UNIVERSITÀ
DEGLI STUDI
FIRENZE

DOTTORATO DI RICERCA IN
Scienze Chimiche

CICLO XXXI

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Synthesis and characterization of new glycoconjugated anthraquinone derivatives for application in textile and leather dyeing industry

Settore Scientifico Disciplinare *CHIM*/06

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Anni 2015/2018

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Chapter 1

Introduction

1.1 The world of dyes

The word "colour" defines a subjective perception of physical phenomenons that happen at the eye level followed by a an elaboration made by the brain through complex biochemical processes. Signals detected by human eye are the electromagnetic radiations in the so-called *visible region* of the light spectrum, between about 370 and 750 nm (Figure 1.1).

Figure 1.1: The incident light pass throw a prism making possible to appreciate its spectrum. © *Science media group*

Our system of vision can elaborate pure colours defined by single-wavelenght radiations, but it can't distinguish between two or more electromagnetic radiations arriving at the same time. The beauty behind this limitation is the possibility to appreciate all the shades of coloration we are used to. Pink and brown are two examples of mixed colours, because it's impossible to reproduce them with a single photon. It's fundamental to distinguish between two different processes that make us able to appreciate colour. The first one is the emission by a system of one or more electromagnetic radiations at a *fixed* energy by a light source. In this case our system of vision detects the waves and elaborates the signals that come directly from the source. Typical examples are the fluorescent lightbulbs or the lasers. In our scope, the main difference between the two sources is the spectral widht covered. Fluorescent lightbulbs light is expressed as the combination of different wavelenghts, while lasers represent a single electronic transition. The large amount of colored objects we can appreciate around us doesn't follow this mechanism. They aren't light-sources. In most cases the coloration of the object is due to the partial absorption of an electromagnetic radiation, coming for example from the sun. When the electromagnetic waves in the visible region reach an object, four situation can be distinguished. [1] If the light is totally reflected in a diffusive way the object appears white. If the solid absorbs all the incoming light, it appears black. A partial absorption over the entire visible spectrum gives all the shades of grey it's possible to observe. White, Black and Grey are the so-called *achromatic* colours. The fourth situation happens when only a part of the incoming radiations is absorbed. In this case the *chromic* colours can be distinguished. Chromic colours are the result of the subtraction of one or more regions from the visible spectrum. It is possible to rationalize the colours observed in intervals. The absorption in the shorten wavelenght regions reflectes a yellow coloration. The other ranges are 430-480 nm, 480-550 nm, 550-600 nm and 600-750 nm, corresponding to orange, red, violet and blue. Other chromic colours can be obtained with the combination of two or more absorptions in these intervals. Green, for example, is the combination of two absorptions lying in the intervals 400-450 nm and 580-750 nm (Figure 1.2). Physical data related to the coloration are represented by the absorption profiles, that can be collected by simple Visible spectrophotometers. The *quality* of a colour isn't reflected only by its absorption maximum. Another important parameter to consider is the bandwidth of the absorption peaks. A smaller width is associate to a more

brillant hue, together with an absorption profile with a steep slope.

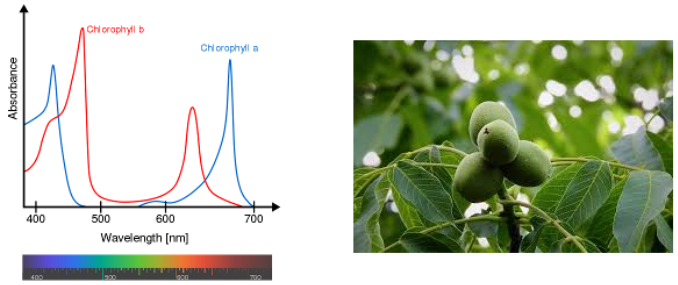


Figure 1.2: Absorption spectrum of chlorofill (**a**) and its expression in sleeves (**b**). The two peaks in the spectra correspond to absorbance in yellow and red-blue region. The colour observed is green.

Even if the perception is widely different from species to species, the recognition of colour play a key role for the largest part of animals. Courting, recognition of danger and safe situations, protection from predators are some of the activities related to colour expression and recognition. [2] These natural-selected uses of colour remained also in human conscious habits, but our ancestor's ability in manufactoring allowed the production of pigments to reproduce nature around them in terms of painting and objects decoration in general. Ancient cave paintings all around the world demonstrates that pigment manufacturing has been developed since early Paleolithic era, and the reproduction of animals and hunting scenes can be considered the first example of human's desires and believes description. Art, as we are used to name it. Dye manufacturing grew in parallel to human evolution. Even if the use of inorganic mineral pigments has been the basis for painting until now (TiO_2 is the most used white chromophore in housewall painting), they aren't used nowdays to dye textiles. Anyway the first evidence of dyed garments in western civilizations belong to the Neolitic period. There are many exmples of linen dyed with red iron oxide during the First Dinasty of the Ancient Egypt, around 3000 years BC. Clothings were

preserved due to the favorable conditions, but it can't be excluded that the dyeing ability was more ancient. Also in China there was knowledge about textile dyeing during the same period using colours extracted from wood and plants. Anyway the key point for the ancient dyeing industry was the discover of tyrian purple. First manufacturing site was dated around 1500 years BC in the city of Tyre, a Phoenician town in the south of Lebanon.

Figure 1.3: An example of *Murex brandaris*, one of the shelfish containing *Tyrian Purple* precursors

The dye production consists in the extraction of the chromophore from shellfish. *Murex trunculus*, *Purpura lapillus*, *Helix ianthina*, and especially the *Murex brandaris* were the most used ones, giving different hues of purple depending on what is the rate of the different purple chromophores contained. The process used by Phenicians consisted in the extraction of the dye from the glands of putrefied crushed shellfish. It is estimated that for the production of 1 gram of dyestuff 10000 shelfish were necessary. During the Roman Empire period it became a *staus-symbol* due to its difficulties to reach it and the costs associated to the production. Caesar was the first general who wore an all-purple *toga*, and from that moment it became the colour of the emperor. The imperial family, magistrates and some elites were permitted to wear the *toga praetexta* which had a purple border and generals coming to Rome after a glorious war used to parade wearing the *toga picta* for their triumph (Figure 1.4).

During the reign of Alexander Severus (222-235 AD) the production of silk dyed with Tyrian Purple became a monopoly, and this demonstrates once

a b

Figure 1.4: *Toga pratexta* (**a**) and *Toga picta* (**b**)

more the importance of this chromophore in Ancient World. Tyrian Purple is withouth any doubt the first example of a large-scale dye production. Around Mediterranean sea many important sites arose. North Africa and southern Italy became importan commercial *hotspots* also for this reason. The popularity of purple in Ancient Greek and Roman culture was strictly connected to the difficulties to find it. Looking for purple hues from different sources led to discover an extraction method from lichenes of the *Umbilicaria* genus. Ancient Greeks already knew this possibility. We could tag it as the research of a new dye for *low-cost* alternative in *fast-fashion* garments.

Another important dye used until now is Indigo. There are evidences that the use of Indigo grew in a parallel way both in Eurasia and in South America. The first uses of indigo dyed textiles were found in the northern cost of Peru near the city of Trujillo [3]. From the study of textile findings from the archelogical site of Huaca Prieta, it was demonstated that Moches handled indigo extraction from the *Indigofera* since 4000 years BC. The first evidence in western civilization was found in the Ancient Egypt, but it is 1500 years more

recent. Anyway the technology of extraction was imported from India (as the name *Indigo* suggests) and China. It's interesting to note that the chemical structures of Tyrian Purple and Indingo are very similar, beeing purple dye a bromo-substituted Indigo molecule (Figure 1.5).

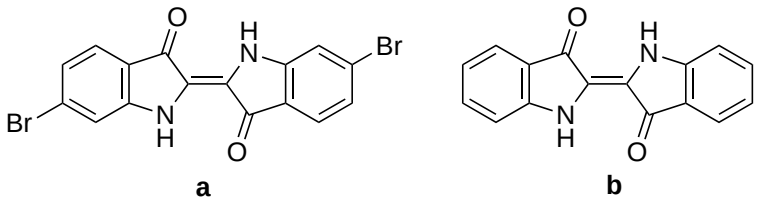


Figure 1.5: Chemical structures of the most abundand chromophore prsent in *Tyrian Purple* (**a**) and chemical structure of *Idigo* (**b**)

Methods for the production of textile dyes didn't change during Middle Age. Other dyes became popular during different periods, from *Brazil wood* to *Cochineal*, an anthraquinone red chromophore linked to a glucose unit extracted from insects of the *Dactilophus* genus (Figure 1.6).

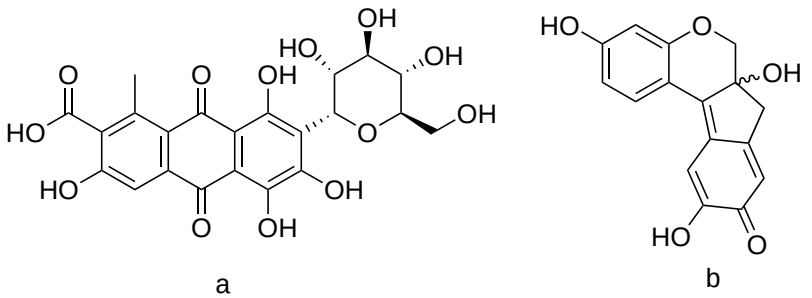


Figure 1.6: Chemical structure of the chromophores *Cochineal* or *Carminic acid* (**a**) and *Brazilian Wood* (**b**)

Dyes supply remained more or less the same until the middle of XIX century. Every colour was the result of an extraction from natural sources. High costs and the large amount of waste were the main problem for extraction processes. But plants, insects, barks and minerals were the same sources for new discovered chromphore molecules until XIX century when the 10000 shellfish to obtain 1

gram of *Tyrian Purple* and the 150000 insects to produce 1 kilogram of *Kermes* have rapidly become a distant memory after 1856 Easter Break. In that period William Perkin (*sir* Perkin, fifty years later), a 18-year old chemist working at the Royal College of Chemistry, was looking for a synthetic method for quinine, an antimalarial drug. He was sure that he could obtain it from the condensation of aniline, toluidine or xilidines[1]. Luckly he noted that in one of his tries he had obtained a red powder soluble in ethanol. He immediately patented the process because the *Mauveine* (as he called the dye later on) he got was perfect to dye silk. As in ancient times *Tyrian Purple* was the ultimate royal dye, in Modern Era Perkin's dye started to become very popular after the Queen Victoria wore a *Mauveine* dyed dress for her daughter's marriage. This moment can be considered the born of the modern dyeing industry. Natural dyes were gradually replaced by new syntehtic ones.

