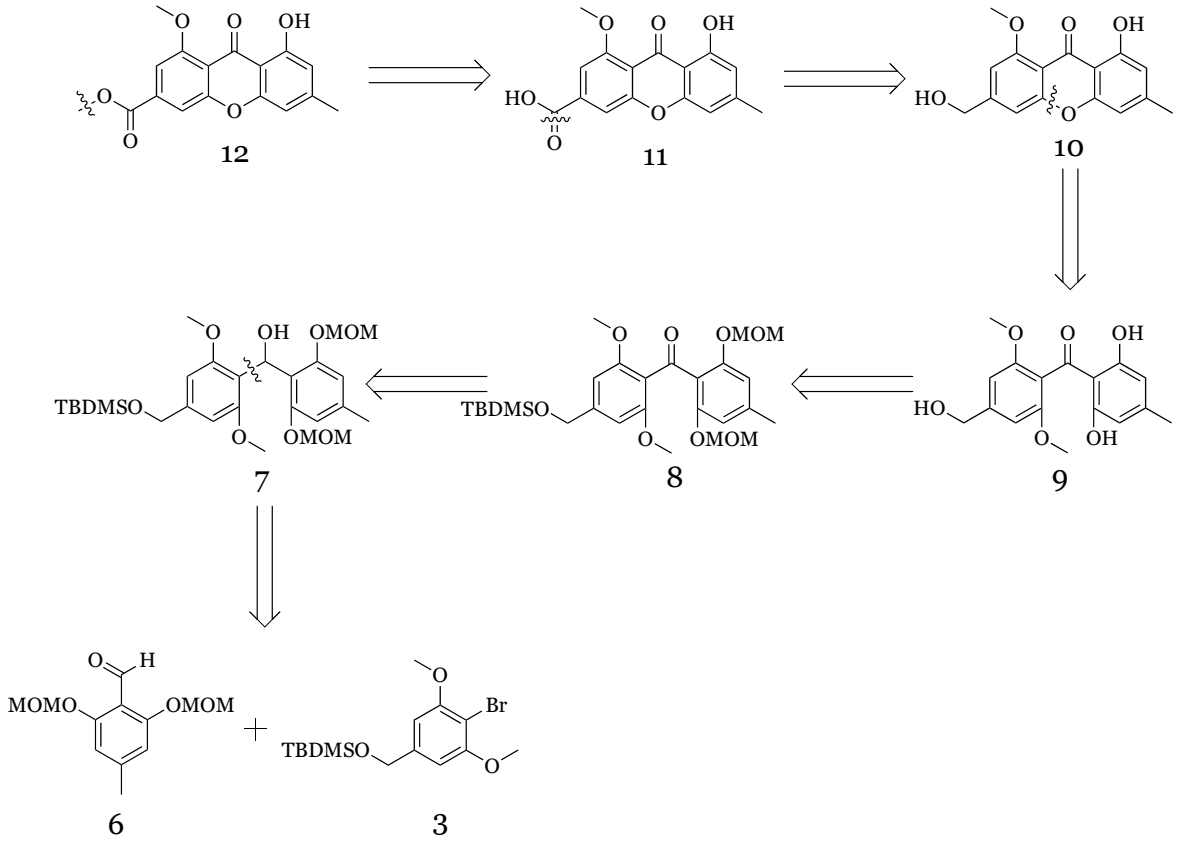


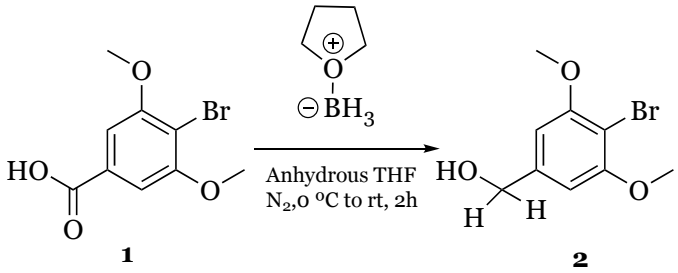
*Figure 7-Retrosynthesis of Yicathins B **(12)** and C **(11)***

2. Synthesis of Building Blocks

2.1. Synthesis of building block A

2.1.1. Synthesis of (4-bromo-3,5-dimethoxyphenyl)methanol **(2)**

Scheme 1 shows the pathways used to synthetize (4-bromo-3,5-dimethoxyphenyl)methanol **(2)**.



Scheme 1-Reduction of 4-bromo-3,5- dimethoxybenzoic acid (1)

The first step in the synthesis of building block A involves the reduction of the carboxylic acid of 4-bromo-3,5- dimethoxybenzoic acid (1) to a benzylic alcohol.

To obtain the desired product one of the most commonly used reducing agents BH_3 was used and normally, this reagent is found in a complex with tetrahydrofuran (BH_3:THF).

Borane is a very strong Lewis acid that allows the selective and a rapid reduction of carboxylic acids [24-25] and when compared to previous procedures with different reducing agents, performs in a similar but fastest way.

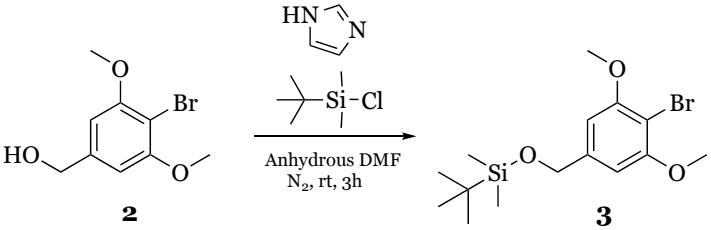
To 4-bromo-3,5-demethoxybenzoic acid **(1)** in tetrahydrofuran, it was added borane:tetrahydrofuran complex and the reaction mixture stayed stirring at room temperature for 2 hours. After work up the desired product was obtained with a good yield (96%).

The identification of compound **2** was based on FTIR, EIMS and ^{1}H NMR. The FTIR spectrum showed a large stretching attributed to O-H at 3223 cm^{-1} and the absence of C=O stretching band. The EIMS show the typical ratio pattern for the bromine isotopic with *m/z* 248 ($[M+2]^{+\cdot}$, 79) and *m/z* 246 ($[M]^+$, 84). The ^{1}H NMR spectrum showed both protons of the methylene group δ_H 4.49 (2H, d), the proton of the hydroxyl group δ_H 5.35 (H, *t*), the

protons of the two methoxyl groups δ_H 3.82 (6H, s) and the aromatic protons δ_H 6.70 (2H, s).

2.1.2. Synthesis of ((4-bromo-3,5-dimethoxybenzyl)oxy)(tert-butyl)dimethylsilane **(3)**

Scheme 2 shows the synthesis of ((4-bromo-3,5-dimethoxybenzyl)oxy)(tert-butyl)dimethylsilane (**3**).



Scheme 2-Protection of (4-Bromo-3,5-dimethoxyphenyl)methanol (2).

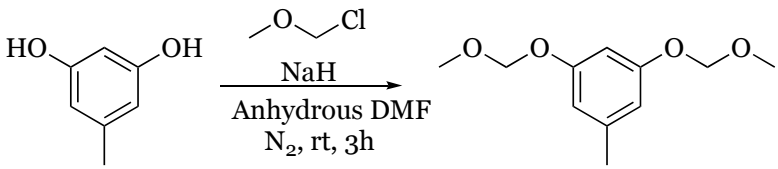
The last step in order to obtain building block A **(3)** was the protection of the hydroxyl with the *tert*-butyldimethylsilyl (TBDMSCl) group, a commonly use protection group of primary alcohols[26]. This reaction step is important and needed since in following reactions it is required basic conditions, and the TBDMS ether is stable[27]. So, TBDMSCl was added to the (4-bromo-3,5-dimethoxyphenyl)methanol **(2)** in anhydrous DMF, in the presence of imidazole, and the reaction was stirred at room temperature for 5 hours[28]. The desired product was achieved with 68 % yield.

The identification of compound **3** was based on FTIR, EIMS and ^{1}H NMR. In the FTIR spectrum the absence of the stretching band attributed to O-H bond was notable. The EIMS, similar to compound **2,** showed the typical bromine isotopic pattern with *m/z* 364 ($[M+2]^{+\cdot}$, 2) and *m/z* 362 ($[M]^{+\cdot}$, 3). The ^{1}H NMR spectrum showed a similar profile to compound **2,** two methoxyl groups δ_H 3.79 (6H, s), the two protons of the methylene group δ_H 4.68 (2H, s) and the aromatic protons δ_H 6.66 (2H, s), with the additional presence of signals corresponding to the methyl groups directly attached to the silyl group δ_H 0.07 (6H, s), the *tert*-butyl protons δ_H 0.90 (9H, s).

2.2.Synthesis of building block B

2.2.1. Synthesis of 1,3-bis(methoxymethoxy)-5-methylbenzene **(5)**

Scheme 3 shows the synthesis of 1,3-bis(methoxymethoxy)-5-methylbenzene (**5**).



4 **5**

*Scheme 3-Protection of orcinol **(4)**.*

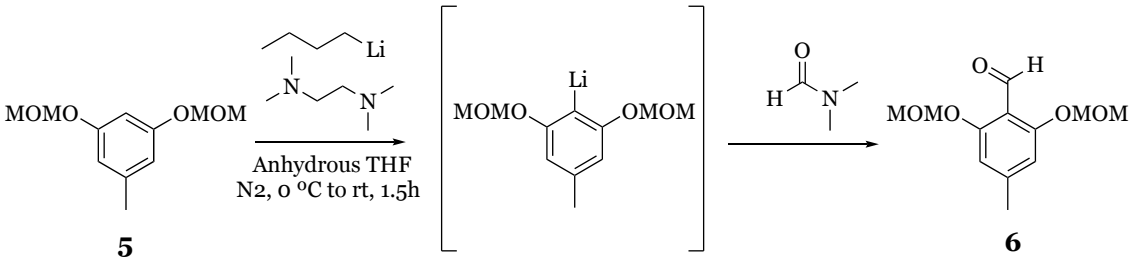
The first reaction for the synthesis of building block B is the protection of the hydroxyl groups of orcinol (4). In a similar way to the synthesis of building block A, this protection is essential to shield against the attack of a strong base, such as *n*-BuLi, used in further ahead reactions. In this case the protecting group used is methoxymethyl (MOM) because is resistant to base conditions and easily cleaved at mild conditions[27].

So, orcinol was treated with MOMCl in anhydrous DMF, in the presence of NaH[29]. The desired compound **5** was isolated, after purification, with 91 % yield.

The identification of compound **5** was based on FTIR, EIMS and ^{1}H NMR. The FTIR spectrum showed the absence of the stretching band attributed to O-H of phenol groups, as expected, and EIMS showed a molecular peak with *m/z* 212 ($[M]^{+\cdot}$) corresponding to the molecular ion. The ^{1}H NMR spectrum showed the expected signals for the methyl group δ_H 2.23 (3H, s), the aromatic protons δ_H 6.47 (1H, m) and δ_H 6.49 (2H, dd) and signals corresponding to the protons of the protecting group introduced δ_H 3.36 (6H, s) and δ_H 5.14 (4H, s).

2.2.2. Synthesis of 2,6-bis(methoxymethoxy)-4- methylbenzaldehyde **(6)**

Scheme 4 shows the synthesis of 2,6-bis(methoxymethoxy)-4- methylbenzaldehyde (**6**).



*Scheme 4- Synthesis of 2,6-bis(methoxymethoxy)-4- methylbenzaldehyde **(6)**.*

The desired benzaldehyde **(6)** is obtain by the formylation which is accomplished in two steps: first a directed *ortho*-metalation (D*o*M) followed by an aromatic electrophilic substitution.

The first step of the reaction is the directed *ortho*-metalation that involves the deprotonation of the carbon *ortho* to a heteroatom-containing direct metalation group (DMG)[29]. In this case the lithium atom coordinates with de oxygen atom of MOM groups originating a lithiated specie. The final step is the treatment of the lithiated intermediate with DMF, producing a hemiaminal that in the work up is easily hydrolyzed into the desired compound[30-31].

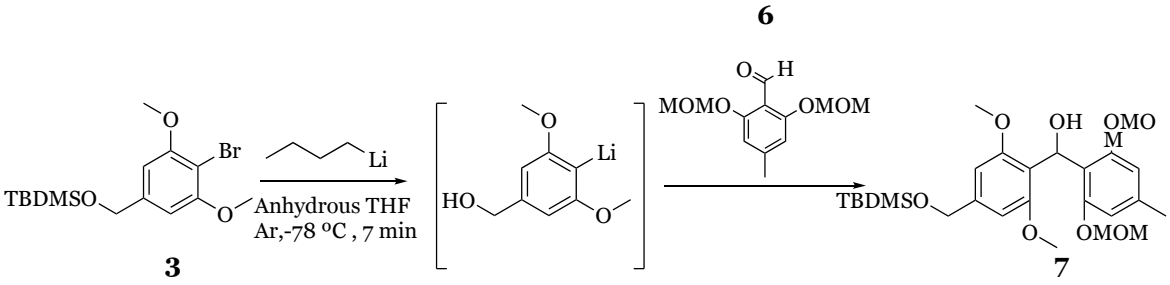
So, to 1,3-bis(methoxymethoxy)-5-methylbenzene in anhydrous THF and in TMEDA, *n*-BuLi was added. Once the lithiaded intermediate was formed, anhydrous DMF was added[29]. The desired compound benzaldehyde (6) was obtained in 43% yield, after purification.

