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Relatório de Projeto/Estágio

Synthesis of new atropisomers based on xanthone derivatives

Síntese de novos atropisómeros baseados em derivados xantónicos

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Abstract

Chiral compounds are “omnipresent” when it comes to biological processes and life itself. Essential compounds such as sugars and amino acids are chiral and indispensable building blocks of all living beings. Nowadays, as medicinal chemistry and pharmacology advances and more studies are conducted, chirality is one of the major areas of interest, along with chiral derivatives of biologically active molecules – such as xanthones.

This work focuses mainly on the synthesis of a particular type of chiral compounds – Atropisomers (ATIs) – whose chirality arises not from a stereogenic centre, but from an axis that due to stereogenic hindrance or other factors, it can exist in more than one distinct 3D structure being not superimposable on its mirror image.

During this project, 10 new atropisomers were synthetized by using suitable building blocks, specifically both enantiomers of an atropisomeric chiral block and carboxylated xanthone derivatives (XCars). To obtain the desired ATIs, the carboxylic acid of XCars were first converted into an acyl chloride and, then coupled, with amine groups from the chiral building blocks. Structure elucidation of the synthesized ATIs was established by spectroscopic methods.

To the best of our knowledge, we provide here the first description of the ATIs based on xanthone derivatives.

Keywords: Chirality; Enantiomers; Atropisomers; Xanthone derivatives

Resumo

Compostos quirais são “omnipresentes” no que concerne a processos biológicos e à própria vida. Compostos essenciais tais como açúcares e aminoácidos são quirais, e blocos indispensáveis para a “construção da vida”. Hoje em dia, à medida que a química medicinal e a farmacologia avançam e mais estudos são realizados, a quiralidade é uma das grandes áreas de interesse, assim como a obtenção de derivados quirais de moléculas biologicamente ativas – como as xantonas.

Este trabalho foca-se principalmente na síntese de um tipo específico de compostos quirais – Atropisómeros (ATIs) – cuja quiralidade não se deve a um centro estereogénico, mas à existência de um eixo quiral, que devido a impedimentos estereoquímicos ou outros fatores, pode existir em mais do que uma estrutura 3D distinta, não sendo sobreposta à sua imagem no espelho.

Durante este projeto, 10 novos atropisómeros foram sintetizados usando reagentes adequados, especificamente ambos os enantiómeros de um bloco quiral atropisomérico e derivados carboxilados de xantonas (XCars). Para obter os ATIs pretendidos, o grupo ácido carboxílico dos XCars foram convertidos em cloreto de acilo e, posteriormente, formam acoplados a grupos amina dos blocos quirais. A elucidação estrutural dos ATIs sintetizados foi realizada por métodos espectroscópicos.

De acordo com o nosso conhecimento, descrevemos aqui pela primeira vez a obtenção de ATIs baseados em derivados de xantonas.

Palavras-chave: Quiralidade; Enantiómeros; Atropisómeros; Derivados xantónicos

Abbreviations and Symbols

^{13}C NMR – Carbon Nuclear Magnetic Resonance

^{1}H NMR – Proton Nuclear Magnetic Resonance

ATI – Atropisomer

CDX – Chiral Derivative of Xanthone

COMU – (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate

CSP – Chiral Stationary Phase

DMF – *N*,*N*-Dimethylformamide

HMBC – Heteronuclear Multiple-Bond Correlation Spectroscopy

HSQC – Heteronuclear Single-Quantum Correlation Spectroscopy

IR – Infrared Spectroscopy

LC – Liquid Chromatography

TBTU – *O*-(Benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate

TEA – Triethylamine

THF – Tetrahydrofuran

TLC – Thin-layer chromatography

XCar – Carboxylated Xanthone Derivative

XD – Xanthone derivative

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1. Introduction

1.1. Chirality

Chirality is a spatial property of several molecules, being many of them essential, such as amino acids (and by extension, peptides and proteins), nucleosides, and carbohydrates [1]. Despite this, chirality is a relatively simple concept at its root. A molecule can be considered chiral if it can exist in more than one distinct form with the same chemical composition, do not present a symmetry plan and it is not superimposable on its mirror image. The two non-superimposable object/mirror image forms of chiral molecules are called enantiomers (**Figure 1**). The presence of asymmetric carbon atoms, or stereocenters – tetravalent carbon atoms in a molecule with four different substituents – is a common cause for chirality in a molecule, but as we will see, it is not the only one [2]. Moreover, other atoms such as sulphur, phosphorus or nitrogen could also be stereocenters [1, 2].

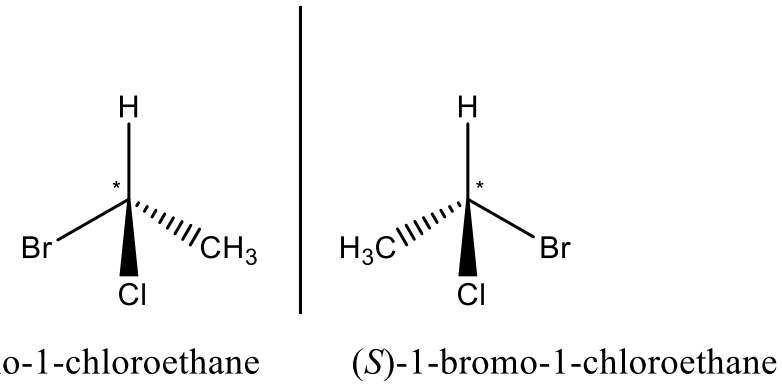


Figure 1: *Example of a pair of enantiomers. Stereocenters are sometimes denoted with an asterisk.*

Enantiomers are also known as optical isomers, due to their effect on plane-polarized light. Actually, the enantiomers rotate plane-polarized light in equal amounts but in opposite directions: one enantiomer rotates the light to clockwise (dextrorotatory) and the other to counterclockwise (levorotatory), referred by the symbols (+) and (-) [1]. Nevertheless, this nomenclature only allows to differentiate the enantiomers based on their optical rotation. Other nomenclature systems are used to differentiate the two enantiomers based on their configuration. One of the most used was devised by three chemists: R. S. Cahn, C. Ingold,

and V. Prelog.; which allows to indicate the "handedness" of the asymmetric centres and molecules. With this system, there is an assigned order of "priority" for the substituents of the stereocenter, and while facing a 3D model of that asymmetric carbon from the opposite side of the lowest priority substituent, it is possible to see that the order of priority either goes clockwise (*R* - Rectus), or counter clockwise (*S* – Sinister) (**Figure 2**) [1].

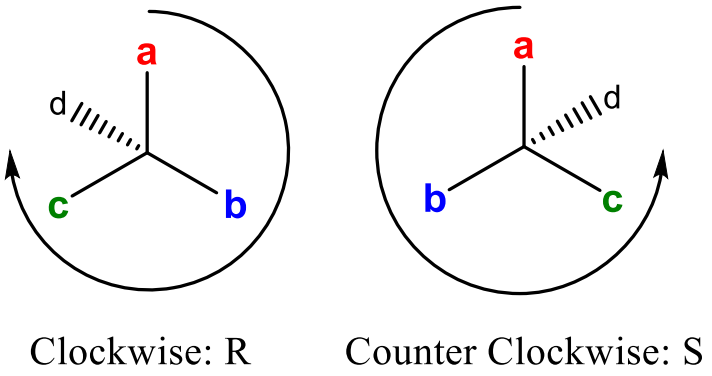


Figure 2: *Determination of handedness. Priority is a>b>c>d, and d is aligned with the central atom, positioned below the plane of the paper, so that the observer is facing from the opposite side.*

Despite most of the physical and chemical properties of enantiomers are similar in an achiral environment, if enantiomers are exposed to a chiral environment such as a living body, their effects may be significantly different [3-4]. One of the most known examples of biological differences between enantiomers was the case of thalidomide (**Figure 3**). Thalidomide was introduced in the pharmaceutical market nearly 60 years ago as a nonaddictive sedative in Germany, and rapidly spread to several other countries around the globe, being advertised as "free from side-effects". It was therefore prescribed to pregnant women to treat morning sickness, and disaster struck: over 10,000 infants were born with severe malformations – and this number does not include miscarriages and stillborn babies [5].