1.2 Textile market

Clothing industry is one of the most important employment sectors all over the world. It is estimated that fashion sector contributes for about 4% to the entire GDP (Gross Domestic Product) of Italy, and it increased about 20% from 2006 to 2016 [4]. Numbers are impressive, and if we have a look to the global fashion market, it is clear how important fashion is for world economy. Apparel, clothing and textile markets have a value of 3000 billion dollars (2% of world GDP) and directly employs about 80 million people all over the world. [5] It is estimated that in the USA the mean expenditure for clothes is 800$ *per-capita*. [6] The importance of apparel industry has become more pronounced since in the last years the demanding of textile fibres increased due to the growth of *fast fashion* market. [7] The higher demand for natural textile fibers at lower prices was reflected in an intense competition among suppliers. Cotton production is historically based in China, India, USA, Pakistan, Brazil and Uzbekistan and sub-Saharan Africa, which cover about the 85% of the market. As public subsides ensure the American competitivity, in the rest of the world it is secured by an effective reduction of production costs, even if it often means low salaries and poor working conditions and a very low attention on environmental aspect. Uzbekistan economy, for example, is dependent from cotton production and up to 50% of it is ensured by government managed child-

[1] 2,4-dimethylaniline or 2,6-dimethylaniline

labour. Fifteen and sixteen years old students are forced to work two months each year in the cotton harvest under teachers' supervision. Thanks to the work made by NGOs, it seems that in the following years this brutal habit will disappear. [8] In Bangladesh, which is another textile-dependent nation, it's normal to hear about people working and living in the same place without any particular side activities instead of working. This is reflected in a twelve hours a day, seven days a week working schedule (even if it is formally illegal). Man-made textile fibers appear the best option to overcome these natural fibers production problems, but the lower quality of the garments and the consumer's demand put the breaks on cotton replacement.

1.3 Dyes classification

The importance of dyeing for textile industry and the necessity to use them in the most direct way by dyers and colorists have developed a series of classification only related to the technical aspects of the dyeing processes during past yers. From this pool of tentatives to rationalize dyes properties, only one database has emerged until now. It is the Colour Index International, an annual pubblication mantained by the english Society of Dyers and Colourists (SDC) and by the American Association of Textile Chemists and Colorists (AATCC). [9] The database covers about 27000 products both dyes or pigments grouped in two main ways. It is possible to divide them from a chemical point of view or from an applicative one. The first one is the Colour Index Constitution Number, a five-digit number that group chemical related compounds. It takes into consideration the chemical structure of the molecule. This classification divides dye molecules depending on the chromophore group responsible for the electronic transition lying in the visible region. The double bond N=N defines the azoic chromophores, the anthracen-9,10-dione unit and the (E)-1,2-diphenylethene unit the anthraquinone and the stylbene dyes. Other relevant structures are the triarylmethine derivatives, the diketopyrrolopyrrole unit and the indigoid dyes (Figure 1.7.) [10]

Even if a large number of dyes belonging to a wide number of categories exists, the most used in tinctorial industry are basicaly three. Azo dyes, anthraquinones and Indigo are the most used both for hystorical reasons and both for their good fastness propirieties. In table 1.1 some of the intervals describing different classes of dyes in the Colour Index Classification Number are

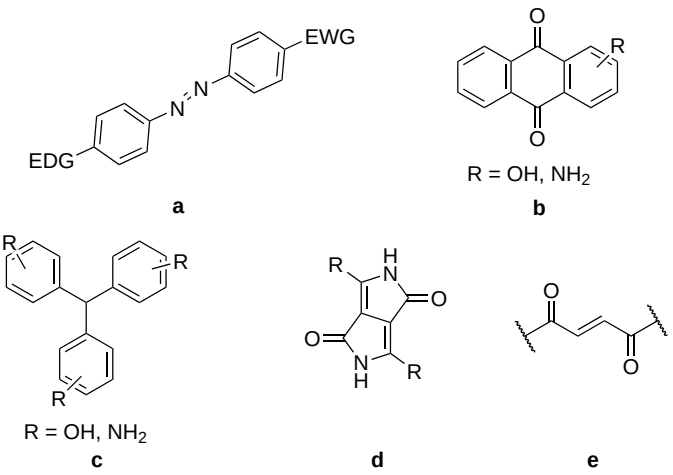


Figure 1.7: Azoic (**a**), anthraquinone (**b**), triarylmethine (**c**), diketopyrrolopyrrole(**d**), indigoid (**e**) chrmophore units

highlighted.

Class	Interval	Class	Interval
Azo dyes	11000–29999	Antraquinones	58000–72999
Stylbene	40000–40799	Indigoids	73000–73999
Triarylmethine	42000–44999	Inorganic pigments	77000–77999

Table 1.1: Principal chromophore classes following the Colour Index Constitution Number

The chemical classification is useful only as an indication of the chromophore structures it is possible to find in the market. This kind of organization doesn't contain any information about the techncal aspects related to dyeing processes. For this reason the most known classification method the Colour Index devoleped is the Identificative Name. Under this definition dyes are grouped for their applicative use in differnet kind of textiles indipendently from the chromophore group. Dyes are indeed known with a trivial name based on this classification. They are grouped in Acid, Basic, Direct, Vat and Disperse dyes. Acid dyes contain one or more sulphonic groups (generally as sodium salts) that

allow dye solubilization. The negative charges play a key role in the interaction with proteic substrates such as wool, silk and leather containg quaternary nitrogen atoms positively charged. Basic Dyes also contain a positive quaternary atom. They are water soluble and are mostly used in the synthetic fibers dyeing and for special uses such for hair dyeing. Direct Dyes are aplied to cellulosic fibers such as yarn and linen. The name is related to their dyeing ability without mordant additives (i.e. metal ions that coordinate both the fiber and the chromophore to fix the dye). Nowadays the mordant technique is considered obsolete, and almost every textile dye is apllied in a direct way, but the historical name wasn't changed. Direct dyes have chemically related structure to acid dyes. They often contain a negative charge to allow water solubility. Vat dyes are water insoluble pigments. They are applied in their reduced (*leuco*) water soluble form and then oxidised once the garment is exposed to air. The most used dye that belong to this class is Indigo. Disperse dyes are commonly used in the polyester and acetate fibers dyeing. They don't have any charged group because they have to interact with neutral fibers, and this is a limitation for the solubility in water, the only medium used in tinctorial process.

Commercial name of tinctorial dyesare all known known following this classification. The name of the category they belong to is followed by their hue and a serial number (Acid Yellow 15, Disperse Violet 17, Vat Blue 1 and so on).

1.4 Dyeing industry

The application of dyes into textiles requires a series of technical aspects that change passig from one textile to another, from a dye class to another and some of them changed over the years following both economical and environmental aspects. The Tyrian Purple itself can't be applied to silk or cotton simply dissolving it in water and waiting the coloration to occur. It required the use of mordants, which are often metal complexes that coordinate both the fiber and the dye. If the use of mordant is avoided, the coloration is less effective or in some cases it can't be performed. This was the most used method until the synthesis of Congo Red was performed in 1883. For this reason its commercial name is Direct Red 1. The application of Indigo requires an *in situ* reduction of blue indigo to obtain the leuco form, which is water soluble and transparent. Once the garment is air-dried, the dye oxideses and the blue coloration is restored. This method was also used for Tyrian purple, and the name Vat comes

from the vessels used for the dyebath. The application of acid and basic dyes require only pH adjustments with variable temperature, but they can all be done at atmospheric pressure. The coloration of man-made textile fibres has opened the distribution of the so called Disperse Dyes. Even if they were first synthesized for the coloration of acetate fibres derived from cellulosic waste, they have become so important since it was found that they were the best option in polyester dyeing, even if High Temperature High Pressure (HTHP) procedures are necessary. As alredy pointed out in section 1.3 Disperse dyes are mostly unsoluble in water, even at high temperatures the dyeing process requires. For this reason it's necessary to use a large amount of chemical additives to ensure an homogeneous coloration of the textile. Commercial available disperse dyes formulation can have up to 70% of chemicals others from the chromophore unit. These added chemicals can be distinguished in two groups: dispersing agents and carriers. Carriers are often phenolic molecules that thanks to the π-stacking interactions help the chromophore to get into the polyester fibers. Dispersing agents are necessary to destroy big chromophore aggregates forming an homogeneous dispersion in hot dyebaths. The quantity of dispersing agents is related to the ability of the dye to form stable aggregates through hydrophobic effect. The most the dye belong as a pigment, the largest is the amount of dispersing agent needed. These additives doesn't play an active role in the coloration of the garments, but they are necessary to make the dyebath as useful as possible. COD and BOD demand for exausted dyebath have to take into accont the presence of these chemicals, so costs for wastewater disposal are larger respect to the coloration performed using other kind of dyes, for example cotton and wool which use water soluble dyes and lower temperatures and pressions. In the whole 20^{th} century a lot of reaserch was made to improve dyeing conditions for synthetic fibres. The main efforts were made in the dispersing agents composition. Nowadays a lot of patented formulations are present in the market, and suppliers tend to sell ready-to-use disperse dyes formulation without any information about the composition. The introduction of processes to limit the use of dispersing agents and carriers is one of the goal for polyester dyeing. The main alternatives are represented by the use of disperse dyes containing temporarely solubilising groups [11] and microencapsulated dyes [12]. The most promising method is the use of water soluble dyes containing a β-sulphatoethyl-sulphonyl groups that can be hydrolized in solution to obtain unsoluble chromophores to incorporate in polyester fibers. The problems related to the microincapsu-

lation methods lye in the complete isolation of microcapsules from the exaust dybath and the low diffusion of the dye into the fibre, even if in the last years the system was improved to separate microcapsules by a simple filtration [13]. Media different from water were studied to solubilize disperse dyes, but only the supercritical CO_2 showed good results, but until now there were no efforts to scale up this process at an industrial level [14].

1.5 Glycoconjugated naturalised dyes

In the past years Bianchini *et al.* [15] developed a method to eliminate chemical additives from the dyeing process of polyesther called *Naturalization*. It consists of a glycoconjugation between an unsoluble disperse dye and a sugar unit. The method was named *naturalization* because it takes inspiration from nature, where there are several examples of glycoconjugated water soluble dyes (Figure 1.8).