The identification of compound **6** was based on FTIR, EIMS and ^{1}H NMR. The FTIR spectrum showed the presence of the carbonyl band at 1683 cm^{-1}, and EIMS showed an peak with *m/z* 241 ([M+1]$^{+\cdot}$). The ^{1}H NMR spectrum displayed similar signals to compound **5** for the methyl group δ_H 2.31 (3H, s), the aromatic protons δ_H 6.70 (2H, s) and the protons of the protecting group δ_H 3.40 (6H, s) and δ_H 5.25 (4H, s), it also showed the signal corresponding to the aldehyde proton δ_H 10.37 (H, s).

3. Synthesis of yicanthins B and C from the building Blocks

3.1. Synthesis of (2,6-bis(methoxymethoxy)-4-methylphenyl)(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6- dimethoxyphenyl)methanol **(7)**

Scheme 5 shows the synthesis of (2,6-bis(methoxymethoxy)-4-methylphenyl)(4- (((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanol **(5)**.



Scheme 5- Synthesis of the benzophenone

One of the most common routes for the synthesis of xanthones implicates the synthesis of an intermediate, a benzophenone[16, 19].The procedure most used and effective is the halogen/lithium exchange that allows the synthesis of benzophenones with good yields[16]. The mechanism by which this reaction occurs is still not completely described in the literature, with two possible mechanisms proposed: either by radical intermediates or by nucleophilic substitution. In the latter case, the halogen exchange by lithium of building block A is the first step and leads to the formation of a lithiated intermediate, to which is added building block B by nucleophilic substitution originating a diarylmethanol[32-33]. So, *n*-BuLi was added, at -78 °C, to building block A in freshly dried THF. After 7 minutes, building block B was added, staying at -78 °C for 1.5 h. After this time, the mixture was kept stirred for 1.5 h at room temperature. The desired diarylmethanol **(7)** was obtained, after purification, in 58 % yield.

The identification of compound **7** was based on FTIR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. The FTIR spectrum showed the presence of O-H stretching band referent to the alcohol group at 3565 cm^{-1}· and EIMS spectrum showed a peak with *m/z* 523 ([M+1]$^{+}$·). The ^{1}H NMR spectrum showed similar signals to the ones attributed to building block A and B. The signals consistent with the ones assigned to building block A were the methyl

groups directly attached to the silyl group δ_H 0.20 (6H, s), the *tert*-butyl protons δ_H 1.04 (9H, s), two methoxyl groups δ_H 3.84 (6H, s), the two protons of the methylene group δ_H 4.78 (2H, d), and the aromatic protons δ_H 6.68 (2H, s). The signals consistent with the ones assigned to building block B corresponded to the proton from the methyl group δ_H 2.34 (3H, s), the protons of the protecting group δ_H 3.34 (6H, s) and δ_H 5.22 (4H, s) and the aromatic protons δ_H 6.64 (2H, s). The presence of signal of the hydroxyl proton δ_H 6.53 (OH, d) and the proton of the attached carbon δ_H 5.51 (H, d), with equal coupling constants (J = 10.3 Hz) certified the presence of the alcohol group. The ^{13}C NMR presented 17 signals. The main connectivities of HMBC are presented in **Figure 8** and all the assignments are presented in table 1.

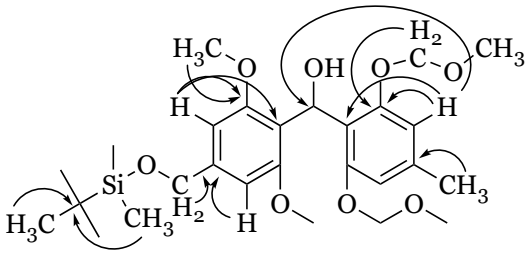
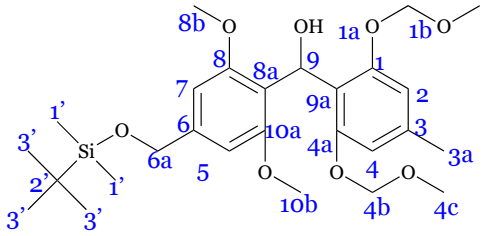


Figure 8-Main connectivities of HMBC of compound 7

Table 1-Chemical shifts and assignments of compound 7



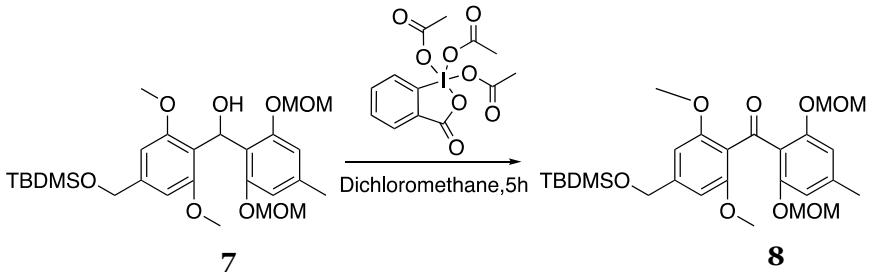
^{1}H NMR Chemical Shifts	δ_H(ppm)[a]
1a-H and 4b-H	5.22(s)
1b-H and 4c-H	3.34(s)
2-H and 4-H	6.64(s)
3a-H	2.34(s)
5-H and 7-H	6.68(s)
6a-H	4.78(s)
8b-H and 10b-H	3.84(s)
9-H	5.51(d,J=10.3)
9-OH	6.53(d,J=10.3)
1´-H	0.20(s)
3´-H	1.04(s)

^{13}C NMR Chemical Shifts	δ_C(ppm)[b]
1 and 4a	155.3
1a and 4b	94.1
1b na 4c	55.5
2 and 4	108.5
3	137.1
3a	21.4
5 and 7	101.8
6	141.3
6a	64.2
8 and 10a	157.7
8a	117.9
8b and 10b	55.6
9	63.4
9a	118.9
1'	-5.3
2'	18.0
3'	25.8

[a]Values in ppm (δ_H) measured at 500.16 MHz, multiplicity and *J* values (Hz) are shown in parentheses; [b]Values in ppm (δ_C) measured at 125.77 MHz

3.2. Synthesis of (2,6-bis(methoxymethoxy)-4- methylphenyl)(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6- dimethoxyphenyl)methanone **(8)**

Scheme 6 shows the synthesis of (2,6-bis(methoxymethoxy)-4-methylphenyl)(4- (((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanone **(8)**.



7 **8**

Scheme 6- Oxidation of the diarylmethanol

The next step required to obtain the key intermediate in the synthesis of xanthones, the benzophenone, is the oxidation of the secondary alcohol into ketone. The oxidation agents choose is Dess-Martin periodinane (DMP). The use of DMP takes into account several positive aspects such as obtaining a high yield without excess oxidation, the reaction is carried out in mild conditions (room temperature, absence of acid or basic conditions) and highly chemosselectivity[34-35].

So, DMP was added to the diarylmethanol in dichloromethane and the reaction was stirred at room temperature for 5 hours. The desired benzophenone was obtained, after purification, in 71% yield.

The identification of compound **8** was based on FTIR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. The FTIR spectrum showed the expected band correspondent to the carbonyl group at 1704 cm^{-1}. Although the EIMS spectrum did not showed a peak with the *m/z* value compatible with the molecular mass of the desired compound, several peaks compatible with the fragmentation of the desired compound were identified (figure 9).

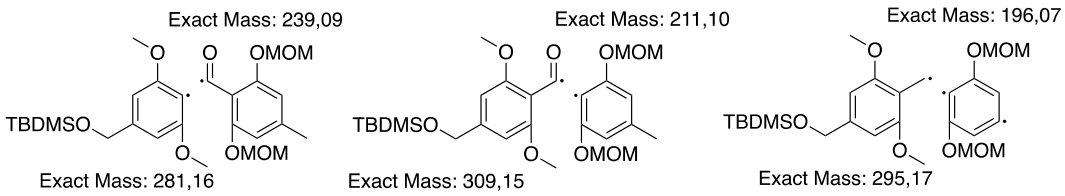


Figure 9-Principal fragments for EIMS

When compared to the ^{1}H NMR and ^{13}C NMR profile of compound **7**, the spectra of compound **8** were similar with the exception of hydroxyl signal absence in the ^{1}H NMR spectrum and the presence of the carbonyl signal in the ^{13}C NMR spectrum. The main connectivities of HMBC are presented in **Figure 10** and all the assignments are presented in table 2.

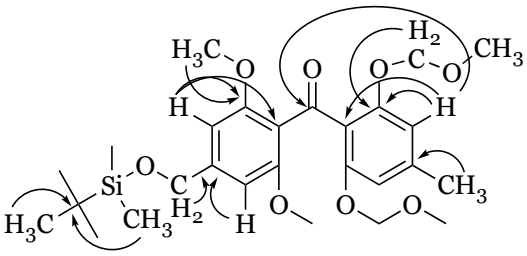
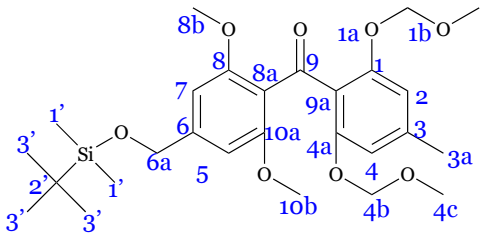


*Figure 10-Main connectivities of HMBC of compound **8***

*Table 2-Chemical shifts and assignments of compound **8***



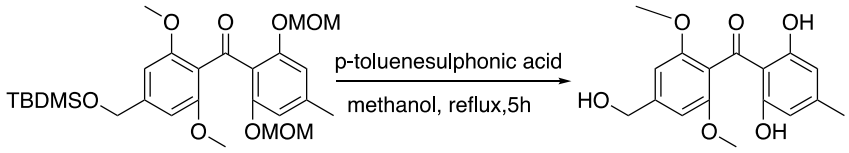
^{13}C NMR Chemical Shifts	δ_C(ppm)[b]
1 and 4a	155.1
1a and 4b	943.9
1b and 4c	55.5
2 and 4	108.6
3	140.9
3a	21.8
5 and 7	101.8
6	145.2
6a	64.2
8 and 10a	157.9
8a	119.8
8b and 10b	55.9
9	192.0
9a	120.4
1'	-5.2
2'	18.1
3'	25.9

^{1}H NMR Chemical Shifts	δ_H(ppm)[a]
1a-H and 4b-H	4.99(s)
1b-H and 4c-H	3.17(s)
2-H and 4-H	6.54(s)
3a-H	2.25(s)
5-H and 7-H	6.59(s)
6a-H	4.68(s)
8b-H and 10b-H	3.60(s)
1´-H	0.07(s)
3´-H	0.91(s)

[a]Values in ppm (δ_H) measured at 500.16 MHz, multiplicity and *J* values (Hz) are shown in parentheses; [b]Values in ppm (δ_C) measured at 125.77 MHz

3.3. Synthesis of (2,6-dihydroxy-4-methylphenyl)(4- (hydroxymethyl)-2,6-dimethoxyphenyl)methanone **(9)**

Scheme 7 shows the synthesis of (2,6-dihydroxy-4-methylphenyl)(4- (hydroxymethyl)-2,6-dimethoxyphenyl)methanone **(9)**.



8 **9**

Scheme 7-Deprotection of benzophenone

In a next step the protective groups (MOM and TBDMS) are removed. By exposing the compound to conditions that decrease the stability of the protecting groups, such as pH changes, addition of acids or bases, and/or temperature, the stability of the protective groups is compromised[36]. The protocol of the disclosed procedure is described for MOM protecting groups, being also possible the removal of the protecting group TBDMS because its stability decreases at low pH at room temperature[37]. Deprotection occurs by a cleavage mechanism using acidic conditions.

So, *p*-toluenesulphonic acid was added to (2,6-bis(methoxymethoxy)-4- methylphenyl)(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanone (8) in methanol. The desired compound 9 was achieved in 71% yield.

The identification of compound **9** was based on FTIR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. As expected the FTIR spectrum showed the typical OH stretching band at 3447 cm^{-1} referent to the unprotected hydroxyl groups and EIMS spectrum showed a structure compatible molecular peak with *m/z* 534 ([M+TMS]$^{+\cdot}$). ^{1}H NMR spectrum showed the signals corresponding to the protons resulting from the deprotection: the phenol groups δ_H 11.62 (2OH, s) and the primary alcohol δ_H 5.10 (OH, s). The ^{13}C NMR shows 12 signals. The main connectivities of HMBC are presented in **Figure 11** and all the assignments are in table 3.