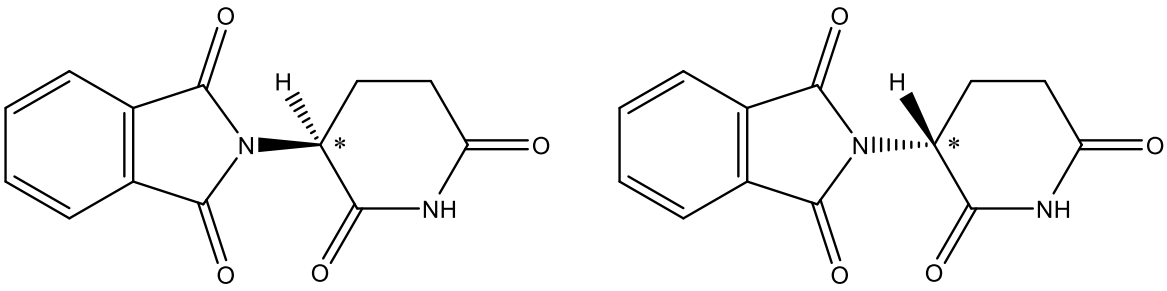


Figure 3: *Structure of thalidomide enantiomers, along with their biological effects.*

Thalidomide is a chiral drug, and one of the enantiomers has a sedative effect, however, the other enantiomer has severe teratogenic effects on humans and other animals [5]. This drug also interconverts rapidly between both forms at physiological pH, making attempts at enantioselective synthesis or separation of the *R* enantiomer fruitless, as it will turn into a racemic mixture inside the body. There are however, several drugs where the strategy to obtain only one enantiomer is advantageous and incentivised, as we will discuss.

1.2. Enantioselectivity

As said before, chirality is a characteristic of several molecules, but not all of them appear as a mixture of enantiomers, especially in nature. Living beings' proteins are predominantly formed by the L-isomers of amino acids – and the production of their D-isomer form when it is required utilizes the naturally produced L-form as substrate [2]. Nevertheless, some exceptions can occur as, for example, bacteria sometimes have D-amino acids as components of their cell wall [6].

So, when even our bodies are selective on the form it produces vital compounds, why shouldn't we be? Several drugs are chiral, and have multiple forms. This leads to cases where, for example, one isomer is 50 or 100 times more efficient than the other, or even where one isomer is responsible for the therapeutic effect while the other is responsible for side-effects [3-4]. This happens because the biotargets comprise chiral molecules being able to recognize and discriminate between the enantiomers of active compounds -

enantioselectivity [2] (**Figure 4**). Therefore, single enantiomers of drugs may exhibit different pharmacokinetic, pharmacodynamic and toxicological properties [7-9].

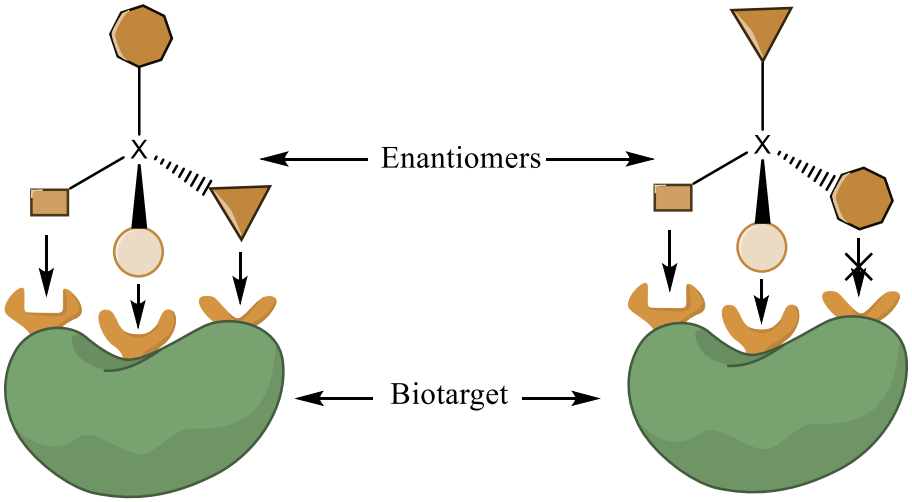


Figure 4: *The biotargets comprise chiral molecules, which can lead to differences in interaction between enantiomers and the target – enantioselectivity.*

Because of this, the tendency of the modern pharmaceutical market has favoured the production of new, single enantiomer drugs in favour of the previously more common racemates – from more than 80% of chiral drugs being used as racemates for therapy in the early 2000's [9] – to the current state of the industry, where chiral molecules make up the majority of new approved entities, and most of these chiral molecules are available as single enantiomers [10] (**Figure 5**).

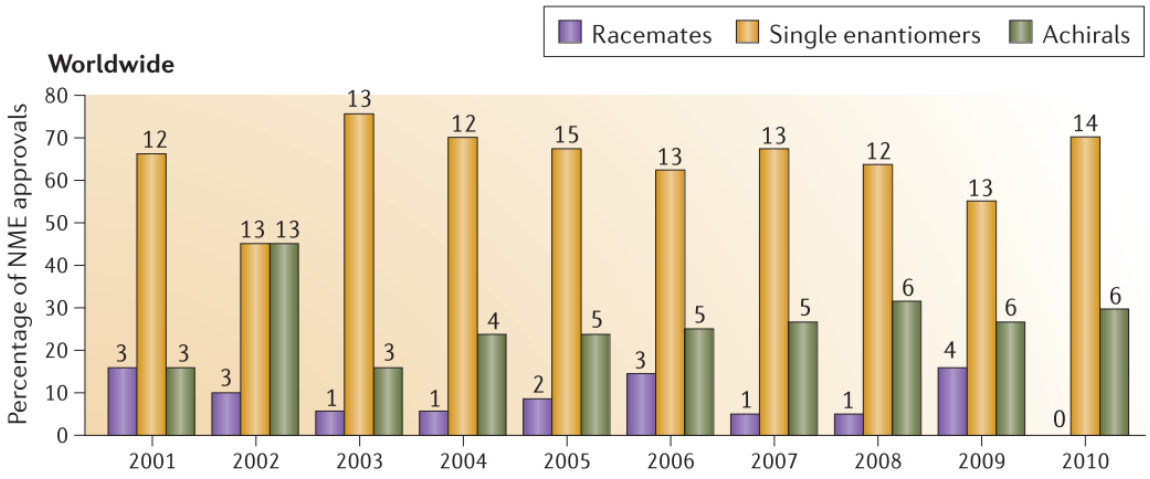


Figure 5: *Number of worldwide approvals of New Molecular Entities from 2001 to 2010 [11]. Note the predominance of single enantiomer drugs against racemates.*

Therefore, the production shifted focus to obtain enantiomerically pure compounds, usually using two methods [2]. One of the methods is the resolution of a racemate – for example, by liquid chromatography (LC) using chiral stationary phases (CSPs) of various types. The CSPs bind more strongly with one of the enantiomers that is more retained in the column, allowing to enantioseparate the enantiomers with high enantiomeric purity. This is the preferred method, especially for the early stages of development in the pharmaceutical industry [12]. Alternatively, and usually post-development, the other method is typically chosen, the enantioselective synthesis to obtain a large amount of one of the target enantiomers [2].

1.3. Atropisomerism

Commonly, chirality is associated with the existence of a stereocenter, but chirality may also be conferred by other elements such as an axis of asymmetry [2]. Examples of this type of chirality are the atropisomers (ATIs) (**Figure 6**) [13].