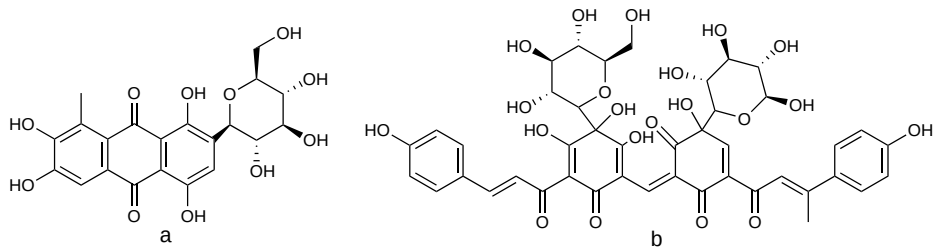


Figure 1.8: Chemical structure of the chromophores *Cochineal* (**a**) and *Cartamin* (**b**)

The main differences from the natural occurring glycoconjugation are two. First of all, natural compounds are all linked to glucose. The first tentatives to solubilize disperse dyes were performed using glucose, even if lactose was at the end chosen both for the better results in the solubilization and both for economical and environmental aspects. Lactose is indeed a byproduct of the diary industry made from whey concentration. The choice of a waste product was also a tentative to give lactose an added value and to develop a more eco-friendly dye. The second difference from the natural glycoconjugated dyes is the way the sugar is linked to the chromophore. In nature the synthesis of chrmophores happens at the biological level thanks to the very powerful syn-

thetic ability of enzymatic transformations. Sugars are covalently linked to the chromophore structure itself. In the case of *Carminic acid* (Figure 1.8) glucose residue is linked in position 2 of the anthraquinone structure, while in the case of *Cartamin* it seems two sugar units had performed a nucleophilic attack on two of the carbonyl groups of the chromophore. On the other hand naturalization process uses two spacers because the idea was to develop a general system suitable for the largest amount of dyes as possible (Figure 1.10). The detailed chemical procedure for the naturalization is highlighted in section 2.3

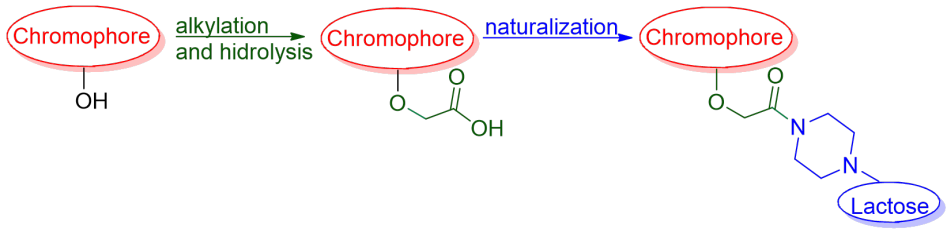


Figure 1.9: A scheme of the main steps of the naturalization process

Since many of the chromophores ready available have an hydroxy group directly bound to the chromophore, it was exploited to introduce a carboxylic moiety using ethylbromoacetate as alkylating agent. On the other side lactose was modified to introduce a piperazine unit. The coupling between the two modified products gives the so called *Naturalized Dye*. For their classification it was decided to reproduce the Colour Index Identificative Name method. As they all derive from commercial avilable disperse dyes, it was decided to replace the word *Disperse* with the word *Naturalized*, leaving both the original hue and the progressive number unchanged. For example the chromophore Disperse Violet 17 (DV17) had become the Naturalized Violet 17 (NV17), even if the hydroxy group alkylation performs a change from violet to dark red.

Piperazine was chosen as the spacer between the sugar unit and the carboxylic acid derivative of the chromophore. It was found that the advantage in the use of piperazine among other amines lies in the presence of a nitrogen atom not involved in the amide bond. The positive charge improves water solubility, but it doesn't affect dyeing proprieties. The naturalised dyes, on the contrary, showed enhanced proprieties respect to the disperse dyes they derive from. A good dyeing ability for leather and hair was noted, also for a trichromy approach in the coloration. [16]

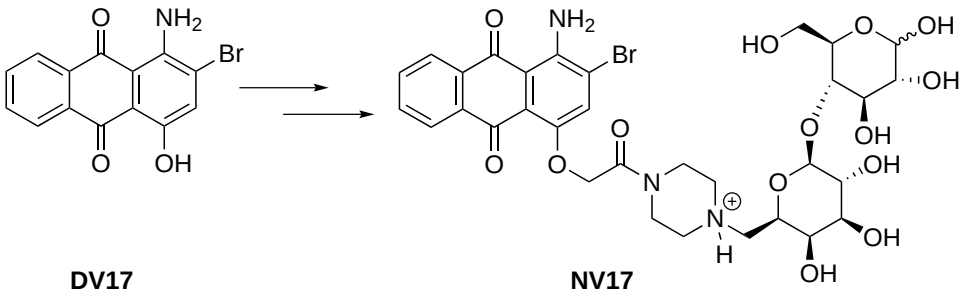


Figure 1.10: Naturalization of Disperse Violet 17

In summary, two building blocks are needed for the synthesis of naturalised dyes. A chromophore containing a carboxylic acid moiety and a piperazine lactose unit.

Chapter 2

Synthesys of new glycoconjugated anthraquinone dyes

2.1 New naturalized dyes

The naturalization method was developed to replace Disperse Dyes in the coloration of polyester fibers. The most used chromophores present at the moment in Disperse Dyes formulations belong to two main classes. Azo-dyes and anthraquinones. (Figure 2.1) The first ones are chemical compounds containing an azo group (-N=N-) linked to aromatic or heteroaromatic units. They can be named mono-, bis- or tris- depending on the number of azo groups present in the molecule.

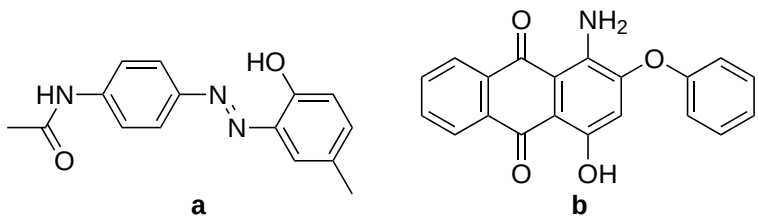
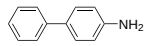
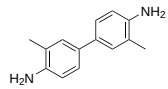
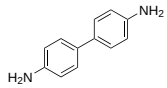
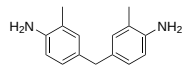
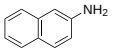
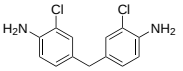
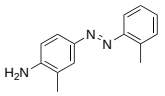
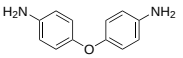
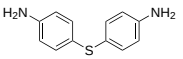


Figure 2.1: Two examples of Disperse Dyes, belonging to the two main classes for polyester dyeing. CI Disperse Yellow 3 (**a**) is sold with a 30% dye content while CI Disperse Red 60 (**b**) can be found with a purity of 95%

Synthesys of this first class of chromophores is essentially related to the diazotization of aromatic amines, followed by a nucleophilic attack performed on the diazonium salt. [1] Using this procedure it is theorically possible to produce azo-dyes that cover all the regions in visible spectra. The high values of molar extinction coefficient, the very good fastness properties and the simple synthetic procedure are the key point for thieir popularity in tinctorial industry. Up to 60% of disperse dyes market is covered by this chemical compounds, while anthraquinone dyes cover about 30% due to their better behaviour for red and blue colorations. Even if azo dyes are the most used chromophores at the moment, it is well known they can undergo reduction of N-N double bond catalyzed by clothing everyday use. Human skin bacteria in vitro were proved to degradate azo dyes at pH values corresponding to common human skin conditions. [17,18] The same happens if they are exposed to hydroxyl radicals for long time. [19] Even if azo dyes can't be absorbed by human skin, aromatic amines formed after degradation can get into the organism. [20] If the chromophore degradation produce carcinogenic aromatic anilines, the dye has to be considered as a carginogenic molecule. In 2007, the European Union published the REACH (Registration, Evaluation and Authorisation of CHemicals), a regulation containing a series of legislation to control production, import and commercialization of chemicals. [21] The aim of the document was to limit the impact of chemical substances on the environment and on human health. In appendixes 8-10 of the annex XVII a list of aromatic amines are cited as carcinogenic (Table 2.1), so every chromophore that can release any of these anilines was immediately banned. Since carcinogenity is demonstrated through long time-consuming experiments on targeted molecules, not every azo dye was studied.

Aniline	CAS	Aniline	CAS
	92-67-1		119-93-7
	92-87-5		838-88-0
	95-69-2		120-71-8

	91-59-8		101-14-4
	97-56-3		101-80-4
	99-55-8		139-65-1
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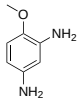
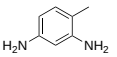
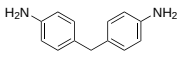
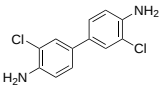
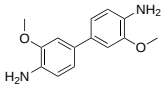
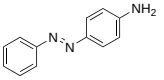
	615-05-4		95-80-7
	101-77-9		137-17-7
	91-94-1		90-04-0
	119-90-4		60-09-3

Table 2.1: List of carcinogenic anilines banned by the REACH

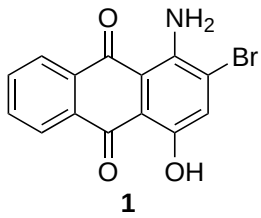
A resonable concern about the danger of azo dyes and their degradation product arose in the past years. Totally *aniline-free* garments production factories were the answer to the request made by a small but motivated number of consumers. As our work is about the reduction of environmental impact of disperse dyes, it was chosen to try to avoid the use of azo dyes from glycoconjugated dyes palette. For this reason research on new naturalised dyes was focused on anthraquinone derivatives. Comparing them with azo dyes, the most important difference lies in their molar extintion coefficient. The value is about the half of common used azo dyes, so it affects the load of dye necessary to obtain the same effect on garments. Anthraquinone are valuable compounds used also in other fields. Differently substituted anthraquinones have been examined for the development of organic light emitting diodes, [22] molecular electronic devices, [23] selective anion sensors, [24,25] and Dye-Sensitized Solar Cells (DSSCs). [26] There are many synthetic methods reported for an-

thraquinone units. The most used is a double Friedel-Crafts acylation on benzene derivatives using phtalyc anhydride. Alternative routes are based on Diels-Alder cycloaddition on naphtoquinones, but the products are obtained in poor yield. Anyway condensation methods common used for massive productions require harsh conditions often described in patented processes. An optimization of reaction conditions is often required to control the substitution degree of auxochrome groups since amino (often obtained after nitro group reduction processes) and hydroxy group are the most used substituents to tune the absorption profile of anthraquinone dyes. The impossibility to reproduce harsh reaction conditions in laboratory and the difficulties found to obtain useful informations from patented methods drove us to the modification of commercial available disperse anhraquinone dyes to introduce new shades of colour in naturalised dyes palette. The modification of anthraquinone core isn't simple, but it is well known that the dicarbonyl moiety of anthraquinones is accomplished by Friedel-Crafts acylation, [27–30] but there are also some reports involving Diels-Alder cycloadditions. [31,32] As the tricyclic structure is assembled, further elaboration may regard the carbonyls, [33–36] the introduction of halogens [37,38] and other substituents via either C-heteroatom [39–41] or C-C bond formation, [42,43] quite often requiring transition metal catalysis. [44–50]

Commercialization of Disperse Dyes chromophores is strictly connected to dyeing industry, that requires only ready-to-use formulations. It is often necessary to extract chromophores from the mixture composed of dispersing agents and carriers that can be up to 70% in weight. CI Disperse Blue 27, CI Disperse Yellow 3 and CI Disperse Red 13 are typical examples of prepared formulations sold with a dye content only up to 50 %. Since the extraction of chromophores from dyeing powders is long time consuming and requires a large amount of auxiliary chemicals, it was decided to make our first modifications on disperse dyes it was possible to find as pure chromophores. It is in this perspective that it was decided to work on the commercial available CI Disperse Violet 17[1] (Figure 2.2).