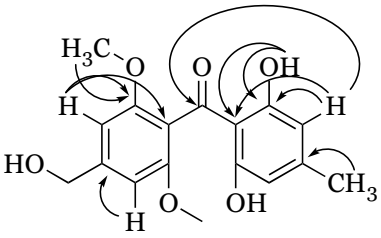
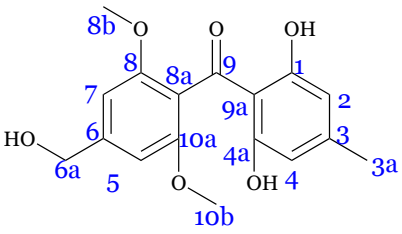


Figure 11-Main connectivities of HMBC of compound ***9***

Table 3-Chemical shifts and assignments of compound ***9***



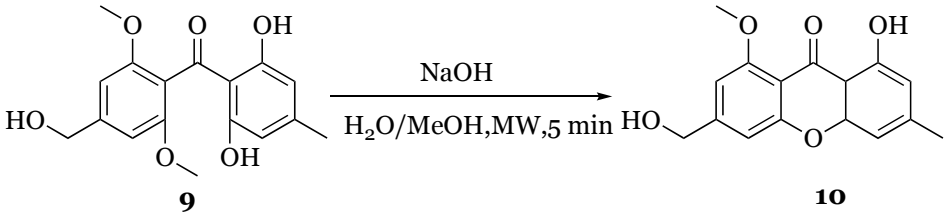
^{1}H NMR Chemical Shifts	**δ_H(ppm)[a]**
1-OH and 4a-OH	11.62(s)
2-H and 4-H	6.14(s)
3a-H	2.20(s)
5-H and 7-H	6.67(s)
6a-H	4.55(s)
6a-OH	5.10(s)
8b-H and 10b-H	3.70(s)

^{13}C NMR Chemical Shifts	**δ_C(ppm)[b]**
1 and 4a	162.3
2 and 4	107.7
3	148.4
3a	21.7
5 and 7	101.9
6	144.8
6a	63.0
8 and 10a	155.7
8a	120.4
8b and 10b	55.7
9	198.8
9a	109.1

[a]Values in ppm (δ_H) measured at 500.16 MHz, multiplicity and *J* values (Hz) are shown in parentheses; [b]Values in ppm (δ_C) measured at 125.77 MHz

3.4. Synthesis of 1-hydroxy-6-(hydroxymethyl)-8-methoxy-3- methyl-9H-xanthen-9-one **(10)**

Scheme 8 shows the synthesis of 1-hydroxy-6-(hydroxymethyl)-8-methoxy-3- methyl-9H-xanthen-9-one **(10)**.



9 **10**

Scheme 8- Microwave Heating assisted Cyclization

The deprotected benzophenone 9 can be easily cyclized to the xanthone skeleton by a nucleophilic aromatic substitution. In literature several methods have been described that promote cyclization, and our group of investigation have reported a green methodology assisted by microwave (MW) heating that uses water as a solvent[16].

So, compound **9** dissolved in a mixture of water/methanol (9:1), in the presence of NaOH was heated under microwave for 5 minutes and the desired product, after purification, was obtained with 58% yield.

The identification of compound **10** was based on FTIR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. The FTIR spectrum showed the presence of a band ascribed to the carbonyl group at 1651 cm^{-1} and the EIMS spectrum showed a structure compatible molecular peak with *m/z* 431 ([M+TMS]$^{+\cdot}$). The ^{1}H NMR showed the disappearance of the signals corresponding to the protons of one methoxy and one phenol group. The ^{13}C NMR shows 16 signals. The main connectivities of HMBC are presented in **Figure 12** and all the assignments are presented in table 4.

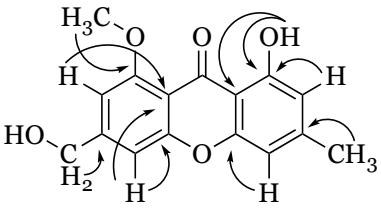
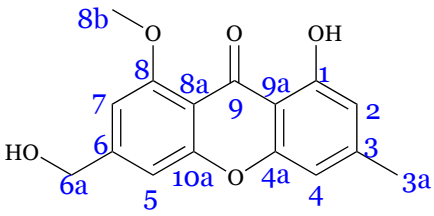


*Figure 12-Main connectivities of HMBC of compound **10***

*Table 4-Chemical shifts and assignments of compound **10***



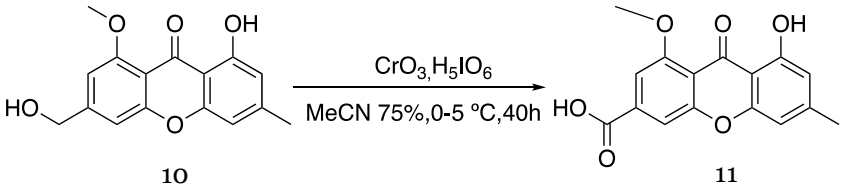
¹³C NMR Chemical Shifts	δC(ppm)[b]
1	161.0
2	111.0
3	148.2
3a	21.9
4	106.8
4a	154.8
5	106.2
6	152.9
6a	62.4
7	103.9
8	160.1
8a	108.8
8b	56.3
9	181.1
9a	106.7
10a	157.4

¹H NMR Chemical Shifts	δH(ppm)[a]
1-OH	13.03(s)
2-H	6.57(s)
3a-H	2.35(s)
4-H	6.78(s)
5-H	7.02(s)
6a-H	4.62(d.J=5.7)
6a-OH	5.61(d.J=5.7)
7-H	6.92(s)
8b-H	3.90(s)

[a]Values in ppm (δ_H) measured at 500.16 MHz, multiplicity and *J* values (Hz) are shown in parentheses; [b]Values in ppm (δ_C) measured at 125.77 MHz

3.5. Synthesis of 8-hydroxy-1-methoxy-6-methyl-9-oxo-9H- xanthene-3-carboxylic acid - Yicathin C **(11)**

Scheme 9 shows the synthesis of Yicathin C **(11)**.



Scheme 9- Oxidation to Yicathin C

The final step to obtain Yicathin C is the oxidation of the primary alcohol to a carboxylic acid. There are several methodologies to perform this synthesis which can be grouped in chromium-based, permanganate-based and oxygen-based methods[38]. Previous in our work group a modified Jones oxidation was tested, where periodic acid was used instead of sulfuric acid, and better yields were obtained with this procedure.

So, a solution of periodic acid and chromium (VI) oxide was added to compound **10** dissolved in wet acetonitrile and compound **11** was obtained in 46% yield.

An oxidation under the catalytic action of pyridinium chlorochromate (PCC)[39] was also tested. However, the desired compound was not achieved, being the major product the starting material, compound **10.**

The identification of compound **11** was based on FTIR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. The FTIR spectrum showed two main characteristic bands of the carboxylic acid at 3446 cm^{-1} and 1718 cm^{-1}, corresponding to the hydroxyl and carbonyl stretching bands. The EIMS spectrum showed the molecular peak with m/z 445 ($[M+TMS]^{+\cdot}$) compatible with the desired compound. The ^{1}H NMR spectrum showed the disappearance of two methylene protons. The ^{13}C NMR showed 16 signals. The main connectivities of HMBC are presented in F**igure 13** and all the assignments are presented in table 5.

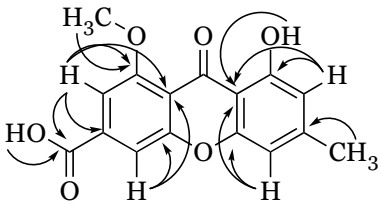
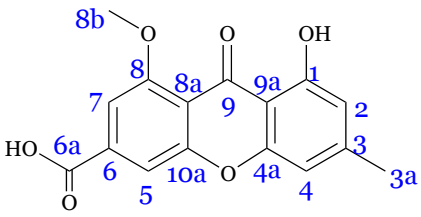


*Figure 13-Main connectivities of HMBC of compound **11***

*Table 5-Chemical shifts and assignments of compound **11***



^{1}H NMR Chemical Shifts	δ_H(ppm)[a]
1-OH	12.74(s)
2-H	6.63(q,J=1.3)
3a-H	2.39(s)
4-H	6.83(q,J=1.3)
5-H	7.54(d,J=1.4)
6a-OH	13.85(s)
7-H	7.36(d,J=1.4)
8b-H	3.93(s)

^{13}C NMR Chemical Shifts	δ_C(ppm)[b]
1	160.9
2	111.4
3	148.9
3a	21.9
4	107.0
4a	154.7
5	110.2
6	135.9
6a	160.4
7	105.8
8	164.8
8a	112-9
8b	53.0
9	180.8
9a	107.1
10a	154.7

[a]Values in ppm (δ_H) measured at 500.16 MHz, multiplicity and *J* values (Hz) are shown in parentheses; [b]Values in ppm (δ_C) measured at 125.77 MHz

3.6. Synthesis of methyl 8-hydroxy-1-methoxy-6-methyl-9-oxo-9H-xanthene-3-carboxylate - Yicathin B **(12)**

As a strategy to purify the extract obtained from the synthesis of 8-hydroxy-1-methoxy-6-methyl-9-oxo-9H- xanthene-3-carboxylic acid - Yicathin C, a Fischer esterification[40] was performed followed by a hydrolysis of the ester.
So, compound **11** was dissolved in methanol and in the presence of sulfuric acid was kept at reflux overnight. After purification, compound **12** was obtained with 51% yield.

The identification of compound **12** was based on FTIR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. The excepted absence the band ascribed to the hydroxyl of the carboxylic acid was observed in the FTIR spectrum and the EIMS spectrum showed the structure compatible molecular peak with m/z 387 ($[M+TMS]^{+}$). The ^{1}H NMR shared a similar profile to compound **11** with the exception of the absence of the hydroxyl signal from the carboxylic acid and the presence of the methyl group from the ester at d_H 5.76 (3H, s). The ^{13}C NMR showed 17 signals. The main connectivities of HMBC are presented in **Figure 14** and all the assignments are presented in table 6.

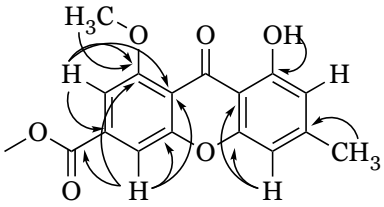
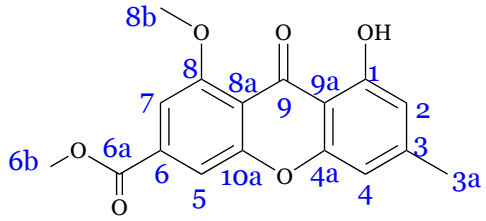


Figure 14-Main connectivities of HMBC of compound 12

*Table 6- Chemical shifts and assignments of compound **12***



^{13}C NMR Chemical Shifts	δ_C(ppm)[b]
1	160.8
2	111.4
3	148.9
3a	21.9
4	107.0
4a	154.7
5	110.2
6	135.8
6a	160.4
6b	56.6
7	105.7
8	164.8
8a	112-9
8b	53.0
9	180.8
9a	106.9
10a	157.0

^{1}H NMR Chemical Shifts	δ_H(ppm)[a]
1-OH	12.72(s)
2-H	6.62(q,J=1.3)
3a-H	2.83(s)
4-H	6.81(q,J=1.3)
5-H	7.51(d,J=1.4)
6b-H	3.98(s)
7-H	7.34(d,J=1.4)
8b-H	3.93(s)

[a]Values in ppm (δ_H) measured at 500.16 MHz, multiplicity and *J* values (Hz) are shown in parentheses; [b]Values in ppm (δ_C) measured at 125.77 MHz

In order to remove the methyl group and convert back to Yicathin C (**11**), hydrolysis of compound **12** was performed. So, to compound **12** in methanol/water (4:1) was added NaOH. The mixture was kept at reflux for 4 hours. Compound **11** was obtained with 74 % yield. The identification of the obtained compound was performed by TLC and the same techniques performed in **3.5.**

C.2. Suzuki carbonylative coupling applied to the synthesis of Yicathin B and C analogues

1. The Carbonylative Suzuki coupling reaction and the boronic acid chemistry

Widely reported in literature, the carbonylative Suzuki coupling reaction is a direct and suitable pathway to obtain carbonyl-containing compounds, like diarylketones[41-45]. Advantages of the cross-coupling are: i) the reaction is mostly not affect by the presence of water, ii) a broad range of functional groups can be use and iii) its normally regio- and chemoselective[46].

Palladium is considered one of the most important transition metals and widely used in both academic and industrial laboratories, and it's the common catalyst use in the Suzuki reaction. When in its lowest oxidation state, palladium(0) is electron-rich and undergoes oxidative addition when in the presence of substrates like halides and triflates, resulting in a palladium(II) complex[33].