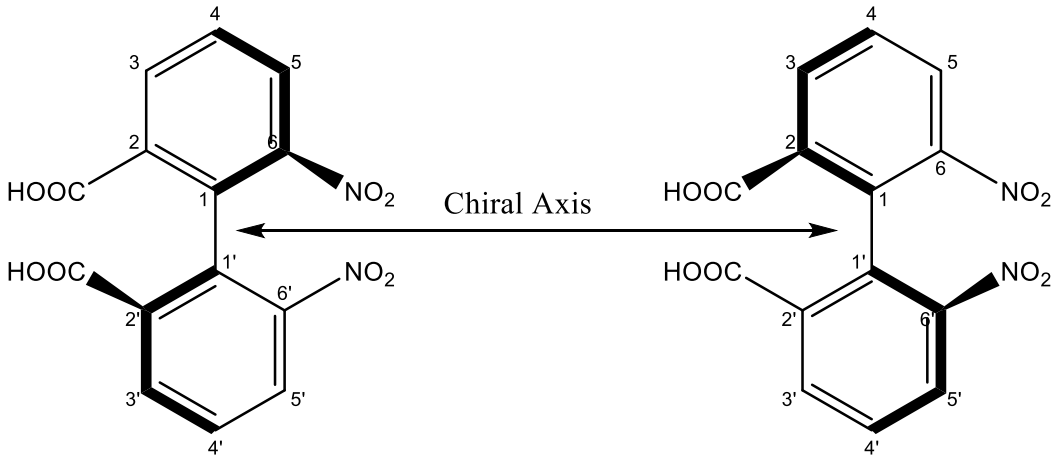


Figure 6: *First experimentally detected atropisomers, with chiral axis highlighted [13].*

Atropisomerism is a property of molecules that contain a hindered bond in their structure, usually a chemical bond connecting to cyclic groups [14]. This feature can lead to substances that appear to be achiral – by a quick look at the structure – to actually possess chirality and be composed of two enantiomers [15]. ATIs may have the potential to revolutionize drug discovery – and maybe even other industries that make use of chirality – leading to new developments in various industries.

ATIs may be able to interconvert, in specific conditions, since their chirality is associated with an axis, and the conformation being held by the steric hindrance and/or electronic factors. Nevertheless, the stability is affected by several factors, such as the substituents on either side of the bond [16]. This means that although the enantiomers can, in principle, interconvert, a stable conformation is more than possible to obtain. ATIs were even classified in accordance to the time it takes for these interconversions to take place – including the difficulties in developing isomers with intermediate half-life time, where the compound does not interconvert rapidly, which would allow for a racemate drug, nor is it stable enough to not interconvert at all or to do it slowly enough that a single enantiomer drug would be viable [16].

Several ATI drugs have been developed, and are being researched [17, 18]. Some of them even contain more than one chiral axis in their structure (**Figure 7**) [19].

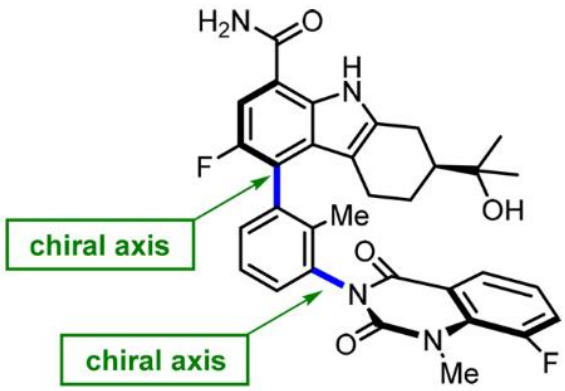


Figure 7: *Active pharmaceutical compound, currently in clinical trials for rheumatoid arthritis [19].*

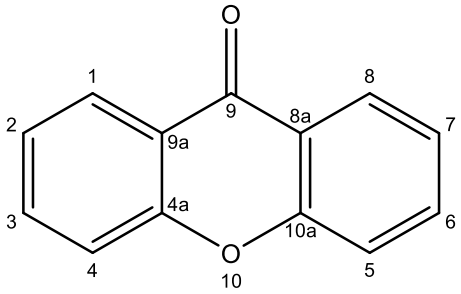
ATIs are a veritable treasure trove, full of potential that we are just beginning to tap into. In this work, we will use a binaphthyl frame, substituted with amino groups for the

synthesis of new ATI derivatives. Due to the bulky nature of the molecule, the interconversion is very slow, making it stable enough for enantioselective synthesis [20].

1.4. Xanthone Derivatives

Xanthone (9*H*-xanthen-9-one) derivatives (XDs) are a class of *O*-heterocyclic compounds with a dibenzo-γ-pyrone scaffold, represented in **Figure 8** [21]. Naturally-occurring xanthones comprise a variety of different types of moieties in certain positions of the xanthone scaffold, which not only lead to a vast diversity of biological and pharmacological activities, but also provide a remarkable basis for the discovery of new potential drug candidates [21-23]. They can be found as secondary metabolites in diverse natural sources including higher plants, fungi, lichens [22-25] as well as in marine environments [23, 26]. XDs have an important role in Medicinal Chemistry mainly considering their great diversity of biological and pharmacological activities, namely antioxidant, anti-inflammatory, antitumor, antimicrobial, among others [27, 28]. Therefore, the synthesis of these molecules and their derivatives is biologically and chemically significant, mostly for search of new bioactive compounds [21-29]. Among the large number of XDs, those containing a carboxylic group, carboxyxanthones (XCars), have shown great significance not only considering their interesting biological activities but also they proved to be suitable molecular scaffolds for synthesis of analogues and derivatives [30], including chiral compounds [31-32].

Synthetic chiral derivatives of xanthones (CDXs) are very interesting compounds leading to a large variety of biological activities [33-35]. These chiral derivatives can be obtained inspired in naturally occurring xanthones or by coupling chiral moieties to the xanthone scaffold [35].



9*H*-xanthen-9-one

Figure 8: *Xanthone scaffold and numbering.*

. In this work, different XCars will be used as suitable building blocks for synthesis of new ATIs.

2. Aims

The principal aims of this project were:

- The synthesis of different pairs of ATIs based on XDs (**Figure 9**), by the coupling between commercially available enantiomerically pure blocks with previously synthetized XCars.

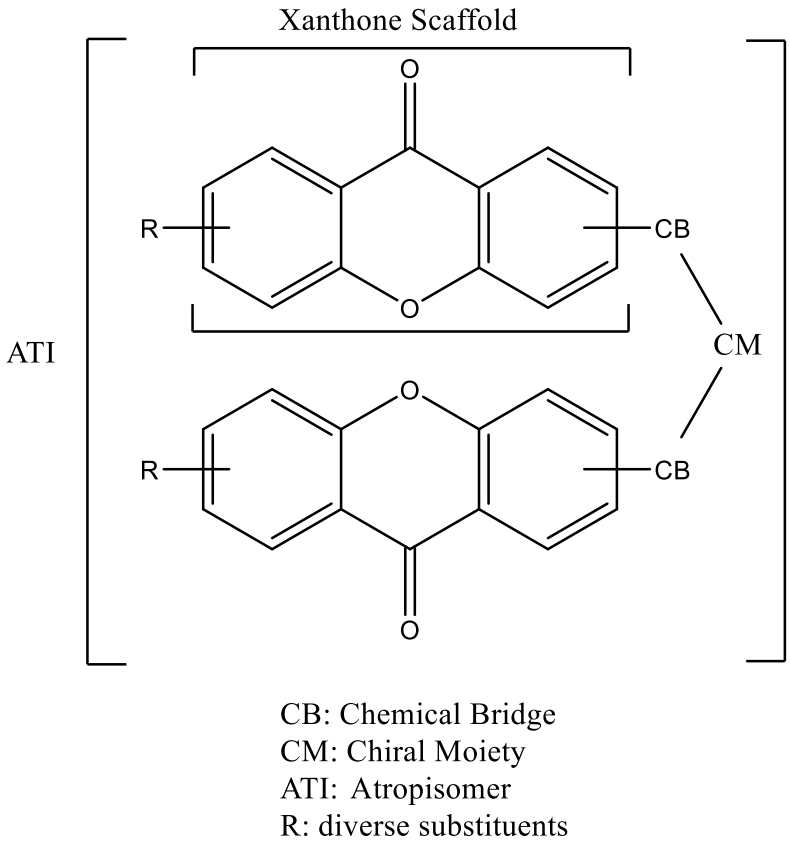


Figure 9: *General structure of the synthetized compounds. Orientation of the xanthone scaffold may vary.*

- The structure elucidation of the obtained ATIs by spectroscopic methods.