This molecule contains two fundamental functional groups for our puroposes. The hydroxy group is the attacching point for the glycoconjugation process. Bromine in position 2 gives the chance to introduce aromatic units through Palladium catalysed cross-coupling reactions. This strategy gives the possibility to extend conjugation of π electrons of the chromophore unit lower-

[1] 1-amino-2-bromo-7-hydroxyanthracen-9,10-dione



1

Figure 2.2: CI Disperse Violet 17

ing the difference between energy levels that are responsible for the absorption in the visible region. In addition, even if some modification strategies of the anthraquinone unit were reported above, none of them is a tentative to extend the conjugation of the molecule and in the literature only one example of Palladium catalyzed cross coupling reaction was found involving a Disperse Violet 17 derivative. [51]

2.2 Synthesis of new dyes for tinctorial use

2.2.1 Suzuki

CI Disperse Violet 17 is one of the poor examples of disperse dye that can be purchased as pure chromophore. The Bromine atom at position 2 and the hydroxy group at position 4 are two fundamental charachteristics for naturalization process. Hydroxy group is the connection point to introduce the piperazinyl-lactose unit, while bromine suggested it was possible to introduce aryl substituents through Palladium Catalysed Cross-Coupling reactions (Figure 2.3). The first part of this project was the tentative to apply the Suzuki-Miyaura reaction on Disperse Violet 17 (Figure 2.3).

A procedure on bromoanthraquinones containing two auxochrome groups wasn't found in the literature, so the starting point for the optimization of a synthetic procedure for DV17 was a method developed by Thiemann *et al* [52] on anthraquinones substitued with bromine atoms in different positions to obtain mono- or poli-substituted phenylanthraquinones. Anyway the different approaches used for the modification of Disperse Violet 17 didn't produce any result, even if there are a lot of examples in the literature involving both bromophenols and anilines. [53,54] In table 2.2 a summary of the different reaction

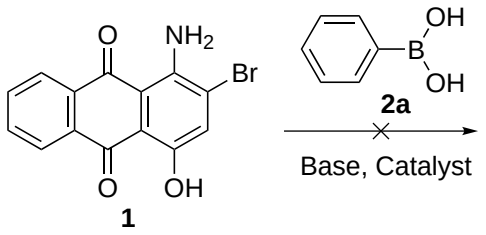


Figure 2.3: The Suzuki reaction on CI DisperseViolet 17 couldn't be performed

conditions performed to derivatise the starting material **1** are presented.

Base	Solvent	Catalyst	Time (h)	Product
K_2CO_3	THF[a]	$Pd(OAc)_2$	18	-
KOH	THF/H_2O 4:1[a]	$Pd(OAc)_2$	18	-
NaOAc	THF/H_2O 4:1[a]	$Pd(OAc)_2$	18	-
KOH	THF/H_2O 4:1[a]	Pd(dba)	18	-

[a]: reflux

Table 2.2: Different reaction conditions for the Suzuki-Miyaura cross-coupling reaction on CI Disperse Violet 17

Every mothod studied to obtain the desired product didn't produce any result. It is well known that the best couple of reagents for Suzuki-Miyaura rection is represented by an electro-deficient bromoaryl derivative and an electron-rich arylboronic acid. The anthraquinone derivative CI Disperse Violet 17 is indeed a electronpoor bromoaryl derivative due to the two carbonyl groups that attract electron density for the extended conjugation over the molecule. The main problem seems to be the hydroxy group, that in the strong basic conditions required to activate the boronic acid can be deprotonated changing the electron density on the aromatic unit. If electron density increases, the oxidative addtion of Pd in the C-Br bond becomes more difficult. These are only hypothesis we tried to think of, but we didn't perform any other tries because our scope was the synthesis of new naturalised derivatives. As the first step to perform the glycoconjugation is the alkylation of the hydroxy unit, it was decided to work on the alkyated derivative for two reasons: it is a key intermediate for naturalisation and the alkylation prevents an eventual deprotonation. It is also well known that alkylation of hydroxy groups directly bound to the aromatic unit changes absorption spectrum of the dye.

A blue shift of the absorption maximum is always detected, so the addition of aromatic gruops at position 2 of Disperse Violet 17 is a tentative to restore the original coloration that is lost after the alkylation. In Figure 2.4 the alkylation and the hydrolysis steps are described. The only problem it was found was the recovering of a small amount of the starting material , so it was necessary to purify the synthesized batch. In every case the purification was performed because it was necessary to obtain pure molecules for every step to charachterize every new product. In an eventual industrial process the small amount of starting material **1** can be eliminated after the final step of the glycoconjugation because it is absolutely water unsoluble.

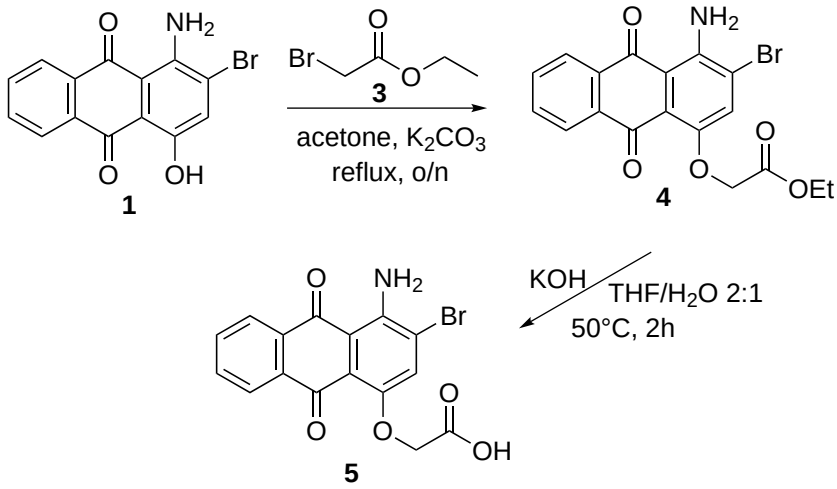


Figure 2.4: The first two steps in naturalization: alkylation of disperse dye and the hydrolisis

First of all, the compound we took in consideration was the first intermediate, the ester **4**. Anyway only an attempt was performed on this substrate because it was seen that the basic acqueos conditions required for the Suzuki-Miyaura reaction gave us the coupling product itself in very low yield. Even if the reagent completely disappeard, the product we found in the highest quantity was the coupling product of the carboxylic acid derivative **5**. It was a consequence of the *in loco* hydrolysis performed on the ethyl ester. Suzuki-Miyaura process was then applied only on the carboxylic acid derivative **5**. The opti-

mization to obtain the coupling product starting from the ester derivative was abandoned even because a subproduct of the process is EtOH, that could be involved in a C-O cupling as in a Ullman-like reactivity. [55]

To perform reactions on Disperse Violet 17 derivative **5** it's important to keep in mind the poor solubility of this anthraquinone derivative in common organic solvents. In more general terms, two critical point were to take into account in the modification of anthraquinone chromophores. The first one is their insolubility in common organic media, both protic and non polar ones. It was previously checked that the starting material **5** is essentialy insoluble in H_2O, Methanol, Ethanol, Dichloromethane and Etyl Acetate. The same happens if the chromophore is dissolved in Petroleum Ether and related aliphatic solvents (such as pentane or exane). Polar aprotic solvents such as DMSO and DMF are absolutely the best options both at low and high temperatures, while in THF, DMA, and some aromatic solvents (benzene, toluene and pyridine) the starting material become soluble only when the reaction mixture is heated over 60 °C. THF was chosen as the main solvent taking into account four factors: price, toxicity, availability in the laboratory and the possibility to remove it in a simple way (Figure 2.5).

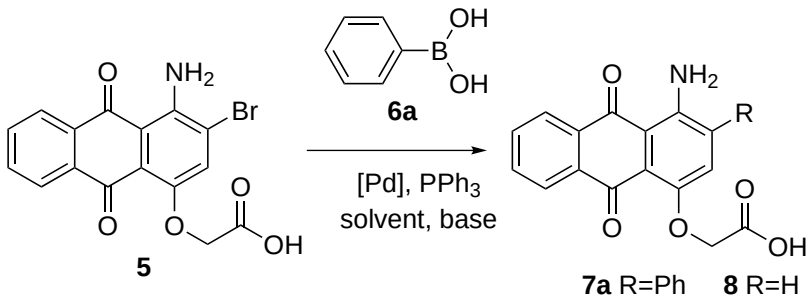


Figure 2.5: Optimization of Suzuki-Miyaura reaction on Dv17 carboxylic acid derivative

Table 2.3 represents the summary of a screening to find the best reaction conditions for the Suzuki reaction on **5**. The last two entries were performed in a different period to understand if the use of different sources of palladium could give better yields of the desired product **7a**.

Base	Solvent	Catalyst	Time	Product

			(h)	(Yield %)
K_2CO_3	THF/H_2O 4:1[a]	$Pd(OAc)_2$	18	**7a**(56)
KOH	THF/H_2O 4:1[a]	$Pd(OAc)_2$	1	**7a**(71)
NaOAc	THF/H_2O 4:1[a]	$Pd(OAc)_2$	18	-
Cs_2CO_3	THF/H_2O 4:1[a]	$Pd(OAc)_2$	3	**7a**(71)
KF	THF[a]	$Pd(OAc)_2$	18	-
KF	Toluene[a]	$Pd(OAc)_2$	18	-
K_2CO_3	DMA[b]	$Pd(OAc)_2$	5	**8**(50)
K_2CO_3	DMA/H_2O 4:1[b]	$Pd(OAc)_2$	4	**7a**(50)
K_2CO_3	DMA[b]	Pd/C	4	**8**(50)
K_2CO_3	DMA/H_2O 4:1[b]	Pd/C	4	**7a**(15)
KOH	THF/H_2O 4:1[a]	Pd(dba)	3	**7a**(70)
KOH	THF/H_2O 4:1[a]	Pd (dppf)	3	**7a**(71)

[a]: reflux (0.05 eq) and [b] 110°C

Table 2.3: Screening to find the best reaction conditions in the Suzuki reaction on compound **5**

The THF/H_2O 4:1 mixture was chosen as reaction medium because water is necessary to use cheap inorganic bases such as potassium carbonate or sodium hydroxyde. THF was chosen because it is an example of solvent that solubilize the starting material **5** when heated and it is simple to remove after the reaction. Reaction times were determined with a *collect and error* method because TLC couldn't be used for many mixtures. The similarity of the chemical structure between the starting material **5** and the products is the reason for the same R_f they show after the eluition with various solvent mixtures. The partial insolubility of the anthraquinone units in the best eluent mixture (DCM/MeOH 20:1) doesn't help the correct run of the compound, so the TLC plate often appears as a series of crawled stains. In this case it is difficult to distinguish between the reagent and the product beacuse it is difficult to undersatand the limits of the spots. Only the addition of a 1% formic acid in the eluent mixture allows the spot to be more compact, but it couldn't be still possible to control the reaction evolution separating the starting material from the reaction product. The procedure to control the reaction course was the following. It was decided to collect a small amount of the mixture after one hour. This part was worked-up as described in section 4 and a ^{1}H-NMR spectra of the crude

was collected. Depending on the integrals ratio between the more deshielded protons of the anthraquinonic core and those who belong to the new aromatic unit appended after the coupling, it was possible to determine the ratio between the proton contained in the starting material and the desired product ones. If it wasn't the same it was expected from a fully converted compound, the reaction mixture was left stirring with the same reaction conditions and controlled every three hours with the same method. If the reaction wasn't completed after 7 hours, the Palladium catalyst and PPh_3 were added to the reaction mixture and it was eventually worked-up after 18 hours of running. For the detailed experimental procedure see Section 4. Interesting results were found when DMA was used as solvent. When water was mixed with it, the desired product was recoverd, even if in lower yields respect the THF based procedure. When it was used as pure solvent, only the dehalogenated product **8** was obtained. The best reaction conditions were those described at the entries **b** and **c**. The lower price for KOH was the key motivation to chose the first one instead of the process requiring Cs_2CO_3, so a selction of aromatic and heteroaromatic boronic acids was used to modify the CI Disperse Violet 17 carboxylic acid derivative, as shown in figure 2.6.