Boronic acids (figure 15) are trivalent boron-containing compounds that bond to a carbon substituent and two hydroxyl groups and acts as mild Lewis acids. Depending on the nature of the substituent directly bonded to boron their properties and reactivity can alter[47]. Boronic acids are an appealing class of synthetic intermediates which presented great advantages, namely: i) stable, ii) low toxicity and iii) are environment friendly. However, some heteroaromatic boronic acids showed low stability and could suffer oxidation when in contact to air[47]. The incorporation of the boronic acid occurs in the transmetalation step (figure 16, step 3), in which is thought that the use of base facilitates the process, turning the arylboronic acid into a nucleophile[41].

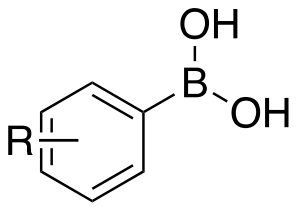


Figure 15- Arylboronic acid

The palladium-catalyzed carbonylative cross-coupling reaction of arylboronic acids with aryl electrophiles mechanism is considered to proceed through a catalytic cycle (Figure 16) in which an oxidative addition (**1**) of Ar-X to a palladium(O) complex affords Ar-Pd-X. With the addition of carbon monoxide(CO) (**2**), ArCO-Pd-X is obtained and a successive transmetalation (**3**) with arylboronic acid and a base gives Ar-CO-Pd-Ar'. After a reductive elimination (**4**) a diarylketones is achieved and the palladium(0) catalyst restored. A disadvantage in this procedure is that the intermediate Ar-Pd-X can react in two ways, either suffer carbonylation or direct coupling originating biaryls, if the addition of CO is slower that the transmetalation the latter is formed with higher yield[41].

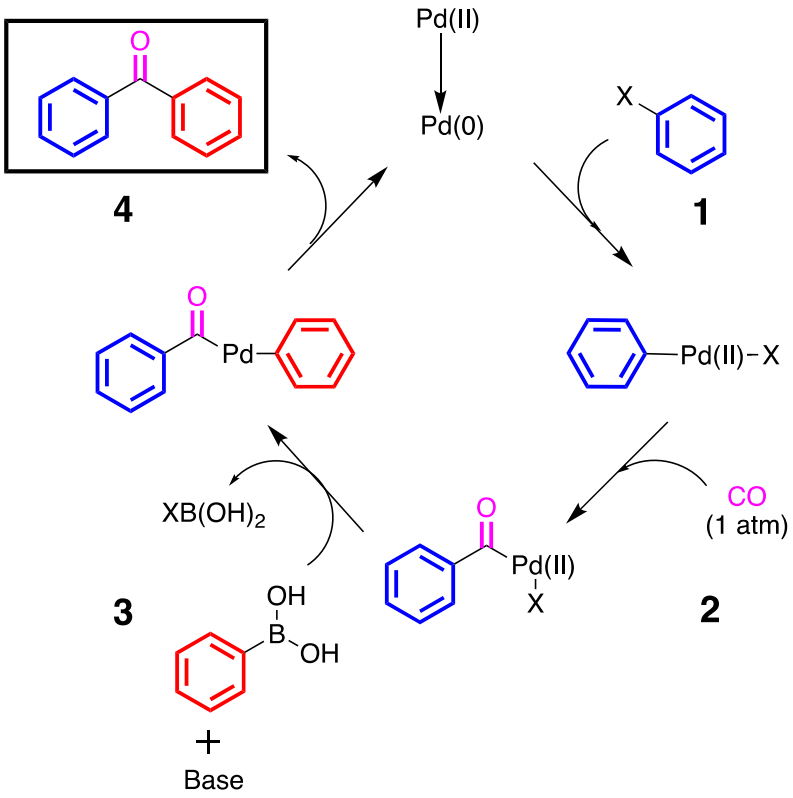


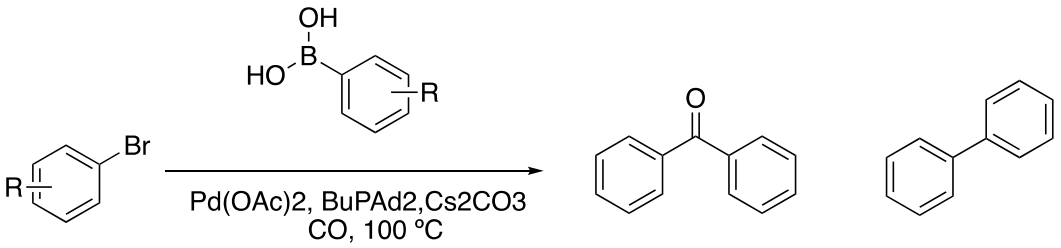
Figure 16-Cycle of the palladium-catalyzed carbonylative coupling

Unlike the oxidative addition and reductive elimination that are mechanisms very well described and known in organometallics reactions, the transmetalation mechanism is still very much unknow. Its reported that the use of bases enhances the nucleophilic of the organic group bonded to the boron atom, by transforming the inert organoboronic acid into a tetracoordinate borate anion[48].

2. Synthesis of yicathin analogues

In order to synthetize Xanthone derivatives, mainly Yicathin analogues, in a faster way, reactions by Carnonylative Suzuki coupling were tested. When compared to the previous retrosynthesis plan presented, this type of reaction allows a significant reduction in the number of steps needed to obtain the analogue. Two carbonylative Suzuki coupling reactions were performed using the same starting material, methyl 4-bromo-3-hydroxybenzoate (**13**), only altering the arylboronic acid substrate, (2,6-difluorophenyl)boronic acid (**14**) and (2,4-difluorophenyl)boronic acid (**16**), in order to evaluate the effect of different positions of the substitutes in the arylboronic acid.

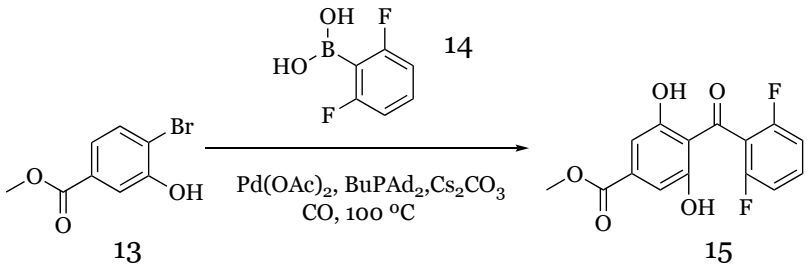
The general synthetic plan is presented in scheme 10. The conditions used in both reactions as well as the aryl halide were maintained. The product expected was the corresponding benzophenone. The formation of a sub product equivalent to the C-C bond is also expected as is a competitive route of the carbonylative Suzuki coupling reaction (scheme 10)[41].



Scheme 10- Carbonilative Suzuki Coupling synthetic plan

2.1. Synthesis of methyl 4-(2,6-difluorobenzoyl)-3,5-dihydroxybenzoate

Scheme 11 shows the synthesis of methyl 4-(2,6-difluorobenzoyl)-3,5-dihydroxybenzoate



Scheme 11- Synthesis of benzophenone by carbonylative Suzuki coupling

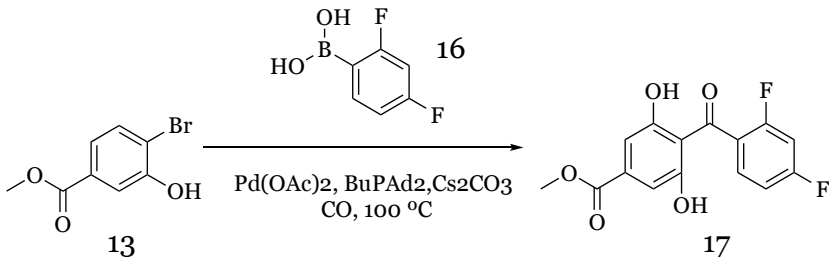
Compound **13** was the chosen halide to execute these reactions because the presence of an electron-withdrawing group, wich was found to successfully carbonylate and couple with arylboronic acids[41].

The substrate arylboronic acid used was (2,6-difluorophenyl)boronic acid in order to make comparisons with 2.2 (Synthesis of methyl 4-(2,4-difluorobenzoyl)-3,5-dihydroxybenzoate) in relation to the effect of different positions of the same substituents.

So, to compound **13** were added (2,6-difluorophenyl)boronic acid **(14)**, diacetoxypalladium, di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphane, cesium carbonate and carbon monoxide in toluene. The reaction was heated to 100 °C and stayed stirring overnight. The evolution of the reaction was followed with TLC. The next day there was still a large quantity of starting material that didn't react, so the reaction was quenched because a lot of sub products were forming. A purification and following identification of the sub products formed was not possible.

2.2. Synthesis of methyl 4-(2,4-difluorobenzoyl)-3,5-dihydroxybenzoate

Scheme 12 shows the synthesis of methyl 4-(2,4-difluorobenzoyl)-3,5-dihydroxybenzoate



Scheme 12- Synthesis of benzophenone by carbonylative Suzuki coupling

The arylboronic acid substrate used was (2,4-difluorophenyl)boronic acid. The presence of one fluor in ortho position to the boric acid functional group has an electron withdrawing inductive effect that weakly deactivates the ring.

So, to compound **13** were added (2,4-difluorophenyl)boronic acid**(16)**, diacetoxypalladium, di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphane,Cesium carbonate and carbon monoxide in Toluene. The reaction was heated to 100 °C and after 4h there was a total disappearance of the starting material. After purification, compound **18** (figure 17) was obtained as the main product in 34% yield.

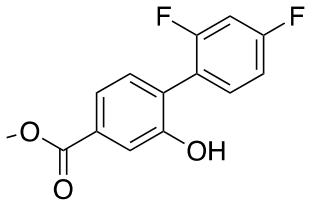
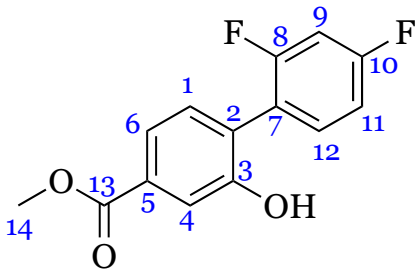


Figure 17- C-C bond product (18)

The identification of compound **18** was based on FTIR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. The presence of the stretching bands corresponding to the hydroxyl and carbonyl, 3410 cm^{-1} and 1705 cm^{-1}, were observed in the FTIR spectrum the EIMS spectrum showed the structure compatible molecular peak with m/z 264 ($[M+TMS]^{+}$).

The ^{1}H NMR spectrum showed signals corresponding to the methyl of the ester group δ_H 03.86 (3H, s), the hydroxyl δ_H 10.14 (1H, s), the aromatic protons: δ_H 7.15 (1H, td); δ_H 7.30 (1H,m); δ_H 7.11 (1H, d); δ_H 7.46 (1H, m); δ_H 7.57 (1H, d). The ^{13}C NMR showed 14 signals, including the expected carbonyl band. The main assignments are presented in table 7.

Table 7- Chemical shifts and assignments of compound 18



^{13}C NMR Chemical Shifts	δ_C(ppm)[b]
1	131.46
2	126.56
3	154.96
4	115.95
5	130.53
6	119.77
7	121.71
8	159.02(dd.J=12.44/193.33
9	103.95(td,J=26.22/26.22)
10	162.30(dd,J=12.24/190.55)
11	111.32(dd,J=3.61/21.04)
12	132.76(dd,J=5.13/9.69)
13	165.99
14	52.21

^{1}H NMR Chemical Shifts	δ_H(ppm)[a]
1-H	7.31(d,J=8.74)
4-H	7.57(d,J=1,39)
6 and 12-H	7.46(m)
9-H	7.30(m)
11-H	7.15(td,J=2.57/8.57/8.53)
3-OH	10.14(s)
14-CH_3	3.86(s)

[a]Values in ppm (δ_H) measured at 500.16 MHz, multiplicity and *J* values (Hz) are shown in parentheses; [b]Values in ppm (δ_C) measured at 125.77 MHz

C.3. Lipophilicity assessment of yicathins and analogues

1. Lipophilicity in drug discovery

In drug discovery, medicinal chemistry is specially involved in *lead* generation and optimization. The main objective is to produce a potent and safe compound that can reach effectively the desired target[49]. Pharmacokinetics properties are a reliable source to designed and synthesize better compounds to obtain a drug candidate, because they determine the fate of the substances when administered to a living organism and describe how the body is affected after the administration.

Lipophilicity plays an important role in determining the overall quality of a drug candidate[50]. After administration, a drug will go through a series of partitioning steps: they have to be dissolved in aqueous environments, then have to leave them to cross lipid membranes, and then have to enter other aqueous environments to reach the receptor. So, evaluating this parameter is an important step to generate a drug candidate.

Druglikeness is also a relevant aspect to consider in the optimization process of lead compounds. This concept can be described as the similarities in terms of structural or pharmacokinetics properties of new drugs with existing drugs and evaluates qualitatively the predisposition of a drug to be orally available according to its bioavailability[51-52]. Lipophilicity is a major determinant on the drug-likeness of a compound because it can affect absorption/permeability, volume of distribution, plasma protein binding, metabolism, and toxicity[53].