3. Results and Discussion

3.1. Synthesis of compounds 1 to 8

Eight new ATIs (**1-8**) were synthesized (**Figures 10** and **11**) by coupling XCars (**9-12**) (**Figure 12**) with suitable commercially available enantiomerically pure amines (**13, 14**) (**Figure 13**). The pure amines are the chiral blocks, which will grant chirality to the final compounds. The following figures depict the structures of the compounds mentioned above, showing the numbering. The ATIs were organized in enantiomeric pairs.

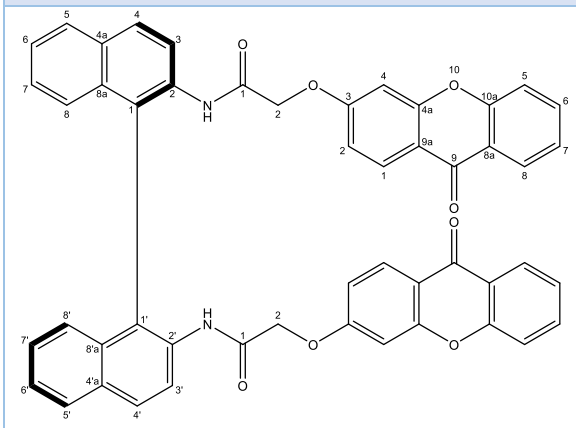
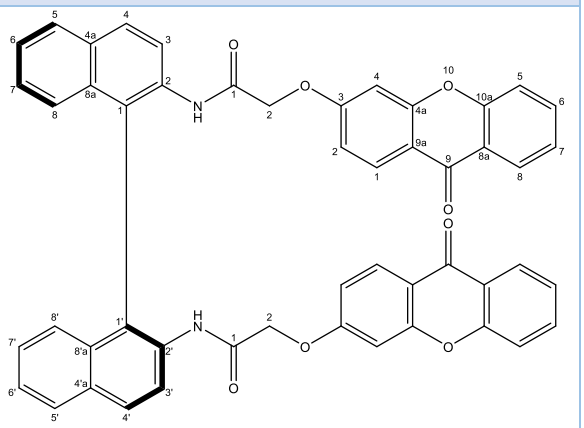
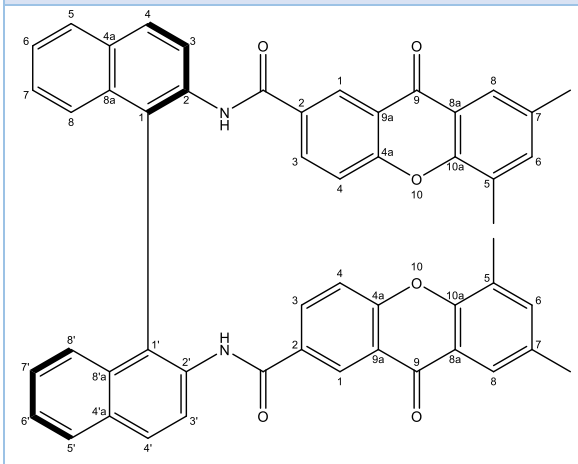
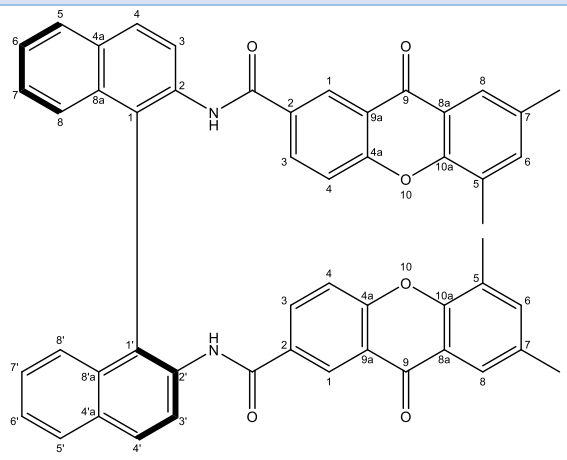
ATI1 (1) – (*R*)-Atropisomer from XCar 1	**ATI2 (2)** – (*S*)-Atropisomer from XCar 1
	
ATI3 (3) – (*R*)-Atropisomer from XCar 5	**ATI4 (4)** – (*S*)-Atropisomer from XCar 5
	

Figure 10: *Structure of synthetized ATIs* ***1-4****.*

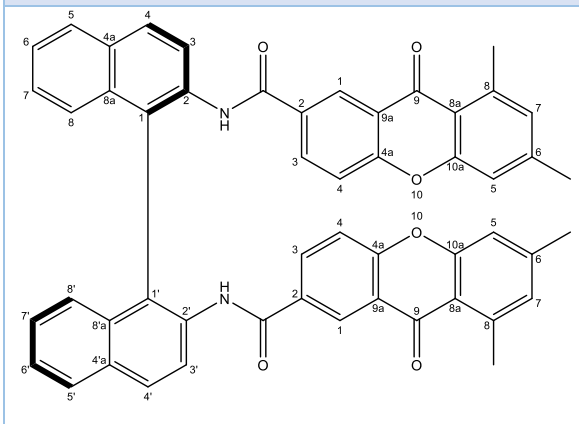
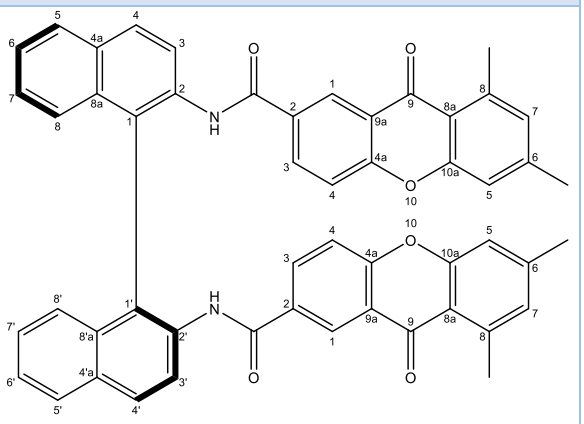
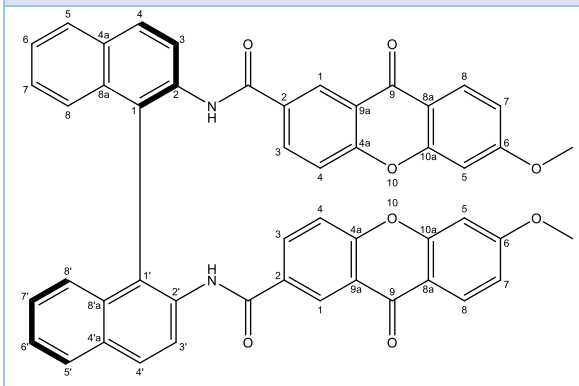
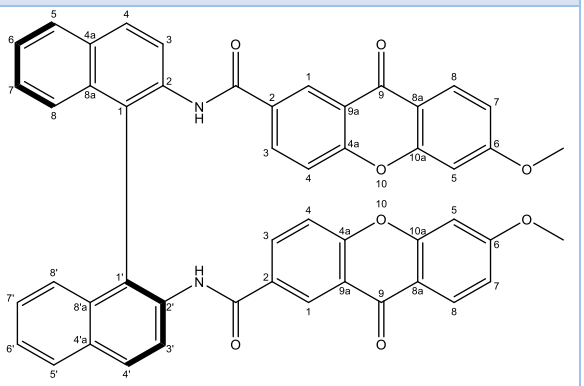
ATI5 (5) – (*R*)-Atropisomer from XCar 4	**ATI6 (6)** – (*S*)-Atropisomer from XCar 4
	
ATI7 (7) – (*R*)-Atropisomer from XCar 2	**ATI8 (8)** – (*S*)-Atropisomer from XCar 2
	

Figure 21: *Structure of synthetized ATIs* ***5-8****.*

All the XCars used in this work were previously synthetized in the Group of Medicinal Chemistry of LQOF (FFUP)/CIIMAR [31, 32], and were chosen for coupling with chiral building blocks through an amide bond. Both enantiomers of (1,1'-binaphthalene)-2,2'-diamine were commercially available in enantiomerically pure form. They were selected taking into account reported interesting synthesis and applications of their derivatives [36-39].