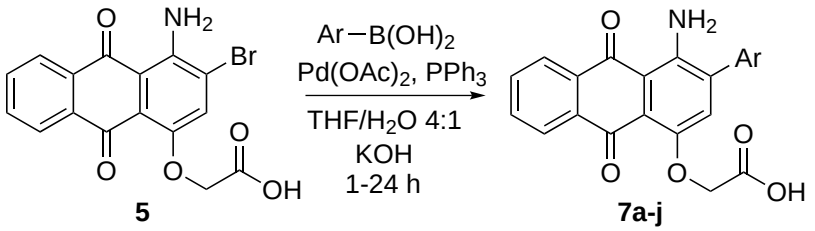
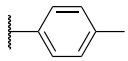
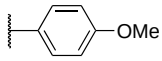
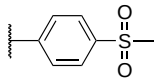
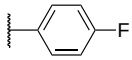
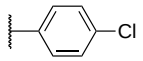
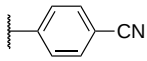
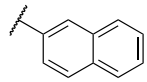


Figure 2.6: Suzuki-Miyaura reaction performed on Dv17 carboxylic acid derivative with differen boronic acids

In table 2.4 the results obtained from the cross-coupling reaction are shown. Visible spectra were all recorded using THF as solvent.

Entry	Ar=	Time (h) (h)	Product (Yield %)	λ_{max} (nm)	ϵ $(1/M^{-1}cm^{-1})$
a		1	**7a** (67)	506	8100

b		1	**7b** (67)	509	10300
c		1	**7c** (65)	516	9800
d		4	**7d** (73)	508	9300
e		4	**7e** (69)	504	9300
f		24[a]	**7f** (68)	504	9500
g		24[a]	**7g** (63)	505	7800
h		1	**7h** (75)	511	10600
i		4	**7i** (73)	506	7000
j		4	**7j** (67)	512	9200

[a]: $Pd(OAc)_2$ (0.05 eq) e PPh_3 added after 7h

Table 2.4: Suzuki-Miyaura on **37** with different boronic acids

Products showed in the previous table were all recovered with the same work-up method. The solvent was evaporated and the slurry was diluited with water ten times compared to the initial volume, the pH was decreased till 2 adding a 5% v/v HCl solution in water and the products were then recovered with a filtration under vacuum. A first method of purification required flash chromatography on silica gel. As the eluition of the product was very simple to follow only watching at the red biggest spot descending the column, it was possible to chose an eluent with increasing polarity. First of all DCM cleans the mixture from the head impurities, then DCM/MeOH 20:1 removes more polar compounds (for example triphenylphosphine oxide) and DCM/MeOH 20:1 with 1% HCOOH to recover the reaction product. This procedure was then improved to avoid chromatographic separation following the method that was developed later for the synthesys of Heck derivatives (for further informations see section 2.2.2).

All the products obtained have values of λ_{max} and ϵ higher than the starting material **5**. In figure 2.7 two examples of THF solutions of the compounds **7g**

and **7c** are compared with a THF solution of the starting material **5**. As it is immediately clear, the differences in the hue is small, in particuar for compound **7g**.

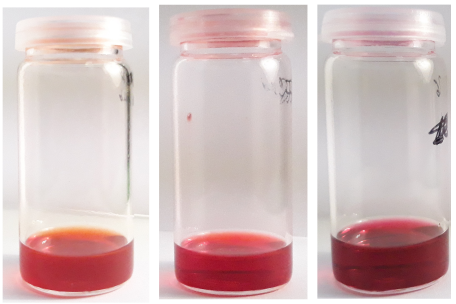


Figure 2.7: Starting compound **5** (**a**), the 4-nitryl **7g** (**b**) and the 4-metoxy **7c** (**c**) phenyl derivatives THF solutions are compared

The three compounds differ each other for 10 nm of λ_{max}, They have an higher component of purple hue passing from the reagent to the product with the more electron-donor substituent. All the new synthesized chromophores contain an aromatic ring. It has a better electron releasing ability than the Bromine group of the starting material. For this reason the absorption profiles are all red-shifted, but they mantain the same shape. The brightness of the different solution is for this reason quitely the same. Difference in hue is bigger when electronrich aromatic units are inserted. The thyenyl derivative **7j** and the 4-metoxy **7c** one have the highest values for λ_{max}, in accordance with the high electon density on aromatic unit. The pyridyl **7i** 4-nitryl **7g**, 4-chlorine **7f** and the 4-fluoro **7e** ones have the lowest values for the opposite reason.

The ability of these substituents to attract electrons lowers the amount of elecron density the aromatic substituent can delocalize on the anthraquinone unit. Figure 2.8 shows the differences in absorption profiles for the examples chosen in the figure 2.7. The relevant change after the coupling reaction is an increase in the ϵ. It is always higher than the value registered for the reagent. The higher delocalization or the better solubility in the solvent could be the reason for the higher values. Even if the introduction of an aromatic unit diectly bound to the anthraquinone unit is a good strategy to change the hue, the p orbitals of the annthraquinone chromophore and the aromatic

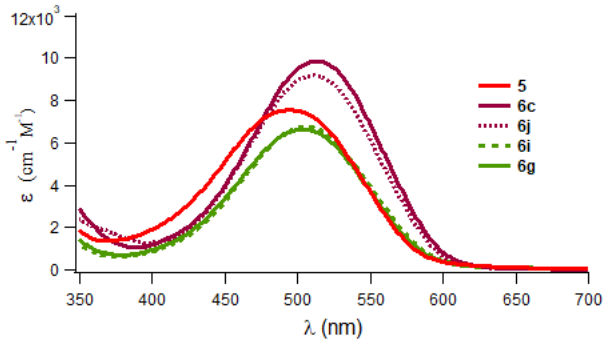


Figure 2.8: Absorption profiles of different aryl derivatives of compound **5**

substituent don't overlap in a perfect way. The aromatic unit is tilted respect to the anthraquinone core, as it is possible to see from the Figure 2.9 that represent a simple energy minimization performed with the semiempirical MM2 method. The structure of the phenyl derivative **7a** was compared to the well known 1,2,3,4-tetrahydroquinoline. Quinoline was chosen beacuse it has an aromatic unit directly bound in *orto* respect to the amine group. In this case the rigid structure of the aliphatic six membered ring forces the aromatic substituent in position 8 to tilt respect to the plane of the aromatic ring of quinoline.

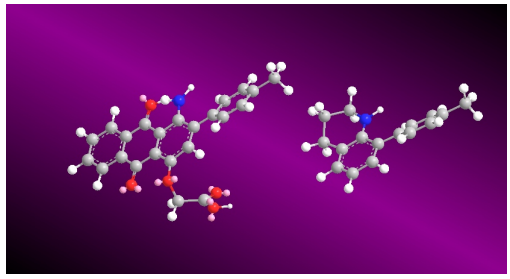


Figure 2.9: Geometry optimization for compound **7a** (left) and for 8-phenyl-1,2,3,4-tetrahydroquinoline (right)

The reason of this conformation for the Disperse Violet derivatives lies in the relative position of the functional groups near the connection between the anthraquinone core and the aromatic substituent. The amine group in posizion 1 is strongly bridged through an hydrogen bond to the carbonylic unit of the

anthraquinone forming a six membered ring (Figure 2.10). This is reflected in a planar conformation of the amino group that forces the hydrogen atom wich is not involved in the hydrogen bond to fill the space near the connection between the anthraquinonic core and the aromatic substituent. The situation reflects the structure of an 8-phenyl-1,2,3,4-tetrahydroquinoline unit, where the amino group directly bound to an aromatic unit is forced to be planar by a C-N covalent bond instead of a weaker H-bond. Anyway it is a good approximation to compare semiemphirical calculation performed on the anthraquionone derivative **7a** with the geometrical optimization performed on the quinoline derivative. The results obtained show that the phenyl ring is twisted respect to the anthraquionic core plane (Figure 2.9).

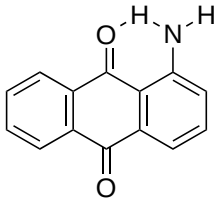


Figure 2.10: H-bond between amino and carbonyl groups in 1-amino anthraquinones

Even if there were no evidences in the literature of Suzuki-Miyaura reaction performed on Disperse Violet 17 derivatives, a general method was developed to introduce both electronrich or electronpoor aromatic compounds. This promising results moved us to investigate other cross-coupling reactions to extend the conjugation of the chromophore unit.

2.2.2 Heck

The promising results in the modification of the Disperse Violet 17 carboxylic acid derivative **5** was a crucial starting point to look for other cross-coupling reaction that could be performed on this substrate. The little differences found for the wavelenghts of maximum absorptions of Suzuki derivatives were assigned to the difficulties to extend π electrons conjugation between the two aromatic units due to the tilted conformation. To overcome this problem a spacer is needed to obtain a more planar conformation between the two aromatic units. The Heck cross-coupling reaction allows the introduction of a carbon-carbon

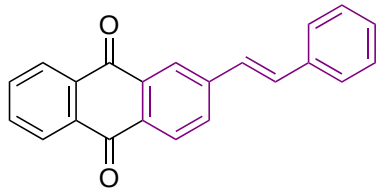


Figure 2.11: Heck derivative of 2-bromoanthraquinone

double bond that pushes away the two aromatic units giving them the possibility to lie in the same plane and to have a better conjugation (Figure 2.11).

In figure 2.11 the substructure highlighted in purple represents a chromophore unit itself named stylbene. It is poorly used in textile dyeing. The only way it is known to dye is a mixed azo-stylbene CI Direct Yellow 11, while it is mostly used as a chromophore group for special application as some of the stylbene compounds possess good fluorescence proprieties. However in our case we aren't interested in finding any flluorescence ability.

As it happened for Suzuki reaction, it wasn't possible to find any reference in the literature describing the Heck cross-coupling reaction in the case of CI Disperse Violet 17. Anyway it was decided to avoid any tentative to optimize this process for the commercial available violet dye **1**. The carboxylic acid was directly chosen, because the basic conditions necessary to apply the Heck procedure could give the hydrolyzed product if starting from the ester derivative. 4-Chlorostyrene was chosen as the other reagent (Figure 2.12).