2. Log P *vs* Log K_p

Lipophilicity represents the affinity of a molecule for a lipophilic environment [54]. The lipophilicity of a compound is classically measured by its partition coefficient (Log P), that is the ratio of the concentration of the compound in *n*-octanol to its concentration in water (equation 1). Usually log P is used to evaluate the distribution behavior in this biphasic system. Log P describes the lipophilicity of a compound taking into account the functional groups and the carbon skeleton, but in the absence of dissociation or ionization. The logarithm of distribution coefficient, log D, takes into account ionized and unionized species and summarizes the overall ratio of a compound between the two phases. But even considering the influence of the ionized state, log D does not represent the full mechanism that occurs in a living organism.

$$Lipophilicity = {}^{[C]organic}\Big/_{[C]aqueous} \qquad (1)$$

Biomimetic models, such as micelles and liposomes, mimics membrane cells and are composed by a hydrophobic core and a hydrophilic exterior. These models take into account for hydrophobic and hydrophilic interactions which is an improvement from the octanol/water method that only considers for non-polar interactions[55]. To determinate the logarithm of membrane-water partition coefficient (log K_p) the most broadly used technique is derivative UV–Vis spectrophotometry, which is based on the change of spectral characteristics such as the absorption parameter of the solute, like its molar absorptivity (ε) or the maximum wavelength (λ_{max}), when the drug permeates from a hydrophilic to hydrophobic environment [56].

3. Advantages of biomimetic models for assessing lipophilicity

The methodologies existent to determine the membrane-water coefficient can be separated in to two key categories: methods that evolve a physical separation of phases and methods that do not require phase physical separation. Separative methods require more time and labor and can disrupt the equilibrium state between phases, factors that favors the non-separative method[57].

When compared to the separative method, the biomimetic model brings additional advantages that help to a better understanding of the drug-membrane interaction[58]. Since it takes into account all intermolecular forces involved in drug partitioning, biomimetic models bear more similarities with membrane cells and also allow the possibility of changing its lipid constitution to better mimic other biological membranes[55].

By using a non-separative method like derivative spectrophotometry, advantages as eliminating the background signals produced by micelles and liposomes light scattering and reducing the interferences on equilibrium state are possible and allow the enhancement of the absorption signal[55, 59].

Apart from the quality of the results acquired, biomimetic models are a fast, simple, not laborious method and also a "green" methodology since a large volume of organic solvents are not required. Even though it carries a lot of advantages, the lack of harmonization between biomimetic models makes the octanol/water model still a highly accepted method to evaluate lipophilicity in drug discovery[55].

Among the numerous biomimetic models available to access lipophilicity, the most common are micelles and liposomes. Lipophilicity of xanthones derivatives was evaluated both with micelles and liposomes and a good correlation of the micelle model with the liposome model was reported, allowing the use of micelles for the determination of partition coefficient for xanthones derivatives[18].

4. Material and Methods

4.1. Reagents and Equipment

Hexadecylphosphocholine (HePC) was purchased from Sigma Aldrich (St. Louis, MO, USA). All compounds were used without further purification.
The buffer solution used was a Phosphate-buffered saline (PBS) buffer (PBS: 10 mmol L–1, I = 0.15 mol L–1, pH 7.4). The buffer was prepared using double deionized water from Arium® water purification system (resistivity > 18 MΩ cm, Sartorius, Goettingen, Germany), and the ionic strength was adjusted with NaCl (I = 0.1 M).
Absorption spectra were recorded at 37.0 ± 0.1 °C with a Jasco V- 660 spectrophotometer, using quartz cells with a 1-cm path length. Temperature was kept constant by a circulating thermostated water in the cell holder.

4.2. Preparation of micelles

The preparation of micelles solution was accomplished by dissolution of hexadecylphosphocholine (HePC) in buffer (PBS: 10 mmol L–1, I = 0.15 mol L–1, pH 7.4).), and mixed by vortex.

4.3. Methodology used to assess partition coefficient, K_p

Derivative UV-Vis spectrophotometry is the used technique to evaluate Log K_p. The procedure followed was adapted from literature[55-56].

The preparation of the samples solutions was as follows: to 15 µL of compound with an established concentration, previously solubilized in DMSO, was added an increasing volume of micelles solution and buffer, to a final volume of 1500 µL per sample. The concentration of micelles ranges from $1.00e^{-4}$ to $1.00e^{-3}$. The samples were vortexed and incubated at 37 ºC, to simulate the human temperature, for 30 min. The absorbance spectra were registered in a double-beam spectrophotometer, at 37 ºC, from 240 nm to 500 nm.

The following equation (2) [56, 59] is used to calculate the K_p values:

$$D_T = D_b + \frac{(D_m - D_b)K_p[L]V\phi}{1+K_p[L]V\phi} \quad (2)$$

,D_T is the derivative intensity of the total amount of compound in the sample, D_b is the derivative intensity of the compound in the buffer, D_m is the derivative intensity of the distribution of the compound in the membrane, [L] is the lipid concentration of micelles, K_p is the partition coefficient and V_ϕ is the lipid molar volume ($Lmol^{-1}$).

5. Results

The Log K_p, was determined for compounds: (2,6-dihydroxy-4-methylphenyl)(4-(hydroxymethyl)-2,6-dimethoxyphenyl)methanone **(9)**, 1-hydroxy-6-(hydroxymethyl)-8-methoxy-3- methyl-9H-xanthen-9-one **(10)**, Yicathin C **(11)** and Yicathin B **(12),** and also for Yicathins analogues, previously synthesized in our work group: (2,6-dihydroxyphenyl)(4-(hydroxymethyl)-2,6-dimethoxyphenyl)methanone **(9A)**, 8-hydroxy-3-(hydroxymethyl)-1-methoxy-9*H*-xanthen-9-one **(10A)**, 8-hydroxy-1-methoxy-9-oxo-9*H*-xanthene-3-carboxylic acid **(11A)** and methyl 8-hydroxy-1-methoxy-9-oxo-9*H*-xanthene-3-carboxylate **(12A)** (Figure 18).

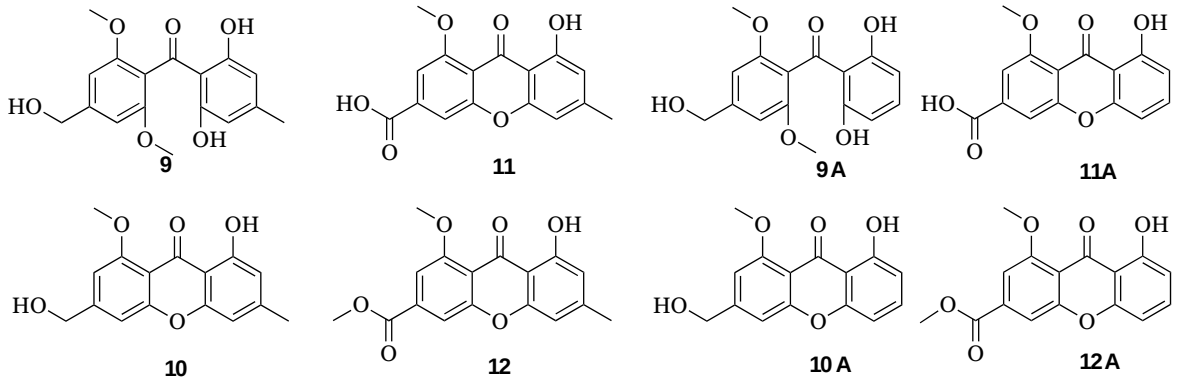


Figure 18-Compounds assessed for Log K_p determination

In this evaluation, HePc micelles were used, because as previously described they are a reliable source for the appraisal of xanthones derivatives[18]. Micelles are a single lipid monolayer vesicle, **Figure 19**, composed by a hydrophilic and an hydrophobic layer, and due to their small size, present a curvature surface effect that resembles to biological membranes and allows an easier penetration of the molecules to the vesicles which can result in higher log k_p values[60].

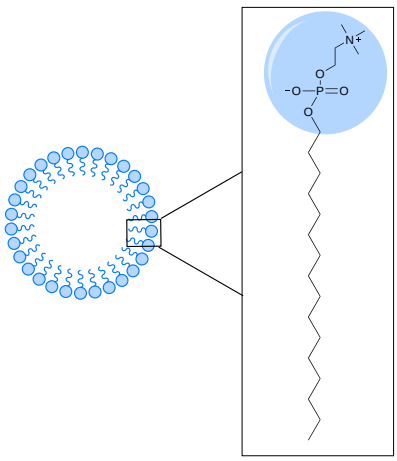


Figure 19-HePc micelles

Partition coefficient between membrane-buffer, Log K_p, was assessed by UV-Vis derivative spectrophotometry. Calibration curves were set in order to choose the most appropriate concentration to use for the assays, that is within the Lambert-beer linearity range. As an example, **Figure 20** shows the absorbance and calibration curve executed for compound **11A** with increasing concentrations**.**

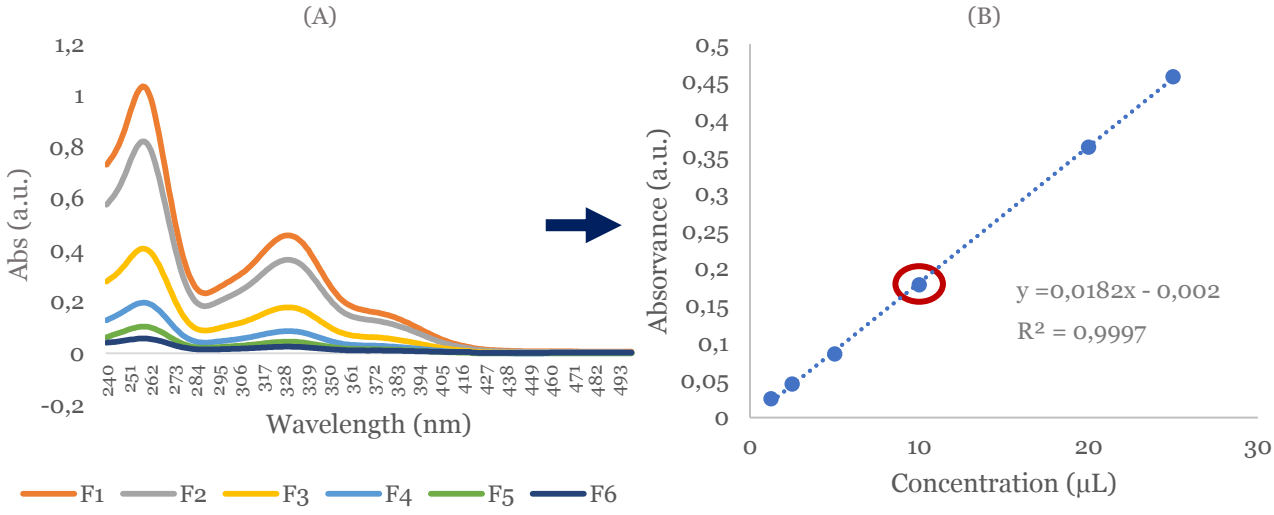


Figure 20-(A) Absorbance spectra and (B) calibration curve at 331 nm for compound 11A

As an example, **Figure 21** shows the UV-Vis spectrum and the second-derivative spectrum obtained for compound **11A**. The derivative spectra were performed to reduce the light scattering effect of micelles. The presence of bathochromic shifts indicates the penetration of the molecules into the hydrophobic layer[61].