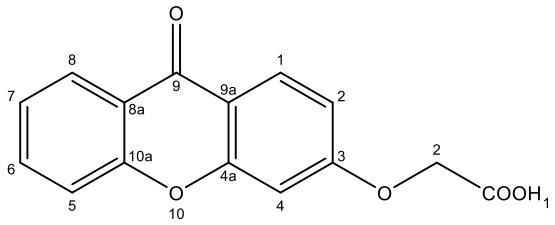
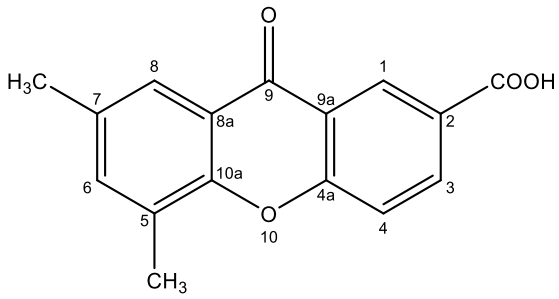
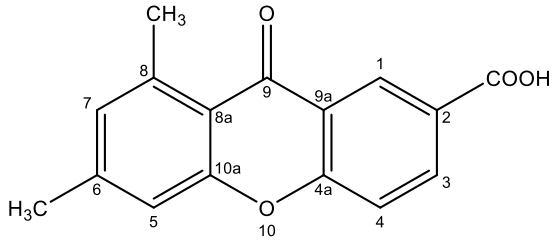
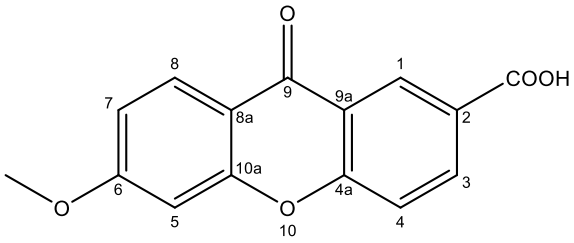
XCar 1 (9): 2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetic acid	**XCar 5 (10):** 5,7-dimethyl-9-oxo-9*H*-xanthene-2-carboxylic acid
	
XCar 4 (11): 6,8-dimethyl-9-oxo-9*H*-xanthene-2-carboxylic acid	**XCar 2 (12):** 6-methoxy-9-oxo-9*H*-xanthene-2-carboxylic acid
	

***Figure 12**: Structures of XCars (**9-12**) used for synthesis of compounds **1-8**.*

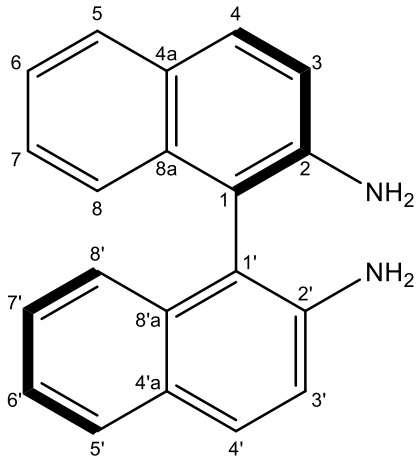
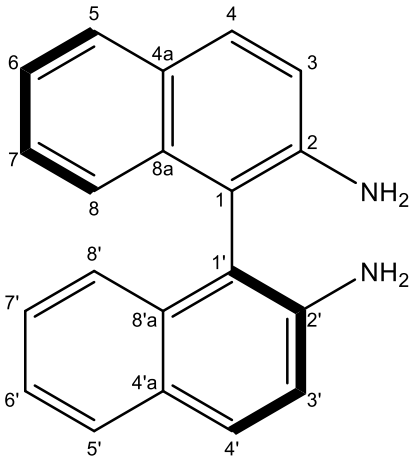
Chiral Building Block 1 (13) – (*R*)-[1,1'-binaphthalene]-2,2'-diamine	**Chiral Building Block 2 (14)** – (*S*)-[1,1'-binaphthalene]-2,2'-diamine
	

***Figure 13**: Structures of enantiomerically pure chiral building blocks (**13-14**) used for synthesis of compounds **1-8**.*

3.1.1. Synthesis attempt by using coupling reagents

First, a coupling reaction between the chiral block **13** and XCar 1 (**9**) was attempted by using *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling reagent, in the presence of a catalytic amount of triethylamine (TEA) in dry tetrahydrofuran (THF) (**Figure 14**), based on [31, 32].

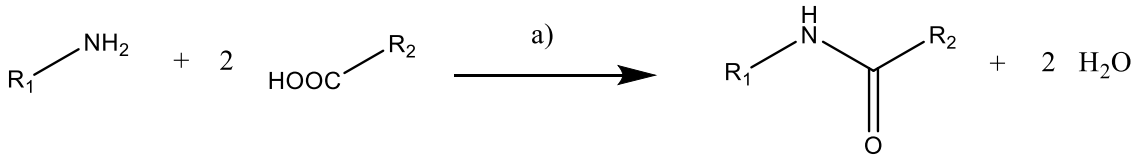


***Figure 14**: General scheme for amide formation using coupling reagents. R_1 being one of the chiral blocks, which has two amine groups to react with two carboxyl groups (R_2) of XCars. a) – 2 mmol TBTU or COMU; 4 mmol TEA; THF (dry); room temperature.*

The reaction progress was controlled via TLC, however, even after 24 hours and addition of more amine and TBTU, the reaction did not occur. By using the same building blocks, a new coupling reagent was devised after the failed coupling using TBTU, the (1-cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), an alternative coupling reagent that also showed very good results in peptide synthesis [40]. Nevertheless, this coupling reagent also demonstrated to be not efficient.

3.1.2. Synthesis by acyl chloride coupling reaction

A new strategy was performed consisting first on the preparation of an acyl chloride of a XCar (**Figure 15**) followed by the coupling reaction with an amine to formation of amide bond (**Figure 16**).