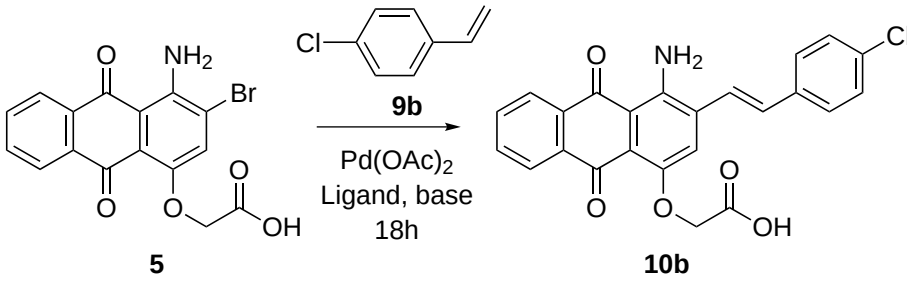


Figure 2.12: Heck reaction on compound **5**

The reaction conditions optimized for the Suzuki reaction on **5** were also

chosen for the Heck process. Solvent mixture was changed eliminating water, so refluxing THF was chosen. TEA was chosen as base instead of KOH because of its better solubility in organic media. Taking into account the longer reaction times required for the Heck process respect to the Suzuki reaction, it was decided to leave the mixture stirring at reflux overnight. In every case, if in the crude there weren't any trace of the desired product, the reaction was stopped after 18 hours. Only a little number of Heck procedures are reported to be so slow to find any trace of product after one night of stirring. In table 2.5 also the other attempts are reported.

Base	Solvent	Ligand	Yield(%)
TEA	THF[a]	PPh_3	-
TEA	DMSO[b]	PPh_3	-
TEA	NMP[b]	PPh_3	-
DIPEA	DMSO[b]	PPh_3	-
TEA	DMSO[b]	P(*o*-toly)$_3$	70
TEA	DMSO[b]	Xanthphos	59
TEA	DMSO[b]	XPhos	66
TEA	DMSO[b]	DPEPhos	32

[a]: reflux and [b] 110°C

Table 2.5: Optimization of reacion conditions for the Heck process on compound **5**

After the refluxing THF try, I immediately move to other solvents because most of the Heck cross-coupling reaction are reported to occcur at higher temperatures than the boiling point of Tetrahydrofuran (66 °C). DMSO was chosen for two reasons. First of all it has a high boiling temperature (189 °C) which is optimal for the screening. The second reason was its miscibility with water. As mentioned in section 4 the first step of the work-up method developed also for Suzuki reaction is the diluition with a large amount of water (ten to twenty times the solvent used for the reaction).

The very good miscibility with water could help in the removal of every trace of the solvent from the reaction mixture, as it can't be evaporated using common rotatory evaporators. The good dissolving ability for the starting material allowed to use less quantity of solvent than the amount of mixture needed for the Suzuki reaction. In any case changing solvent from DMSO to NMP and base from TEA to DIPEA didn't produce any appreaciable result. It seems the problem was the ligand itself. Once PPh_3 was replaced with a more electronrich P(*o*-toly)$_3$ the best result was obtained. The use of other phosphines didn't improve the yield, so it was decided to applly the best reaction conditions on other styrene derivatives (Figure 2.13).

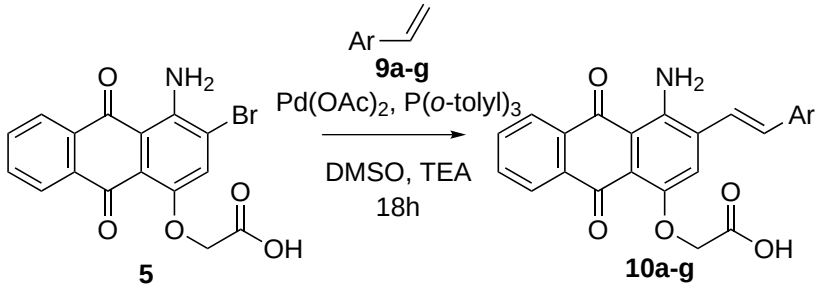
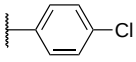
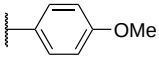
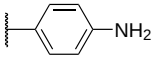
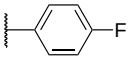


Figure 2.13: Heck reaction on Disperse Violet 17 carboxylic acid derivatives with different styrenes

In table 2.6 the products obtained were reported.

Entry	Ar=	Time (h) (h)	Product (Yield %)	λ^a_{max} (nm)	ϵ $(1/M^{-1}cm^{-1})$
a		1	**10a** (71)	529	12700
a		1	**10b** (67)	531	11600
b		1	**10c** (65)	532	13700
c		24[a]	**10d** (72)	537	13700
d		4	**10e** (54)	557	9500
e		4	**10f** (63)	528	10100

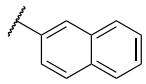
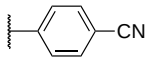
f		24^a	**10g** (75)	533	12200
g		24^a	**10e** (75)	527	9500

Table 2.6: Heck reaction on compound **5** with different styrenes

To purify the Heck derivatives the cromatographic method was tried but it was impossible to recover any product because they remained trapped in the silica gel and only a little yield of pure compound was recovered. For this reason it was necessary to develop a method that avoided the use of the chromatographic separation. The main problem was the presence of the P(*o*-tolyl)$_3$ and its oxide derivative, as it was clearly observable from the singlets around 2 ppm belonging to the methyl substituent on the aromatic rings bounded to the phosphorous atom. It was decided to take advantage from the partial insolubility of the chromophores in the common organic solvents to remove the impurities. From an article by Hu et *al* [56] it was found that the triphenilphosphine oxide is soluble in EtOH, while the anthraquinone unit isn't. So the crudes were suspended in EtOH as the solutions appear almost transparent with an unsoluble residue. The big aggregates were destroyed using an ultrasound sonicator, and then the solution was left stirring for 3-4 hours. The filtration allowed to recover the pure products in good yields. [57] As the method worked very well in the purification of the Heck derivative, it was extended in the purification of a second batch of Suzuki derivatives reported in section 2.2.1.

The products obtained with the Heck reaction showed an appreaciable blue shift for λ_{max}. The two limits are represented by the 4-nitryl and the 4-amino derivatives. Unluckly the yield obtained for the amino one was very poor, and it wasn't possible to improve it. For this reason it was decided to consider the 4-metoxy derivative as the upper limit of the Heck modified dyes. The differences in this case are lower, but it is possible to appreciate a change in the coloration respect to the starting material (Figure 2.14).

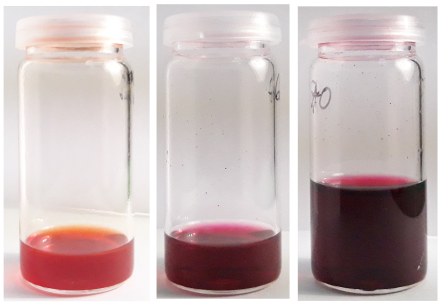


Figure 2.14: THF solutions of the starting compound **5** (**a**), the 4-nitryl **10e** (**b**) and the 4-metoxy **10d** (**c**) styril derivatives

In this case, as it happened for Suzuki derivatives, the difference in the λ_{max} between the coupling products lie in an interval of 10 nm, so it was highlated that there were no substantial differences in the hue when electron donors or electrowithdrawing substituents were chosen. The good result in terms of wavelenght of maximum absorption obtained for the 4-aminostyrene derivative were minimized by the poor yield obtained.

2.2.3 Sonogashira

The last group of CI Disperse Violet 17 derivatives was synthesized using the Sonogashira cross-coupling reaction, that allows the introduction of a C-C triple bond bridge between the anthraquinone unit and the aromatic substituent. The best procedure for the synthesis of the Sonogashira compounds of the carboxylic acide derivative of CI Disperse Violet 17 were more simple to find. In the literature there was a work by Stepanov *et al* [51] that describes a Sonogashira cross coupling reaction on an alkylated derivative of the Disperse Violet 17

using Phenylacetylene as reagent. I tried only to modify the procedure to avoid the use of Pyridine and the results are reported in table 2.7. In every procedure Pd(OAc) was used as catalyst, CuI as the source of Copper (I) and Phenylacetylene as coupling reagent.

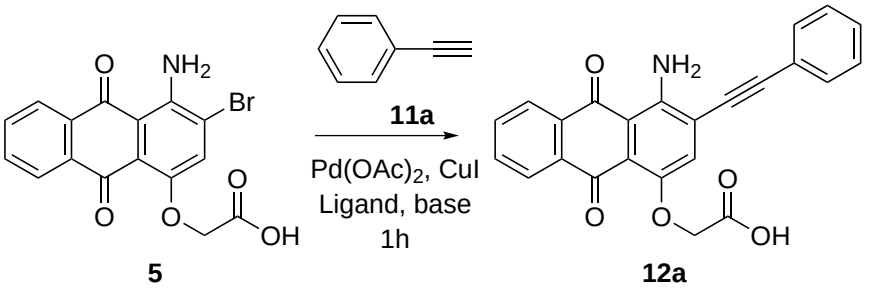


Figure 2.15: Sonogashira reaction on Disperse Violet 17 carboxylic acid derivatives with phenylacetylene

Base	Solvent	Ligand	Yield(%)
TEA	Py	PPh_3	70
TEA	DMSO	PPh_3	72[a]
TEA	DMSO/Py 10:1	PPh_3	68[a]
TEA	DMSO/Py 10:1	P(*o*-toly)$_3$	65[a]
TEA	Py	P(*o*-toly)$_3$	66

[a]: NMR spectra broad signals show the presence of the paramagnetic Cu(I) impurity

Table 2.7: Optimization of reacion conditions for the Sonogashira process on compound **5**

The work-up procedure was the same performed for the Heck reaction. The slurry was diluited with water and the pH was adjusted to 2. Then the mixture was filtered, washed with water, toluene and petroleum ether and the crude was dissolved in EtOH to remove phosphine derivatives. The ^{1}H-NMR spectrum analysis revealed one problem when DMSO was used as solvent. Signals in the whole spectrum appeared broad, and it was immediately thought that some paramagnetic Cu(I) residues remained trapped in the filter, maybe coordinated

by the amino group of the dye itself. The chelating proprieties of pyridine allows the coordination of the copper, so the attempts made using this solvent didn't show any paramagnetic influence in the ^{1}H-NMR spectra. Two tentatives performed using a DMSO/Pyridne 10:1 solvent mixture were made to exploit the chelating ability of Pyridine for copper(I) ion mantaing the safer DMSO as solvent. Two different phosphine were changed, PPh_3 and P(*o*-toly)$_3$. The second one was used because it gave the best result in the Heck process when DMSO was used as solvent. The broadening of the signals was still observed, so it was decided to synthesize Sonogashira derivatives using the small amount of pure Pyridine as possible, eventually increasing the quantity of TEA, if necessary, to better solubilize the starting material.

Following the procedure decribed at the section 4 different sonogashira derivatives were synthesized as highlighted in table 2.8.