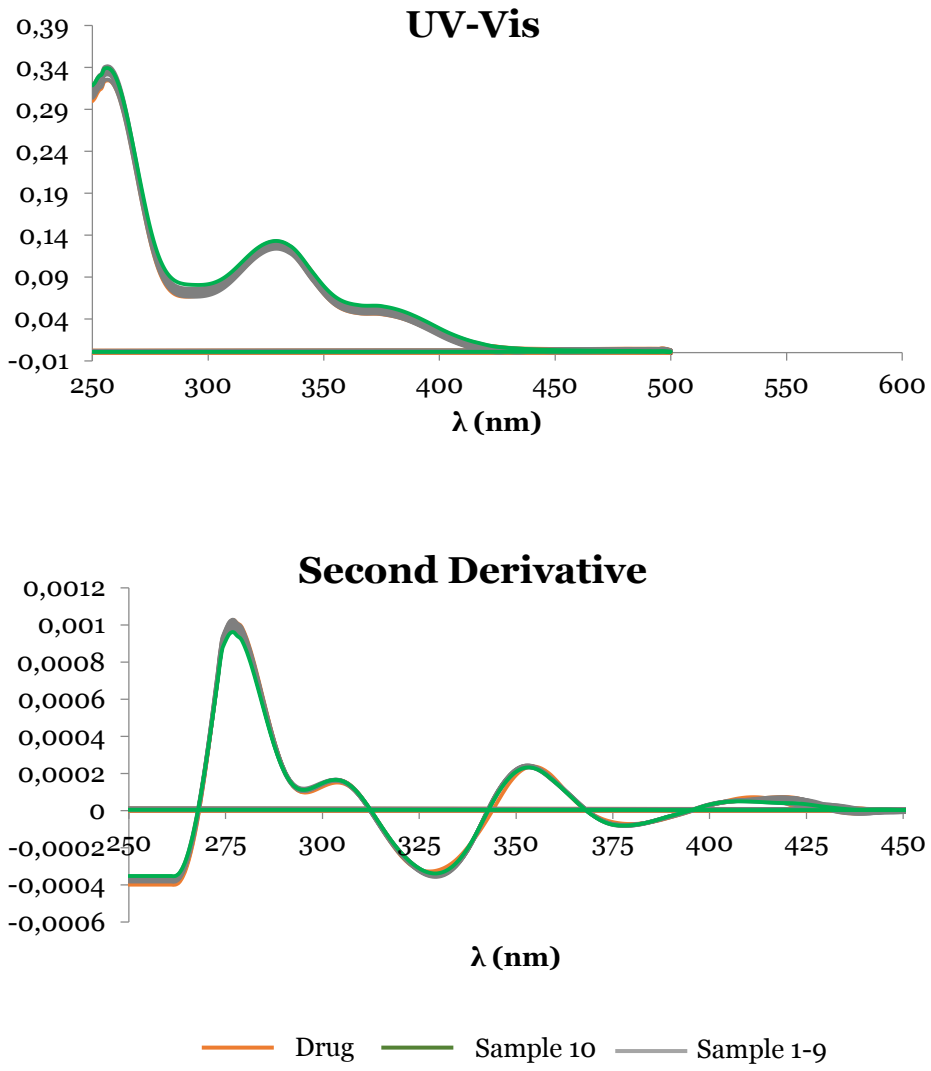
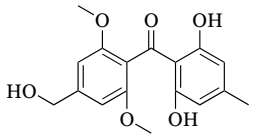
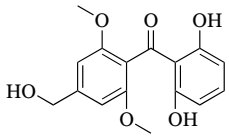
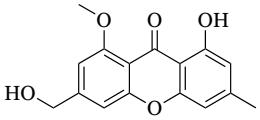
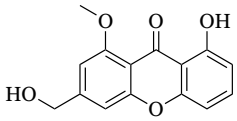
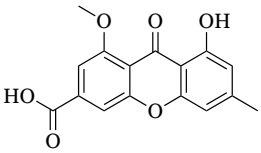
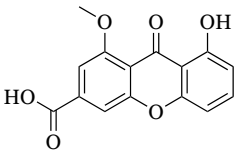


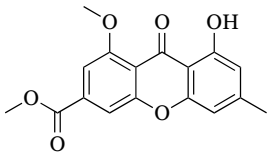
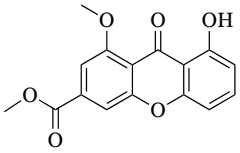
Figure 21- UV-Vis and Second derivative spectra of 11A in presence of rising concentrations of HePC

The fitting of the second derivative was then executed at several wavelengths where the scattering was eliminated, an adequate wavelength was chosen and Log K_p was calculated following equation (2), using a nonlinear regression.

In table 8 the mean values of Log K_p micelle/buffer, average of Log $D_{7.4}$ predict by ACD/Labs, MarvinSketch and PreADMET, and the estimated Log p obtain in Chemdraw for all compounds.

Table 8-LogD7.4, Log kp and Log p (ChemDraw)

Compounds	Log $D_{7.4}$	Log $K_{p\ micelles}$	Log P (ChemDraw)
 YBC7-**9**	2.73 ± 0.30	3.47 ± 0.2	2.12
 AYC5-**9A**	2.19 ± 0.34	3.56 ± 0.3	1.64
 YBC8-**10**	2.69 ± 0.40	3.23 ± 0.2	2.14
 AYC6-**10A**	2.17 ± 0.42	3.21 ± 0.2	1.66
 YBC9-**11**	0.20 ± 1.33	3.48 ± 0.2	2.27
 AYC7-**11A**	-0.34 ± 1.31	3.20 ± 0.3	1.79

 YBC10-**12**	3.34 ± 0.35	3.39 ± 0.2	2.54
 AYC8-12A	2.85 ± 0.42	3.09 ± 0.2	2.05

Regarding the acquired values, all compounds tested are in accordance with some druglikeness rules, like Lipinski[62], Ghose[63] and Muegge[64], that in general state that the partition coefficient should range between -2 and 5. As expected, the Log K_p obtained is higher in value than the log p predicted by chemdraw, because biomimetic models take into account for more interactions than the traditional octanol/water method. The Yicathin class compounds have similar values of log K_p because the only differ in 1 or 2 functional groups structurally. The same applies to the compounds of the analogues class.

Figure 22 shows the difference between Log P(Chemdraw), Log $D_{7.4}$ and Log K_p.

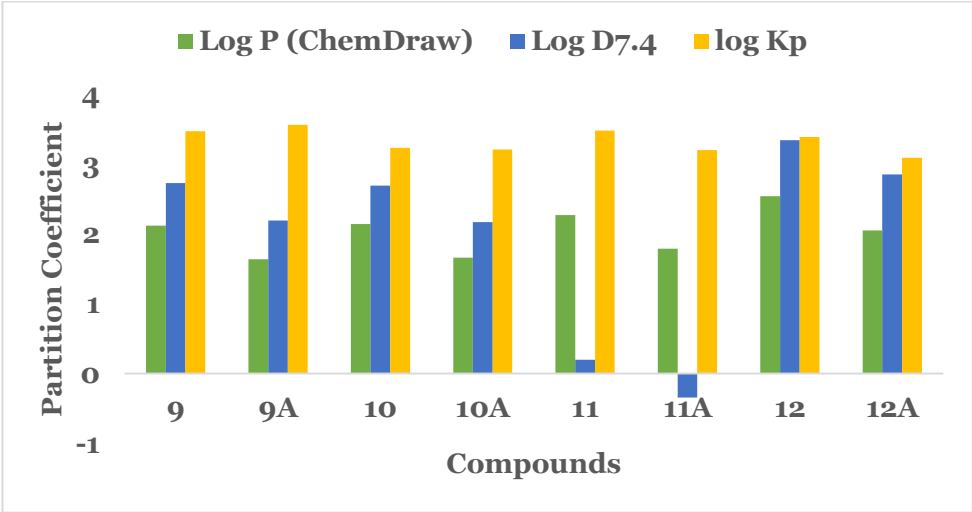


Figure 22-Difference between Log P(Chemdraw), Log $D_{7.4}$ and Log K_p

At physiological pH, Log $D_{7.4}$ can be seen as a good metric to evaluate the *in vivo* lipophilicity, but as seen in **Figure 22** it is not very accurate for molecules containing, for example, carboxylic acid groups, compound 11 and 11A. When only regarding Log $D_{7.4}$ values, the initial conclusion made would be that the molecules are almost to totality in a hydrophilic state at pH 7.4 and wouldn't be possible to cross membranes. The assessments made with biomimetic models make it possible to predict a more accurate coefficient partition because not only acknowledges the possibility of ionization at pH 7.4 but it also takes into account for all the intermolecular and membrane interactions. The remaining compounds analyzed showed a quite similar value of Log $D_{7.4}$ and Log K_p, being coefficient partition measured with biomimetic models the highest for all.

When comparing Log P values and Log K_p, as expected Log K_p values were higher, especially for compound 11 and 11A, that contain a carbonyl and a hydroxyl group and can form intramolecular hydrogen bonding[18].

D. Experimental

1. General methods

All compounds were prepared in the Laboratory of Organic and Pharmaceutical Chemistry of the Faculty of Pharmacy of the University of Porto. All the reagents were purchased from Sigma Aldrich, Acros or TCI and all the solvents were PA used without further purification. Solvents were evaporated using rotary evaporator under reduced pressure (Buchi Waterchath B-480). Anhydrous solvents were either purchased from Sigma-Aldrich or dried according to the published procedures[65]. MW reactions were performed in a CEM Discovery SP from CEM Corporation. All experiments were performed in a closed vessel of 10 or 35 mL. Reactions were monitored by TLC and/or GC-MS. The visualization of the chromatograms was made under UV light at 254 and 365 nm. Gas chromatography analyses (GC) were carried out on Trace GC 2000 Series (DB5 –capilar column, RTX® - 5MS (crossbond 5% diphenyl 95% dimethylpolysiloxane)) with electron-impact mass spectra recorded on GCQ plus and referred to m/e (fragments %). Injections were performed using compounds directly dissolved in ethyl acetate or previously derivatized with MSTFA at 80 °C for 30 minutes. Purifications of compounds were performed by flash column chromatography by using Merck silica gel 60 (0.040-0.063 mm). Melting points were obtained in a Köfler microscope and are uncorrected. IR spectra were measured on a KBr microplate (cm-^{1}) in a FTIR spectrometer Nicolet iS10 from Thermo Scientific with Smart OMNI-Transmisson accessory (Software OMNIC 8.3). ^{1}H and ^{13}C NMR spectra were performed in the Departamento de Química, Universidade de Aveiro, and were taken in DMSO-*d*6 (Deutero GmbH) at room temperature, on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) or Bruker DRX-500 (500.13 and/or 300.13 MHz for ^{1}H and 125.77 and/or 75.47 MHz for ^{13}C) spectrometers. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference and assignment abbreviations are the following: singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), multiplet (*m*), doublet of doublets (*dd*). ^{13}C NMR assignments were made by 2D HSQC and HMBC experiments (long-range C, H coupling constants were optimized to 7 and 1 Hz) or by comparison with the assignments of similar molecules. Compounds were identified according IUPAC nomenclature, but the numbering used in NMR assignments was used for convenience.

2. Synthesis of Building Block A

2.1. Synthesis of (4-bromo-3,5-dimethoxyphenyl)methanol(**2**)

In a two-necked round-bottom flask of 500 mL was placed 4-bromo-3,5-dimethoxybenzoic acid (5g, 19.2 mmol) with 105 mL of anhydrous THF under nitrogen atmosphere. The solution was cooled until 0 ^{o}C and then added borane-tetrahydrofuran complex (BH_3:THF) (47 mL, 42.1 mmol) dropwise. The reaction was allowed to reach room temperature and stirred for 2 hours. The reaction was quenched by the addition of a saturated solution of potassium carbonate (K_2CO_3) and then extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The compound was used in the next step without further purification step was attained and compound **2** was obtained as a fine white powder (4.56 g, 96%).

m. p.: 97 – 99 ^{o}C

^{1}H NMR (300.13 MHz, DMSO-*d*6) δ (ppm): 6,70 (2H, *s*), 5,35 (H, *t*, J = 5.6 Hz), 4.49 (2H, *d*, J = 5.6 Hz), 3.82 (6H, *s*).

IR υ_{max} (cm^{-1}) (KBr): 3223, 3003, 2929, 2840, 1346, 1076, 1055, 1035, 822, 633

EIMS m/z (%): 248 (79, $[M+2]^{+\cdot}$), 246 (84, $[M]^{+\cdot}$), 231 (17), 217 (21), 167 (18), 139 (100), 138 (72), 137 (17), 124 (92), 109 (28), 108 (40), 96 (17), 95 (19), 79 (27), 78 (26), 77 (38), 66 (18), 65 (30), 64 (27), 53 (38), 51 (40).

All spectroscopic values are in agreement with published data[66].

2.2. Synthesis of ((4-bromo-3,5-dimethoxybenzyl)oxy)(tert- butyl)dimethylsilane**(3)**

In a two-necked round-bottom flask of 100 mL was placed (4-bromo-3,5-dimetoxiphenil)methanol **(2)** (1.0126g, 4.09 mmol), imidazole (697.5 mg, 10.24 mmol), and TBDMSCl (741.20 mg, 4.92 mmol). The mixture was placed under nitrogen atmosphere and 20 mL of DMF anhydrous was added. The solution was kept under stirring at room temperature for 3 hours. The reaction mixture was then poured into water (10 mL) and extracted with 3 x 15 mL of ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2) and the compound **3** was isolated as a white solid (1.01 g, 68%).

^{1}H NMR (300.13 MHz, DMSO-*d*6) δ (ppm): 6.66 (2H, *s*), 4.68 (2H, *s*), 3.79 (6H, *s*), 0.90 (9H, *s*), 0.07 (6H, *s*).

IR υmax (cm^{-1}) (KBr): 2955, 2929, 2856, 1590, 1462, 1417, 1258, 1232, 1126, 838, 815, 777.

EIMS m/z (%): 364 (2, $[M+2]^{+\cdot}$), 362 (3, $[M]^{+\cdot}$), 323 (12), 305 (28), 303 (36), 275 (52), 273 (48), 231 (100), 229 (84), 224 (61), 209 (17), 169 (13), 129 (26), 92 (33), 77 (21), 75 (17).
All spectroscopic values are in agreement with published data[66].