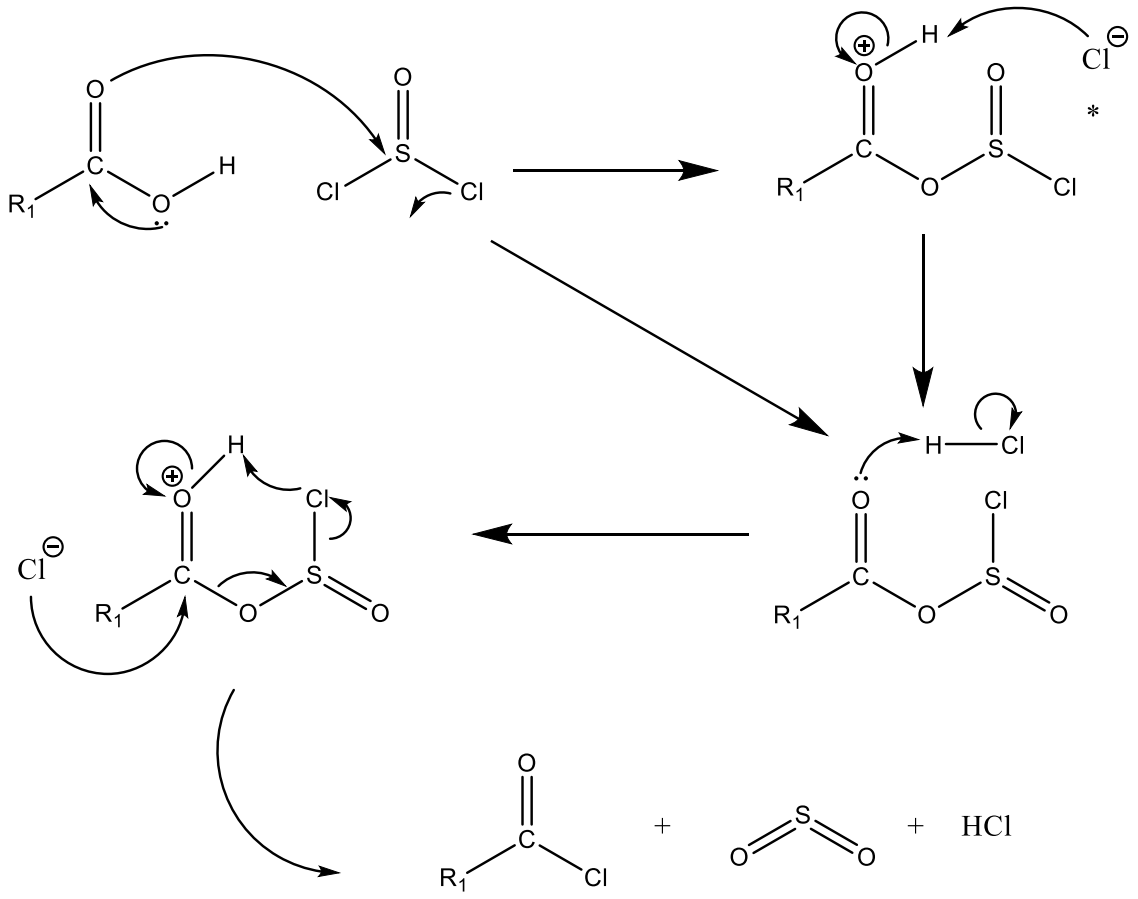


***Figure 15**: Reaction mechanism of thionyl chloride with a carboxylic acid. R_1 stands for the xanthone scaffold. An unstable intermediate is marked with an asterisk.*

The reaction was controlled via TLC after 1 hour and showed complete reaction. After confirming this, in subsequent synthesis the reactions in this intermediate step were not controlled, due the other XCars being structurally similar to XCar1 and to avoid opening the reactional system. The amount of XCar was increased, to make sure that it was in excess and trying to make sure that only one product was obtained, avoiding obtaining other products (compound where only one of the amine groups of the chiral block is coupled to the XCar). After preparation of the acyl chloride, the coupling between the xanthone acyl chloride to the amine was carried out for 12 hours.

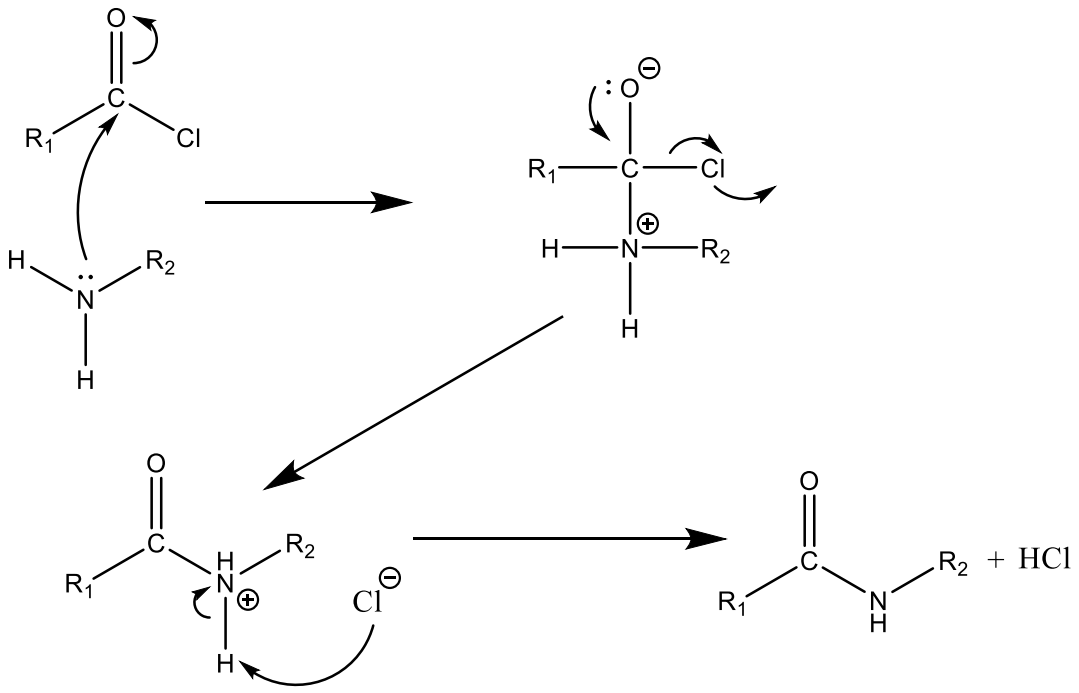


***Figure 16**: Reaction mechanism between the acyl chloride and the amine groups of the chiral block. R_1 stands for the xanthone scaffold and R_2 stands for the chiral moiety. Of note that each chiral building block has two amine groups, which will therefore react with two acyl chloride groups.*

There are also some points to have in attention about this method of synthesis:

- All the material used in the experimental montage was left in the oven for 24 hours prior to use, to guarantee that it was anhydrous, since the thionyl chloride would react with water – making the reaction unviable. The same would happen to the acyl chloride.
- Reagents were left in the desiccator overnight before the reaction. A diluted solution of NaOH was prepared to neutralize any remains of thionyl chloride and/or acidic by-products of the reaction in the material.
- Despite the need for an anhydrous environment – since thionyl chloride and the acyl chloride we pretend to obtain react easily with water – we utilized a single neck reactional flask. This choice was made due to the byproducts of the reaction, which include chloridric acid in gaseous form, and for greater ease of evaporating the solvent in the intermediate process of the reaction.
- This by-product could possibly corrode through rubber septum's, compromising the anhydrous atmosphere completely. For the sake of not destroying the laboratory material, we used a single opening in the reactional balloon, and a nitrogen

campanula was used whenever there was a need to access the reactional environment and create a vacuum to re-impose a nitrogen atmosphere afterwards.

3.2. Synthesis of compounds 15 and 16

After synthetize of compounds **7** and **8**, a demethylation reaction of the methoxy groups of both compounds, promoted by the NaOt-Bu and 2-(diethylamino)ethanethiol hydrochloride, in *N*,*N*-dimethylformamide (DMF) was performed (**Figure 17**) yielding two new ATIs – compounds **15** and **16**, respectively (**Figure 18**), based on [41].

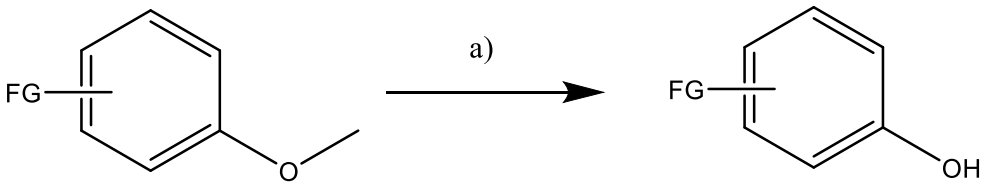


Figure 17: *General scheme of a demethylation reaction. FG stands for the rest of the molecule (ATI), and each ATI has two methoxy groups associated with the XCars. a) – 2 mmol $Et_2NCH_2CH_2SH{\cdot}HCl$; 4 mmol NaOt-Bu; DMF (dry), reflux; 2 hours.*

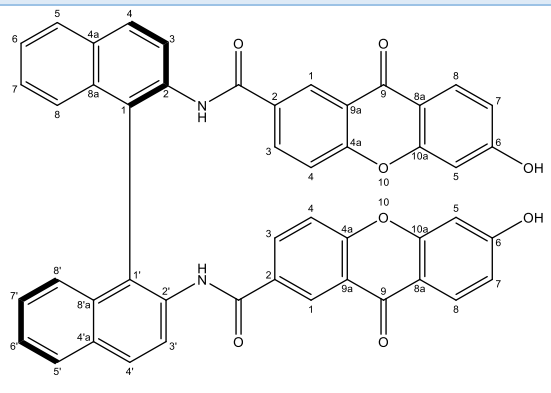
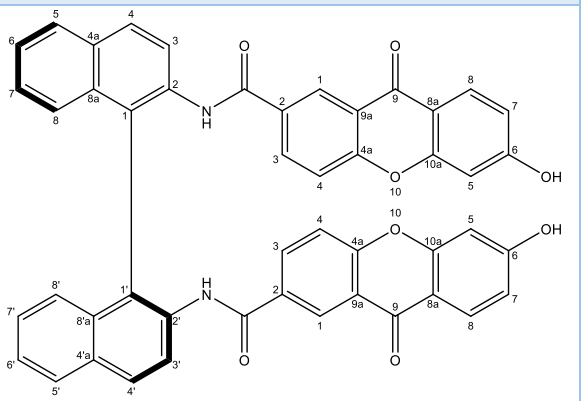
ATI9 (15) – Demethylated ATI7	**ATI10 (16)** – Demethylated ATI8
	

Figure 18*: Structures of two new ATIs (**15** and **16**) obtained from the demethylation of synthetized ATIs, **7** and **8**, respectively.*

3.3. Structure elucidation

^{1}H NMR and IR analysis were performed to confirm the success of the synthesis of compounds. ^{13}C NMR, HSQC, HMBC and HRMS experiments are in progress.