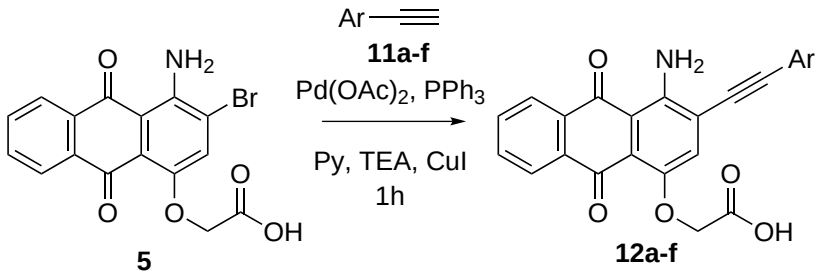
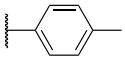
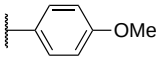
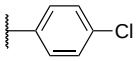
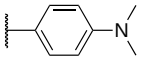


Figure 2.16: Sonogashira reaction on Disperse Violet 17 carboxylic acid derivatives with phenylacetylene

Entry	Ar=	Time (h) (h)	Product (Yield %)	λ_{max} (nm)	ϵ $(1/M^{-1}cm^{-1})$
a		1	**12a** (68)	517	12700
b		1	**12b** (70)	519	11600
c		1	**12c** (72)	521	12300
d		24[a]	**12d** (68)	515	10200
e		24[a]	**12e** (69)	537	15200

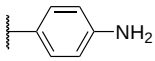
f		1	**12f** (63)	535	14800

Table 2.8: Sonogashira reaction on **5** with different phenylacetylenes

Crudes were all purified with a method similar to the Suzuki process one. Pyridine wasn't evaporated since it was the responsible for the coordination of copper ions, and the mixture was diluited with water 20 times respect to the solvent volume. The pH was lowered to 2 and the crude was left stirring for 6 hours. It was then filtered under vacuum and washed with a small amount of pyridine, water, toluene and petroleum ether to remove any soluble impurities. The filtered mixture was at the end suspended in EtOH to remove posphine oxide impurity in the same way as it was made for Heck and Suzuki derivatives. All the synthesized products showed good yields and λ_{max} values higher than the starting material. Wavelenght of maximum absorption values are all between the Suzuki and the Heck derivatives as it was expected since the C-C triple bond always gives poorer results in extending the conjugation. In this case the amino derivative and the N-N-dimethyl ones were synthesized in good yields, and their λ_{max} are comparable with those obtained for the Heck derivatives, indicating them as alternatives for the styrene derivatives. Looking at the other derivatives, the differences in λ_{max} are less pronounced than those obtained for the other two groups of compounds. Even if the 4-nitryl derivative wasn't synthesized, the difference from the two limiting derivatives is 6 nm instead of 10 nm. Anyway, since it was impossible to distinguish the diferent hue in the cases described before, it was the same for Sonogashira derivatives. In figure 2.17 the chloro and the metoxy derivative THF solutions are compared to the starting product.

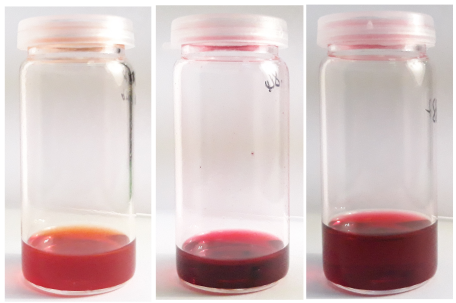


Figure 2.17: Starting compound **5** (**a**), the 4-chloro **12d** (**b**) and the 4-metoxy **12c** (**c**) phenylacetylene derivatives THF solutions are compared

2.3 Naturalization

The three processes for the modification of the carboxylic acid derivative of the commercial available CI Disperse Violet 17 allowed us to obtain three different groups of new anthraquinone chromophores. All the three group of chromophores have wavelenght absorption maxima higher than the starting material **5**. The aromatic substituents were chosen for their different electro-donating ability. In our idea, the most was the electrodonating capacity of the the substituent, the most the absorption maximum had a red-shift. That was exactly as we expected, even if the differences between the products were very small. In the case of Suzuki derivatives the wavelenghts of maximum absorption of the synthesized products lie in an interval of 12 nm, and the limits are represented by the nitryl derivative (λ_{max} value of 504) and the 4-phenylmetoxy one (516). From an applicative point of view in dyeing industry, there isn't any macrospcopic difference in coloration. For this reason they were all grouped into the *Suzuki derivative* tag and it was decided to perform the glycoconjugation only for one product on behalf of the entire group. The same conclusions were made for the Heck and Sonogashra derivatives. Exept for the amino group containg dyes, they all have the same excursion between the two limits. Also for these two others group, even in the case of *Heck derivatives* and the *Sonogashira derivatives* only one compound was chosen for the glycoconjugation. For all the three processes the 4-methyl derivative was chosen because it was available at the moment in good quantities. Anyway it wasn't only a decision based on availability of starting material. As it is highlighted in Patent by Bianchini *et al.*, [15] the naturalization method has a good tolerance over a great numbers of functional groups, so the choice of one compound instead of another one couldn't give any particular problem in terms of tolerance of functional groups. The naturalization of one of the derivative can be extended over the others, so it was thought to extend it if it was necessary to perform any particular tinctorial test.

The naturalization process is a glycoconjugation between a chromophore and lactose. The sugar unit has to be protected follwing the well known method by Barili et *al.* [58] This compound was already available in large quantities in our laboratory. First of all a selective tosylation was performed on the secondary hydroxy group (Figure 2.18).

A pyridine/acetonitrile solution of the protected lactose **13** was added dropwise to a solution of TsCl in the same solvent mixture. The reaction was stirred

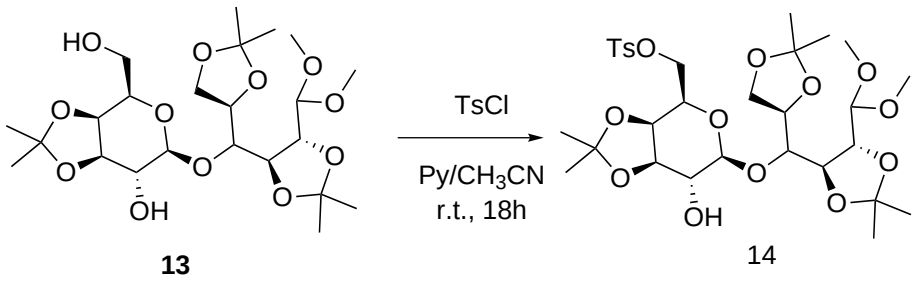


Figure 2.18: Selective tosylation of the secondary hydroxy group in the protected lactose unit

at room temperature overnight. Water and Et_2O were then added to the solution and the acqueos phase were extracted with ether. Na_2SO_4 was used as drying agent and the organic phase was then evaporated. The crude was purified with a flash cromatographyc column to obtain the desired product in good yields. The following step is the Nucleophilic substitution of tosylate with a piperazine unit (Figure 2.19).

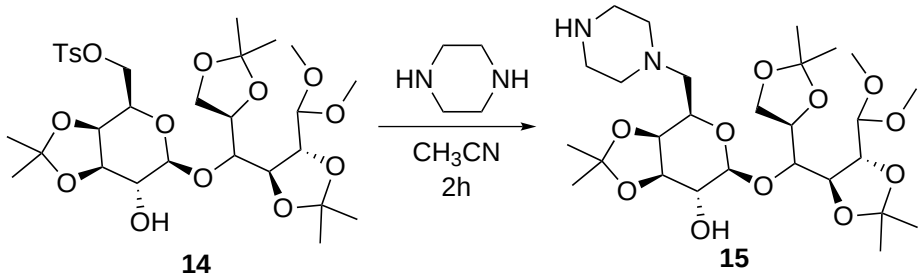


Figure 2.19: Heck reaction on Disperse Violet 17 carboxylic acid derivatives with different styrenes

Compound **14** was prepared starting from 60 g of the starting material, as the process was already scaled-up in past years. The tosylated lactose derivative was dissolved in CH_3CN and stirred at reflux. Then a CH_3CN solution of the tosylated lactose derivative **14** was added slowly to the stirring solution and left at reflux for 2 hours. Once the solution was cooled at r.t. the solvent was evaporated and CH_2Cl_2 was added to dissolve the residue. The organic

phase was washed only once to prevent any loss of reagent and it was dried using Na_2SO_4. The evaporation of CH_2Cl_2 was the most difficult passage because the sticky solid swells under reduced pressure and it has to be monitored until it stops growing. It was often necessary to manually destroy the bubbles plugging the flask neck. The *protected piperazine-lactose* unit **15** is the starting compound to obtain the amide of the disperse dyes derivatives. In our case the compounds that have to be naturalyzed are the 4-methyl derivatives for each group of cross-coupling reaction. The procedure consists of a simple coupling between the two units using DMTMM as coupling agent (Figure 2.20) and a deprotection (Figure 2.21).

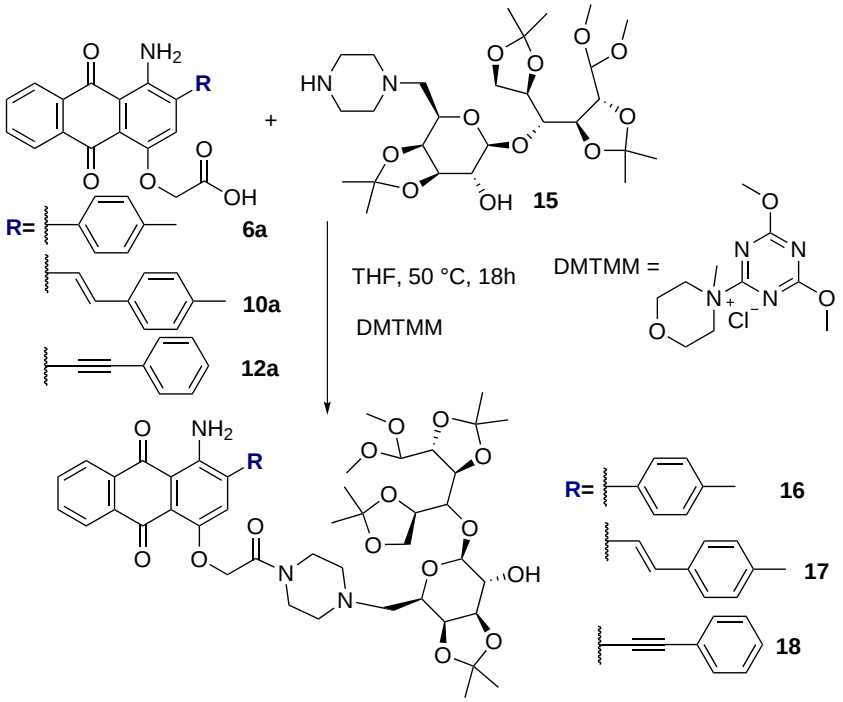


Figure 2.20: Coupling reaction between the *protected piperazine lactose unit* and the cross-coupling derivatives