3. Synthesis of Building Block B

3.1. Synthesis of 1,3-bis(methoxymethoxy)-5-methylbenzene**(5)**

In a two-necked round-bottom flask of 250 mL, it was placed orcinol (3.01 g, 24.4 mmol) and NaH (2.9 g of a 60% suspension in mineral oil, 73.1 mmol) under nitrogen atmosphere and then added 10 mL of DMF anhydrous. The system was cooled in an ice bath and after 15 minutes, it was added, dropwise, MOMCl (5.55 mL ,73.1 mmol). The mixture was kept stirring for 3 hours at room temperature. Water was added to the reaction mixture and it was then extracted with ethyl acetate (3 x 15 mL). The organic layer was dried under Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by a silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2). The compound**5** was obtained as a light yellowish oil (4.71 g, 91 %).

^{1}H NMR (300.13 MHz, DMSO-*d6*) δ (ppm): 6.49 (2H, *dd*, J = 1.9 Hz, J = 0.5 Hz), 6.47 (H, *m*), 5.14 (4H, *s*), 3.36 (6H, *s*), 2.23 (3H, *s*).

IR υ_{max} (cm^{-1}) (KBr): 2955, 2852, 2826, 2360, 2342, 1595, 1540, 1472, 1399, 1331, 1316, 1291, 1257, 1215, 1145, 1084, 1039, 996, 923, 839, 688, 669.

EIMS m/z (%): 213 ($[M+1]^{+\cdot}$), 212 (100, $[M]^+$), 181 (33), 151 (18).

All spectroscopic values are in agreement with published data[67].

3.2. Synthesis of 2,6-bis(methoxymethoxy)-4-methylbenzaldehyde **(6)**

In a two-necked round-bottom flask of 250 mL, it was placed 1,3-bis(methoxymethoxy)-5-methylbenzene **(5)** (3.88 g, 18.3 mmol) under nitrogen atmosphere and then added anhydrous THF and anhydrous TMEDA (6.03 mL, 40.2 mmol). The mixture was cooled until -5 ºC and then added *n*-BuLi (25 mL, 40.2 mmol) and kept at room temperature for 2 hours. After this period, DMF (4.25 mL, 54.8 mmol) was added and the mixture stayed at room temperature for 2 more hours. To the reaction mixture, it was added NH_4Cl, followed by extraction with ethyl acetate (3 x 30 mL). The organic layer was dried under Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by a silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2), yielding compound **6** as a yellow oil (1.89 g, 43 %).

^{1}H NMR (300.13 MHz, DMSO-*d6*) δ (ppm): 10.37 (H, *s*), 6.70 (2H, *s*), 5.25 (4H, *s*), 3.40 (6H, *s*), 2.31 (3H, *s*).

IR υmax (cm^{-1}) (KBr): 3525, 3359, 2956, 2829, 2780, 1683, 1607, 1455, 1392, 1309, 1241, 1195, 1154, 1049, 963, 921, 827, 801, 690.

EIMS m/z (%): 241 (12, $[M+1]^{+\cdot}$), 240 (2, $[M]^+$), 208 (10), 195 (10), 179 (28), 178 (100), 165 (16), 163 (15), 135 (11), 121 (14), 91 (13), 76 (11), 51 (13)

All spectroscopic values are in agreement with published data[67].

4. Synthesis of yicathin B and C

4.1. Synthesis of (2,6-bis(methoxymethoxy)-4-methylphenyl)(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6- dimethoxyphenyl)methanol**(7)**

In a two-necked round-bottomed flask of 250 mL, it was placed ((4-bromo-3,5-dimethoxybenzyl)oxy)(tert-butyl)dimethylsilane**(3)** (1.55 g, 4.29 mmol) – building block A –and then added anhydrous THF, in argon atmosphere. The apparatus was cooled down to -78 ºC and added, dropwise, *n*-BuLi (4 mL, 6.43 mmol), staying stirring for 7 minutes. After that time, 2,6-bis(methoxymethoxy)-4-methylbenzaldehyde**(6)** (1.23 g, 5.14 mmol) – building block B – was added. The mixture stayed at – 78 ºC for 1.5 hours and then warmed to room temperature for 2 hours. To the reaction mixture, it was added a saturated solution of NH_4Cl and the solution was extracted with ethyl acetate (3 x 20 mL). The organic layer was dried under Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2), yielding compound **7** as a colorless oil (1.30 g, 58 %).

^{1}H NMR (300.13 MHz, DMSO-*d*6) δ (ppm): 6.68 (2H, *s*), 6.64 (2H, *s*), 6.53 (OH, *d*, J = 10.3 Hz), 5.51 (H, *d*, J = 10.3 Hz), 5.22 (4H, *s*), 4.78 (2H, *s*), 3.84 (6H, *s*), 3.38 (6H, *s*), 2.34 (3H, *s*), 1.04 (9H, *s*), 0.20 (6H, *s*).

^{13}C NMR (75.47 MHz, DMSO-*d*6) δ (ppm): 157.7, 155.3, 141.3, 137.1, 118.9, 117.9, 108.5, 101.8, 94.1, 64.2, 63.4, 55.6, 55.4, 25.8, 21.4, 18.0, -5.3.

IR υ_{max} (cm^{-1}) (KBr): 3565, 2956, 2859, 2827, 1613, 1586, 1456, 1396, 1294, 1223, 1112, 965, 923, 826, 781, 725, 684.

EIMS m/z (%): 523 (4, $[M+1]^{+\cdot}$), 329 (30), 326 (25), 325 (54), 298 (25), 295 (100), 282 (59), 269 (78), 255 (44), 238 (27), 237 (88), 226 (60), 211 (58), 209 (67), 195 (72), 194 (87), 180 (38), 178 (32), 165 (42), 163 (37), 151 (66), 137 (30), 135 (42), 89 (56), 73 (83).

4.2. Synthesis of (2,6-bis(methoxymethoxy)-4-methylphenyl)(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6- dimethoxyphenyl)methanone **(8)**

To a solution of (2,6-bis(methoxymethoxy)-4-methylphenyl)(4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanol **(7)** (440 mg, 0.84 mmol) in dichloromethane (3 mL), it was added solid Dess-Martin periodinane (DMP) (536 mg, 1.26 mmol), at room temperature, allowing a concentration of 0.3 M of DMP. The reaction mixture instantly turned bright pink and was kept stirring for 5 hours. After that time, it was added a solution of NaOH 10% and a saturated solution of $Na_2S_2O_3$. The mixture was extracted with DCM (3 x 10 mL). The organic layer was dried under Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 8:2), yielding compound **8** as a yellow solid (370 mg, 49 %).

^{1}H NMR (500.16 MHz, DMSO-*d*6) δ (ppm): 6.59 (2H, *s*), 6.54 (2H, *s*), 4.99 (4H, *s*), 4.68 (2H, *s*), 3.60 (6H, *s*), 3.17 (6H, *s*), 2.25 (3H, *s*), 0.91 (9H, *s*), 0.07 (6H, *s*).

^{13}C NMR (75.47 MHz, DMSO-*d*6) δ (ppm): 192.0, 157.9, 155.1, 145.2, 140.9, 120.4, 119.8, 108.6, 101.8, 93.9, 64.2, 55.9, 55.5, 25.9, 21.8, 18.1, -5.2.

IR υmax (cm^{-1}) (KBr): 2957, 2828, 1704, 1608, 1584, 1463, 1455, 1393, 1153, 1112, 1046.

EIMS m/z (%): 309 (22), 296 (17), 295 (100), 269 (17), 239 (18), 209 (16), 194 (22), 193 (24), 163 (23), 135 (38), 89 (32), 73 (50).

4.3. Synthesis of (2,6-dihydroxy-4-methylphenyl)(4-(hydroxymethyl)- 2,6-dimethoxyphenyl)methanone**(9)**

In a round-bottom flask of 50 mL, it was placed (2,6-bis(methoxymethoxy)-4-methylphenyl) (4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)methanone**(8)** (297.8mg, 571.9 μmol) in MeOH. At once, it was added *p*-toluenesulfonic acid (163.2 mg, 857.9 μmol) and the mixture turned red. The apparatus was warmed until the boiling point of MeOH, staying stirring for 5 hours. After that time, water was added to the mixture and the solution was extracted with ethyl acetate (3 x 10 mL). The organic layer was dried under Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by silica gel flash chromatography (dichloromethane/acetonitrile 9:1), yielding compound **9** as a yellow solid (130 mg, 71 %).

m. p.: 83 – 86 ºC.

^{1}H NMR (300.13 MHz, DMSO-*d*6) δ (ppm): 11.62 (2OH, *s*), 6.67 (2H, *s*), 6.14 (2H, *s*), 5.10 (OH, *s*), 4.55 (2H, *s*), 3.70 (6H, *s*), 2.20 (3H, *s*).

^{13}C NMR (75.47 MHz, DMSO-*d*6) δ (ppm): 198.8, 162.3, 155.7, 148.4, 144.8, 120.4, 109.1, 107.7, 101.9, 63.0, 55.7, 21.7.

IR υ_{max} (cm^{-1}) (KBr): 3447, 2922, 1717, 1641, 1611, 1583, 1465, 1418, 1385, 1373, 1294, 1265, 1237, 1214, 1127.

EIMS m/z (%): 535 (2, $[M+TMS]^{+\cdot}$), 520 (1), 519 (13), 416 (10), 415 (28), 283 (15), 282 (14), 281 (54), 267 (10), 209 (13), 191 (10), 163 (11), 149 (15), 147 (11), 89 (15), 75 (15), 73 (100).

4.4. Synthesis of 1-hydroxy-6-(hydroxymethyl)-8-methoxy-3-methyl- 9*H*-xanthen-9-one **(10)**

In a reaction vessel of 35 mL, it was placed (2,6-dihydroxy-4-methylphenyl)(4-(hydroxymethyl)-2,6-dimethoxyphenyl)methanone **(9)** (18.1 mg, 56.9 μmol) and then added H_2O/MeOH (9:1). To the solution was added NaOH (27.3 mg, 628 μmol) and the reaction vessel was placed in the microwave and heated until 130 ^oC for 5 minutes. After that time, HCl 5% and water were added to the vessel and mixture was filtered under pressure. The crude product was purified by silica gel flash chromatography (DCM/ACN 9:1), yielding compound **10** as a yellow solid (9.5mg, 58 %).

m. p.: 207 – 209 ^oC.

^{1}H NMR (300.13 MHz, DMSO-*d*6) δ (ppm): 13.03 (OH, *s*), 7.02 (H, *s*), 6.92 (H, *s*), 6.78 (H, *s*), 6.57 (H, *s*), 5.61 (OH, *t*, J = 5.7 Hz), 4.62 (2H, *d*, J = 5.7 Hz), 3.90 (3H, *s*), 2.35 (3H, *s*).

^{13}C NMR (75.47 MHz, DMSO-*d*6) δ (ppm): 181.1, 161.0, 160.1, 157.4, 154.8, 152.9, 148.2, 111.0, 108.8, 106.8, 106.7, 106.2, 103.9, 62.4, 56.3, 21.9.

IR υ_{max} (cm^{-1}) (KBr): 3460, 2924, 2853, 1651, 1608, 1560, 1468, 1426, 1265, 1229, 1110, 1075, 1064, 1052, 1031, 819, 773.

EIMS m/z (%): 431 (1, $[M+TMS]^{+\cdot}$), 416 (15), 415 (26), 311 (22), 310 (17), 283 (60), 253 (20), 237 (15), 89 (32), 73 (100), 59 (42).

4.5. Synthesis of 8-hydroxy-1-methoxy-6-methyl-9-oxo-9H-xanthene- 3-carboxylic acid-**Yicathin C(11)**

In a Erlenmeyer of 25 mL, it was placed the periodic acid (0.78 g, 3.4 mmol) and Chromium(VI) oxide (3.4 mg, 34 μmol) and then dissolved in wet ACN (75 %). In a round-bottom flask was placed 1-hydroxy-6-(hydroxymethyl)-8-methoxy-3-methyl-9*H*- xanthen-9-one **(10)** (39 mg, 0.14 mmol) and dissolved in wet acetonitrile (75 %), posteriorly adding 12.5 mL of the H_5IO_6/CrO_3 solution over 40 hours. The reaction mixture stayed at room temperature, stirring for 40 hours. After this time, $NaHSO_3$ was added and the solution was extracted with ethyl acetate (3 x 15 mL). The organic layer was dried under Na_2SO_4, filtered and the solvent evaporated. 46 %

m. p.: 203 – 206 ºC.

^{1}H NMR (500.16 MHz, DMSO-*d*6) δ (ppm): 13.85 (OH, *s*), 12.74 (OH, *s*), 7.54 (1H, *d*, J = 1.4 Hz), 7.36 (1H, *d*, J = 1.4 Hz), 6.83 (1H, *q*, J = 1.3 Hz), 6.63 (1H, *q*, J = 1.3 Hz), 3.93 (3H, *s*), 2.39 (3H, *s*).

^{13}C NMR (125.77 MHz, DMSO-*d*6) δ (ppm): 180.8, 164.8, 160.9, 160.4, 157.0, 154.7, 148.9, 135.9, 112.9, 111.4, 110.2, 107.1, 107.0, 105.8, 53.0, 21.9.