3.3.1. IR Analysis

IR analysis was performed for synthetized compounds **1-8**, **15** and **16**. IR data obtained after spectrum's analysis are depicted in **Tables 1** and **2**. As the enantiomers of the same pair have similar spectral data, only the values of the (*R*)-enantiomer (**1**, **3**, **5**, **7** and **15**) are shown.

__Table 1__: IR frequencies in cm^{-1} of compounds __1__, __3__, __5__ and __7__.

Bond	ATI1 (1)	ATI3 (3)	ATI5 (5)	ATI7 (7)
C=C (Xanthone)	1465	1426	1426	1444
C=C (Xanthone)	1504	1473	1452	1478
C=C (Xanthone)	1520	1506	1483	1505
C=O (Xanthone)	1657	1662	1661	1660
N–H (Amide)	3380	3420	3416	3416
C=O (Amide)	1620	1614	1610	1617

__Table 2:__ IR frequencies in cm^{-1} of compound __15__.

Bond	ATI9 (15)
C=C (Xanthone)	1450
C=C (Xanthone)	1478
C=C (Xanthone)	1503
C=O (Xanthone)	1649
N–H (Amide)	3416
C=O (Amide)	1615
O–H (Phenol)	3200-3600

Considering the IR data, all compounds present typical bands corresponding to aromatic C=C bonds and C=O bond of the xanthone scaffold, with similar frequencies for all compounds. Additionally, the IR spectra of all compounds showed the presence of absorption bands corresponding to N-H around 3400 cm^{-1} and C=O of amide group around 1617 cm^{-1}, being indicative that the coupling reaction was successfully achieved.

For compound **15**, the presence of a large and intense band with a shift at 3200-3600 cm^{-1}, representative of a phenol group, confirms the demethylation of the aromatic ether of its precursor (compound **7**) and, consequently, the success of the synthesis.

3.3.2. NMR Analysis

The data obtained by analysis of ^{1}H NMR spectra of compounds **1**, **3**, **5** and **7** are listed in **Table 3**. Since the enantiomers of the same pair have similar spectral data, the ^{1}H NMR data of (*S*)-enantiomers are not shown. The ^{1}H NMR spectra of compounds **1**, **3**, **5** and **7** showed chemical shifts corresponding to the aromatic protons of the xanthone scaffold of XCar 1 (**9**) [31], XCar 5 (**10**) (unpublished results), XCar 4 (**11**) (unpublished results) and XCar 2 (**12**) [32], respectively.

Moreover, it is important to point out the presence in ^{1}H NMR spectra of the chemical shift around 8.00 ppm corresponding to the proton of amide group in addition to 6 aromatic protons of the chiral moiety.

^{1}H NMR experiments for compounds **15** and **16** are ongoing. Moreover, ^{13}C NMR, HSQC, and HMBC and experiments are in progress to undoubtedly confirm the structure of all synthetized compounds.

Table 3. ^{1}H *NMR data of compounds* ***1***, ***3***, ***5*** *and* ***7****.*

	ATI1 (1)	ATI3 (3)	ATI5 (5)	ATI7 (7)
Xanthone scaffold				
H-1	8.07 (*d*, *J*=9.0)	8.29 (*d*, *J*=3.0)	8.34 (*d*, *J*=3.0)	8.32 (*d*, *J*=3.0)
H-2	6.19 (*dd*, *J*=9.0, 3.0)	-	-	-
H-3	-	7.86 (*dd*, *J*=9.0, 3.0)	7.78 (*dd*, *J*=9.0, 3.0)	7.88 (*dd*, *J*=9.0, 3.0)
H-4	6.35 (*d*, *J*=3.0)	8.13 (*d*, *J*=9.0)	8.04 (*d*, *J*=9.0)	8.13 (*d*, *J*=9.0)
H-5	8.33 (*dd*, *J*=9.0, 3.0)	-	7.05 (*s*)	6.80 (*d*, *J*=3.0)
H-6	7.71 (*ddd*, *J*=9.0, 9.0, 3.0)	7.41 (*s*)	-	-
H-7	7.17 (*ddd*, *J*=9.0, 9.0, 3.0)	-	6.90 (*s*)	6.90 (*dd*, *J*=9.0, 3.0)
H-8	8.06 (*dd*, *J*=9.0, 3.0)	7.43 (*s*)	-	8.28 (*d*, *J*=9.0)
NH	7.99 (br *s*)	8.17 (br *s*)	8.21 (br *s*)	8.27 (br *s*)
Ar-CH_3	-	2.48 (*s*) **position C5**	2.81 (*s*) **position C8**	-
Ar-CH_3	-	2.45 (*s*) **position C7**	2.40 (*s*) **position C6**	-
Ar-OCH_3	-	-	-	3.90 (*s*) **position C6**
-CH_2O-	4.45 and 4.38 (2*d*, *J*=15.0)	-	-	-
Chiral moiety				
H-3'	8.73 (*d*, *J*=9.0)	8.36 (*d*, *J*=9.0)	8.31 (*d*, *J*=9.0)	8.31 (*d*, *J*=9.0)
H-5' and H-8'	7.44 and 6.96 (*dd*, *J*=9.0, 3.0)	7.98 and 7.27 (br *d*, *J*=9.0)	7.93 and 7.23 (br *d*, *J*=9.0)	7.94 and 7.23 (br *d*, *J*=9.0)
H-6' and H-7'	7.38 and 7.28 (*ddd*, *J*=9.0, 9.0, 3.0)	7.50 and 7.35 (*ddd*, *J*=9.0, 9.0, 3.0)	7.45 and 7.32 (*ddd*, *J*=9.0, 9.0, 3.0)	7.46 and 7.32 (*ddd*, *J*=9.0, 9.0, 3.0)
H-4'	7.83 (*d*, *J*=9.0)	7.29 (*d*, *J*=6.0)	7.29 (*d*, *J*=6.0)	7.23 (*d*, *J*=6.0)

4. Experimental

4.1. General Methods

Reagents and solvents were purchased from Sigma-Aldrich Co (St. Louis, Missouri, USA) and used without purification, apart from the XCars, which were previously synthetized [31, 32].

Solvent evaporation took place in a rotary evaporator under reduced pressure – Büchi rotative evaporator.

Reaction control and purification procedures were controlled by thin-layer chromatography (TLC) – Merck Silica gel 60 F_{254}– with appropriate mobile phases, and revealed by UV light at 245nm and 365 nm.

^{1}H NMR spectra were performed in the Department of Chemistry of the University of Aveiro, and were taken on Brücker DRX-300 spectrometer (300.13 MHz for ^{1}H), and in CEMUP, taken on a Brücker AVANCE III spectrometer (400.14 MHz for ^{1}H), using $CDCl_3$ as solvent for all samples.

IR spectra were obtained on an ATI Mattson Genesis Series FTIR spectrophotometer using the 188 OMNIC 8.3 software, in KBar microplates (cm^{-1}).

The optical rotations were recorded on a Polartronic Universal polarimeter (ADP 410 polarimeter).

The melting points were determined in a Köfler microscope.

4.2. Synthesis of compounds 1-8

In an oven-dried round-bottom flask, a suitable XCar (2 mmol) was dissolved in anhydrous THF (10 mL), followed by the addition of thionyl chloride (4 mmol), under nitrogen atmosphere. The mixture was heated to reflux and allowed to react for one hour. After then, the mixture was allowed to cool, a distillation head was installed, and the solvent was distilled. To the dry residue, anhydrous THF was added (5 mL) followed by a suitable chiral building block (1 mmol) dissolved in anhydrous THF (5 mL) under an ice water bath.