IR υmax (cm^{-1}) (KBr): 3446, 2924, 2853, 1718, 1652, 1615, 1559, 1478, 1419, 1386, 1329, 1301, 1250, 1203, 1141, 1115, 1087, 1006, 895, 824, 770.

EIMS m/z (%): 445 (0.5, $[M+TMS]^{+\cdot}$), 429 (10), 369 (10),313 (22), 312 (100), 297 (21), 283 (33), 241 (15), 217 (15).

All spectroscopic values are in agreement with published data[23].

4.6. Synthesis of methyl 8-hydroxy-1-methoxy-6-methyl-9-oxo- 9H-xanthene-3-carboxylate - **Yicathin B**(**12**)

In a round-bottom flask, it was placed 8-hydroxy-1-methoxy-6-methyl-9-oxo-9H-xanthene-3-carboxylic acid **(11)** (64 mg, 0.21 mmol) in MeOH and then added H_2SO_4 (36 μL, 64 μmol). The reaction mixture was heated until the boiling point of MeOH and stayed stirring overnight. Water and sodium bicarbonate were added to the flask and the solution extracted with chloroform (3 x 5 mL). The organic layer was dried under Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by flash chromatography (n-hexane/ethyl acetate 8:2), allowing a yellow solid (34 mg, 51 %).

m. p.: 155 -157 °C.

^{1}H NMR (500.16 MHz, DMSO-*d*6) δ (ppm): 12.72 (OH, *s*), 7.51 (H, *d*, J = 1.4 Hz), 7.34 (H, *d*, J = 1.4 Hz), 6.81 (H, *q*, J = 1.3 Hz), 6.62 (H, *q*, J = 1.3 Hz), 5.76 (3H, *s*), 3.93 (3H, *s*), 2.83 (3H, *s*).

^{13}C NMR (125.77 MHz, DMSO-*d*6) δ (ppm): 180.8, 164.8, 160.8, 160.4, 157.0, 154.7, 148.9, 135.8, 112.9, 111.4, 110.2, 107.0, 106.9, 105.7, 54.9, 53.0, 21.9.

IR υmax (cm^{-1}) (KBr): 3004, 2955, 2920, 2850, 1735, 1659, 1564, 1508, 1474, 1428, 1360, 1333, 1305, 1272, 1242, 1209, 1189, 1155, 1139, 1114, 1090, 989, 880, 835, 823, 807.

EIMS m/z (%): 387 (1, $[M+TMS]^{+\cdot}$), 371 (18), 356 (14), 312 (10), 299 (16), 298 (83), 297 (10), 271 (22), 270 (100), 269 (18), 242 (17), 241 (51), 227 (10), 143 (18), 134 (11).
All spectroscopic values are in agreement with published data[23].

5. Synthesis of Yicathin Analogues

5.1. Synthesis of methyl 4-(2,6-difluorobenzoyl)-3,5-dihydroxybenzoate

In a two-necked round-bottomed flask of 50 mL, it was placed methyl 4-bromo-3-hydroxybenzoate (250 mg, 1.08 mmol), (2,6-difluorophenyl)boronic acid (256 mg,1.62 mmol), diacetoxypalladium(12.1 mg,54.1 μmol), di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphane (38.8 mg,108 μmol), Cesium carbonate (1.06 g,3.25 mmol) in Toluene. The flask was evacuated and backfilled with argon 3 times. It was then evacuated once more and fitted with a Carbon monoxide (30.3 mg, 1.08 mmol) balloon (equipped with a $CaCl_2$ drying filter) freshly prepared from oxalyl chloride (0.4 mL, 4.7 mmol). The flask was then heated at 100 °C overnight. The reaction was cooled to rt, carefully vented, diluted with water, and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4. The crude product was purified by flash chromatography.

5.2. Synthesis of methyl 4-(2,4-difluorobenzoyl)-3,5-dihydroxybenzoate

In a two-necked round-bottomed flask of 50 mL, it was placed methyl 4-bromo-3-hydroxybenzoate (250 mg, 1.08 mmol), (2,4-difluorophenyl)boronic acid (256 mg, 1.62 mmol),diacetoxypalladium(12.1 mg,54.1 μmol), di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphane (38.8 mg,108 μmol), Cesium carbonate (1.06 g,3.25 mmol) in Toluene. The flask was evacuated and backfilled with argon 3 times. It was then evacuated once more and fitted with a Carbon monoxide (30.3 mg, 1.08 mmol) balloon (equipped with a $CaCl_2$ drying filter) freshly prepared from oxalyl chloride (0.4 mL, 4.7 mmol). The flask was then heated at 100 °C for 4 hours. The reaction was cooled to rt, carefully vented, diluted with water, extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4. The crude product was purified by flash chromatography (n-hexane/ethyl acetate 8:2; 100% ethyl acetate :1% formic acid). The main product was methyl 2',4'-difluoro-2-hydroxy-[1,1'-biphenyl]-4-carboxylate (97 mg, 34 %).

^{1}H NMR (500.16 MHz, DMSO-*d6*) δ (ppm): 10.14(1H,s), 7.57(1H,d), 7.46 (2H,m),7.31(1H,d), 7.30(1H,m), 7.15(1H,td), 3.86(3H,s).

^{13}C NMR (75.47 MHz, DMSO-*d6*) δ (ppm): 165.99, 162.30, 159.02, 154.96, 132.76, 131.46, 130.53, 126.56, 121.71, 119.77, 115.95, 111.32, 103.95, 52.21.

IR υmax (cm^{-1}) (KBr): 3410, 1705, 1498, 1443, 1429, 1416, 1302, 1270, 1215, 1193, 1142, 1110, 1096, 936

EIMS m/z (%): 246 ($M^{+\cdot}$), 234(85), 233(85), 205(69), 204(55), 177(84), 175(79), 157(85), 151(85), 117(39), 102(27), 89(19), 79(23).

E. Conclusions

In this dissertation the total synthesis of two xanthones, Yicathin B and C is presented. The total synthesis was already approached previously in our group, In this work the synthetic routes were confirmed and as result Yicathin B and C were obtained, in order to perform lipophilicity assays. The structure of all the synthesized compounds was elucidated by IR, EIMS, ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. A new pathway to obtain Yicathins analogues was explored by Carnonylative Suzuki Coupling with low success in yield, since the main product was the byaryl product.

Lipophilicity assays of Yicathin B, C and analogues were performed using biomimetic models, and their values assessed and discussed. Regarding the values obtained, all compounds are in accordance with the Lipinski, Ghose and Muegge descriptors of lipophilicity for oral bioavailability.

Next work will involve the continuous study of the Carbonylative Suzuki Coulpling pathway in order to obtain analogues in bigger quantities and at a fastest rate.

F. References

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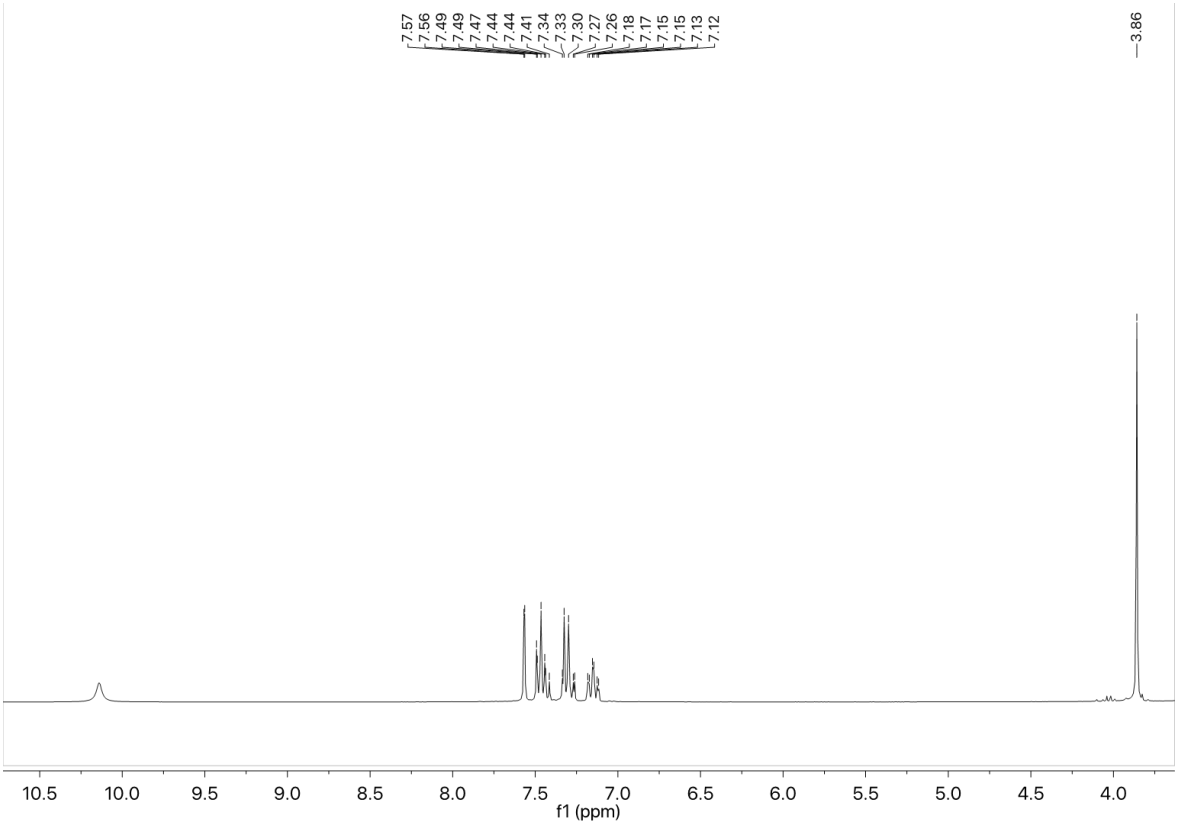
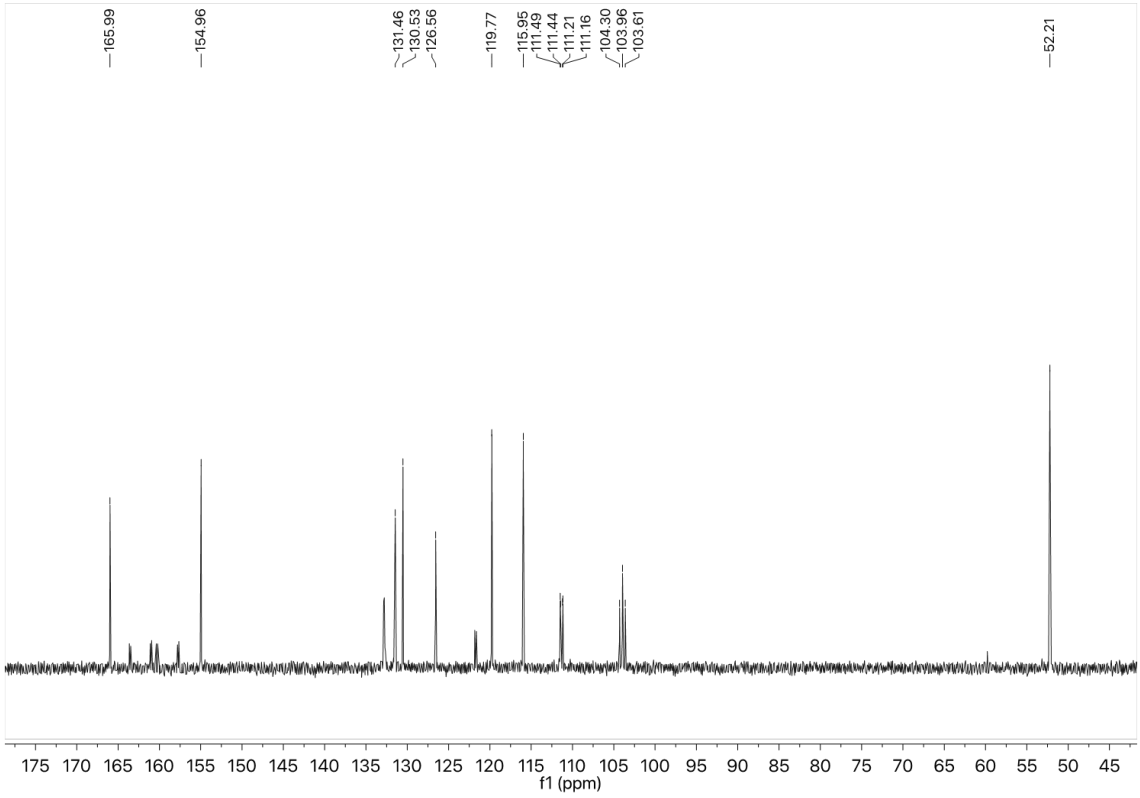
G. Appendix

Appendix 1: NMR spectra for compound 18

NMR spectra (^{1}H and ^{13}C) of compound 18.




165.99
154.96
131.46
130.53
126.56
119.77
115.95
111.49
111.44
111.21
111.16
104.30
103.96
103.61
52.21
175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45
f1 (ppm)