The mixture was left to react and gradually warm up to room temperature overnight. Afterwards, the organic solvent was evaporated under reduced pressure and CH_2Cl_2 was added (50 mL). The solution was washed with 1M HCl solution (3 x 50 mL), saturated $NaHCO_3$ solution (3 x 50 mL) and H_2O (3 x 50 mL), dried with anhydrous Na_2SO_4 and evaporated under reduced pressure, resulting in an oil. The oil was crystallized from CH_2Cl_2 and hexane. In some cases, a further crystallization from methanol was needed, affording compounds **1-8**, as solids of colours ranging from white to light brown. XCar that was not consumed in the reaction was recovered after precipitation from the basic fraction of the extraction by acidification with HCl and further filtration.

(R)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(2-((9-oxo-9H-xanthen-3-yl)oxy)acetamide) (1)

Yield (52%, very pale yellow solid). m.p.: 196-199°C (CH_2Cl_2:hexane); $[\alpha]_D^{29^{\circ}C}$ -133.3 (*c* = 0.3×10^{-3} gmL^{-1} in $CHCL_3$); IR ν_{max} (cm^{-1}) (KBr): **Table 1**. ^1H NMR (300.13 MHz, $CDCl_3$) δ: **Table 3**.

(S)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(2-((9-oxo-9H-xanthen-3-yl)oxy)acetamide) (2)

Yield (53%, very pale yellow solid). m.p.: 196-198°C (CH_2Cl_2:hexane); $[\alpha]_D^{29^{\circ}C}$ +133.3 (*c* = 0.3×10^{-3} gmL^{-1} in $CHCL_3$); IR ν_{max} (cm^{-1}) (KBr): data similar to **1** (enantiomeric pair), **Table 1**. ^1H NMR (300.13 MHz, $CDCl_3$) δ: data similar to **1** (enantiomeric pair), **Table 3**.

(R)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(5,7-dimethyl-9-oxo-9H-xanthene-2-carboxamide) (3)

Yield (not determined, light brown solid). m.p.: 238-241°C (MeOH; CH_2Cl_2:hexane); $[\alpha]_D^{29^{\circ}C}$ -166.7 (*c* = 0.3×10^{-3} gmL^{-1} in $CHCL_3$); IR ν_{max} (cm^{-1}) (KBr): **Table 1**. ^1H NMR (300.13 MHz, $CDCl_3$) δ: **Table 3**.

(S)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(5,7-dimethyl-9-oxo-9H-xanthene-2-carboxamide) (4)

Yield (not determined, light brown solid). m.p.: 238-240°C (MeOH; CH_2Cl_2:hexane); $[\alpha]_D^{29^{\circ}C}$ +166.7 (c = 0.3 × 10^{-3} gmL^{-1} in $CHCL_3$); IR ν_{max} (cm^{-1}) (KBr): data similar to **3** (enantiomeric pair), **Table 1**. ^1H NMR (300.13 MHz, $CDCl_3$) δ: data similar to **3** (enantiomeric pair), **Table 3**.

(R)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(6,8-dimethyl-9-oxo-9H-xanthene-2-carboxamide) (5)

Yield (not determined, pale brown solid). m.p.: 184-188°C (MeOH; CH_2Cl_2:hexane); [α] not determined; IR ν_{max} (cm^{-1}) (KBr): **Table 1**. ^1H NMR (400.14MHz, $CDCl_3$) δ: **Table 3**.

(S)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(6,8-dimethyl-9-oxo-9H-xanthene-2-carboxamide) (6)

Yield (not determined, pale brown solid). m.p.: 185-187°C (MeOH; CH_2Cl_2:hexane); [α] not determined; IR ν_{max} (cm^{-1}) (KBr): data similar to **5** (enantiomeric pair), **Table 1**. ^1H NMR (400.14MHz, $CDCl_3$) δ: data similar to **5** (enantiomeric pair), **Table 3**.

(R)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(6-methoxy-9-oxo-9H-xanthene-2-carboxamide) (7)

Yield (not determined, white solid). m.p.: 285-288°C (MeOH; CH_2Cl_2:hexane); $[\alpha]_D^{29^{\circ}C}$ -200.0 (c = 0.3 × 10^{-3} gmL^{-1} in $CHCL_3$); IR ν_{max} (cm^{-1}) (KBr): **Table 1**. ^1H NMR (400.14MHz, $CDCl_3$) δ: **Table 3**.

(S)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(6-methoxy-9-oxo-9H-xanthene-2-carboxamide) (8)

Yield (88%, white solid). m.p.: 284-288°C (MeOH; CH_2Cl_2:hexane); $[\alpha]_D^{29^{\circ}C}$ +200.0 (c = 0.3 × 10^{-3} gmL^{-1} in $CHCL_3$); IR ν_{max} (cm^{-1}) (KBr): data similar to **7** (enantiomeric pair), **Table 1**. ^1H NMR (400.14MHz, $CDCl_3$) δ: data similar to **7** (enantiomeric pair), **Table 3**.

4.3. Synthesis of compounds 15 and 16

An oven-dried 50-mL reactional balloon, equipped with a magnetic stirrer and under nitrogen atmosphere, was loaded with solid NaOt-Bu (4 mmol) and cooled in an ice water bath. A solution of 2-(diethylamino)ethanethiol HCl (2 mmol) dissolved in DMF (10 mL) was added via syringe dropwise. After 5 minutes, the ice water bath was removed, and the resulting suspension was allowed to warm to room temperature. After 15 min, a suitable compound (**7 o**r **8**, 1 mmol), dissolved in DMF was added in one portion, and the mixture were heated to reflux for two hours. After the mixture has cooled to room temperature, the balloon was placed in an ice water bath. HCl (5 M) was added dropwise to bring the pH to 1, then water was added (30 mL). The aqueous phase was extracted with diethyl ether (3 x 50 mL) and with 5% NaOH (3 x 50 mL). The aqueous phase was acidified with 5M HCl and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with water (3 x 100 mL), saturated brine (100 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was crystallized from CH_2Cl_2/hexane to afford compounds **15** and **16**.

(R)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(6-hydroxy-9-oxo-9H-xanthene-2-carboxamide) (15)

Yield (not determined, light yellow solid). IR ν_{max} (cm^{-1}) (KBr): **Table 2**. NMR in progress

(S)-N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(6-hydroxy-9-oxo-9H-xanthene-2-carboxamide) (16)

Yield (not determined). IR ν_{max} (cm^{-1}) (KBr): in progress. NMR in progress.

5. Conclusions and Future Work

As a result of this work, 10 new atropisomers (ATIs) based on xanthone derivatives (XDs) were successfully synthesized. The synthetic strategy involved first the preparation of acyl chloride of carboxyxanthone derivatives (XCars) followed by coupling reactions between the acyl chloride groups with amine groups of commercially available chiral building blocks.

The direct coupling between the XCars and chiral amines were attempted by using two different reagents, namely TBTU and COMU. However, the feasibility of these reaction proved to be unlikely, possibly due to steric hindrance.

The structure of 8 new atropisomers (compounds **1-8**) was successfully elucidated by ^{1}H NMR, and IR analysis. The presence of the phenol groups in compounds **15** and **16** was confirmed by IR data indicating the existence of NH and C=O bonds of amide groups, so we can assume that both compounds were also successfully synthesized. Nevertheless, ^{13}C NMR and HRMS are needed to undoubtedly confirm the structure of all synthetized compounds.

Although the specific rotation values obtained for each enantiomeric pair indicated that racemization did not occur during their synthesis and purification, in the future, it would be interesting to evaluate the enantiomeric purity of the synthetized compounds by liquid chromatography (LC) using chiral stationary phases (CSPs).

Considering that upon heating, ATIs may have enough energy to surpass the rotational energy barrier and racemize, another interesting study would be to analyse the thermal stability of the synthetized ATIs by chiral LC following the change in enantiomeric ratio at different temperatures.

Finally, the biological activities of all synthetized ATIs will be performed. The enantioselectivity in biological screening assays will be explored.

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