The first step is the coupling itself. The protected piperazine lactose unit and the caroxylic acid derivative of each chromophore (compounds **6a**, **10a**, **12a**) were dissolved in THF and left stirring for 7 hours at 50 °C. Then

DMTMM was added and the solution was left stirring overnight. The work-up method is the same used in almost every rection performed in organic media. To improve the washing with water step, THF was evaporated with a rotary evaporator to obtain a slurry that was diluted with AcOEt. The crude was then purified with a flash cromatographyc column. The three Disperse Violet derivatives were separted using one chromatgraphic procedure for each compound. The choice of the eluent mixture wasn't trivial as the TLC controls supposed it was. The first compound I tried to separate with flash cromathography was the Sonogashira derivative. From the ^{1}H-NMR control it was clear that the conversion was full. It ws confirmed by the analysis of a TLC plate where I used pure DCM as eluent. Using this solvent the carboxylic acid had to remain on the baseline, but any visible traces were found. The best eluent seemed the DCM/THF 10:1 mixture, but it took a long time and an excessive amount of solvents to recover the product, even if it was in very good yield. To overcome the loss of a large quantity of solvent the chromatographic step was modified for the other separtions. The Suzuki derivative was eluted with a DCM/THF 10:1 mixture with 1% MeOH and 1% of a concentrated solution of NH_3 in water (33% v/v). The product was recovered diminushing the amount of solvent used. The separation of the Heck derivative was much more difficult. The first tentative was made using the same eluent used for the separation of the Suzuki derivative, even if the amount of ammonia solution was halved. The column didn't hve any problem when adding the eluent mixture, but the product obtained was analyzed via ^{1}H-NMR and an impurity was found. The compound was then purified again but it seemed the impurity increased after the second column. The reaction was performed again and another separation method was developed. A DCM/THF 10:1 solution was chosen as the starting eluent. Then a DCM/THF 10:1 solution with 1% of HCOOH instead of MeOH was used. The last step was the introduction of a 0.5% of ammonia solution in water and this addition allowed to recover the product in good yields. One thing that has to be pointed out is the fact that the purification of the protected derivatives **16-18** isn't necessary. The chromatographic column was necessary only to purify the product for its characterization. Once the process is developed, the deprotection step can be performed also on the crude product. The best option is to evaporate the THF, then dilute with AcOEt and at the end wash with water and collect the organic fraction. Once the AcOEt is evaporated the crude can be used for the deprotection step because the impurities can be

eliminated at the end of the glycoconjugation simply washing the mixture. The last passege of the naturalization is the deprotection step (Figure 2.21).

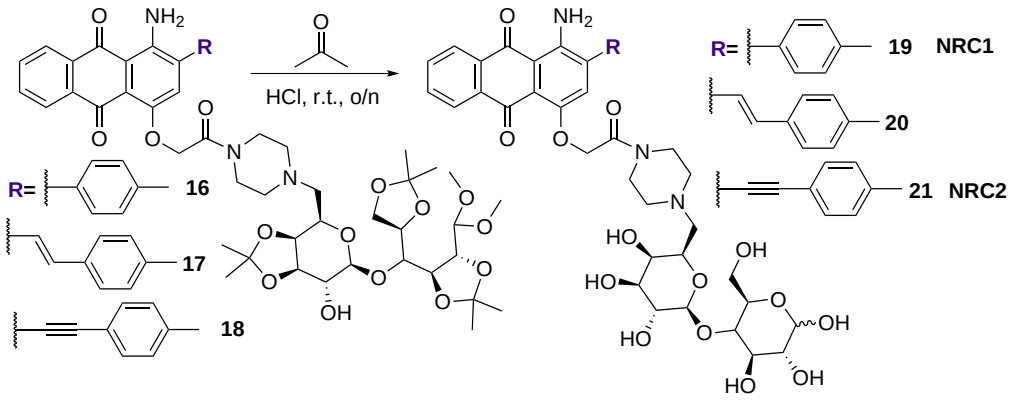


Figure 2.21: Deprotection with conc. HCl in acetone. The product higlighted is the totally deprotected glycoconjugated dye

Each product was dissolved in acetone mantaining a temperature of 0 °C. Then a solution of concentrated HCl (33% v/v in water) in acetone was added dropwise and the solution was warmed at room temperature. Then it was left stirring o/n. The crude was filtrated washing with acetone. As the product is insoluble in organic media, it can be recovered on the paper filter. The process was developed by our research group and it is described in the patent by Bianchini *et al* [15]. It was chosen because it avoids the use of Trifluoracetic acid (TFA), which is the main reagent used in the sugar deprotection from acetonides. Its corrosive ability makes it difficult to handle in large-scale production. However the deprotection with acetone has one problem. It was demonstrated by ESI-Ms analysis that a mixture of products are always recovered. The main compound it the total deprotected naturalized dye in α and β anomers, while the other two the partial deprotected derivative. As it is highlited in figure 2.22 it is the monomethylated derivatives.

As the molecular masses of the two derivatives are comparable and their chemical structure is similar, it's possible to obtain semi-quantitative informations from the ESI-Ms recorded spectra. In this approximation the quantity of the partially deprotected naturalized dye lies in an interval between 10% and 25% of the totally deprotected one, depending on the chromophore. It was also

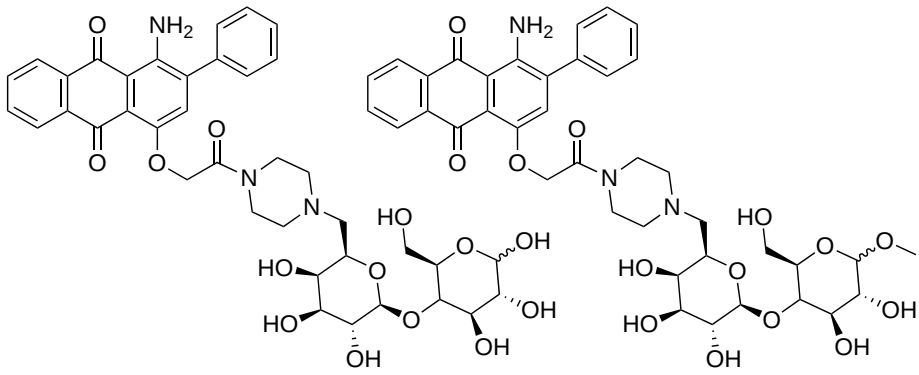


Figure 2.22: Products identified after the deprotection of the compound **16**

demonstrated from tinctorial tests performed on other naturalized derivatives that it doesn't affect the dyieng ability of the naturalized chromophores, so we didn't care about separating the mixture, even because it could have been a long time consuming method as these compound are only soluble in water. In the case of the cross-coupling derivatives the same problem was found, and a quantity from 10% to 20% of the partial deprotected unit was found. Compounds **19** and **20** showed good water solubility and they were named **NRC1** and **NRC2** as new naturalized dyes. The *Heck derivative* showed a poor solubility even at 0.1 mg/mL concentration, and it was the first example of a naturalised dye that didn't show solubility in H_2O. The naturalization of *Sonogashira derivative* **18** didn't give only the desired product **20**. A 50% of the derivative is the result of the HCl addition on the C-C triple bond. Any other attemps made using TFA or lower quantities of HCl didn't produce any appreaciable results. It was decided to mantain the unknown composition for the carachterization of the *Sonogashira derivative* because there are other cases of chromophores used as a mixture of constitutional isomers such as the Direct Blue 33. [59]

Chapter 3

Characterization of the new naturalised dyes NRC1 and NRC2

Thanks to naturalization process it was possible to obtain two water soluble dyes, **NRC1** and **NRC2** respectively. It was already mentioned that the compound **NRC2** is a mixture of two or three different chromophore species with indistinguishable absorption profiles. More than one dye can be found as a mixture of different chromophores, for example Direct Blue 33 (better known as Oxamine Dark Blue) is sold as an unseparable mixture of two positional isomers. The unsolubility of the naturalized Heck derivative was the first example of water-unsoluble naturalized dyes until now. For this reason it wasn't tagged with an acronym, but it was named *Methyl Heck derivative*.

Since the aim of the work is an industrial application of the dyes in tinctorial processes, a large part of characterization measurments were performed at fixed concentrations. They are 0.5, 1, 1.5 and 2 mg/mL as they are the common values for polyester dyeing. They don't consider any differences in the molecular masses of dye molecules related to the different chemical structure for the disperse dyes used. Anyway most of the dyes have similar chemical compositions and the change in molarity isn't high. Naturalised dyes contain a lactose unit which is about the half of the molecular weight of the entire compound so, if only the chromophore concentration is considered, molarity of glycoconjugated dyes is the half of a common used disperse dye at the same concentration. However the composition of disperse dyes formulations contain a large amount of auxiliary chemicals and the dye content can be less then the

half in weight of the entire mixture. All the terms involving *solubility* or the adjective *soluble* are referred to a visive analysis of the solutions. Tinctorial processes require a clear solution without any eye-visible aggregate. The presence of self-organized supramolecular structures of chromophores in solution isn't a problem for dyebaths. Water soluble dyes such as Acid and Basic dyes present aggregates, but they are common used in tinctorial processes due to the ability to get into the fibers even if there aren't any *free* molecule in solution. On the other hand, the presence of macroscopic aggregates has to be solved before using the dye for tincotorial purposes. If disperse dyes are used, the solution for this problem is a decrease in dye concentration or an increse of the surfactant amount. Anyway in most cases the ready-to-use formulations are all prepared to overcome any solubility problem in dyebaths, and for this reason it is difficult to find pure disperse dyes in the market. To better understand the behaviour of naturalised dyes in solution and to understand if there were any criticism in dyebaths preparation, a phisico-chemical characterization on water soluble naturalized dyes was performed. The preliminar phisico-chemical characterizations of this chapter were all performed in collaboration with CSGI consortium at the University of Florence, in particular with Silvia Fogli, dott. Paolo Tempesti, dott. Claudio Resta and prof. Debora Berti. The SAXS and AFM data are still under preparation and will not be discussed in this document.

The first analysis was the study of solubility in water of the naturalized dyes. It was noted that for some of the dyes previously synthesized it was difficult to obtain water solution with a concentration higher than 1.5 mg/mL. Two glycoconjugated dyes already present in naturalised dyes palette, the Naturalised Red 222 (NR202) and the Naturalised Yellow 42 (NY42) highlated in figure 3.1, showed the presence of macroscopic aggregates in water at the concentration of 2 mg/mL. NY42 also showed a different behaviour depending on the kind of water used to prepare the solution. In demineralized water it is soluble until a concentration of 2 mg/mL, while if the drinking water from the public aqueduct is used, the dye precipitates even at the concentration of 0.5 mg/mL. Tinctorial test performed on polyester for this yellow compound didn't show any relevant tinctorial ability since normal drinking water was used. [60]

Starting from this consideration, the behaviour of the two water soluble naturalized dyes **NRC1** and **NRC2** was studied to understand if it was possible to use them in tinctorial tests. Solubility tests showed that for these two

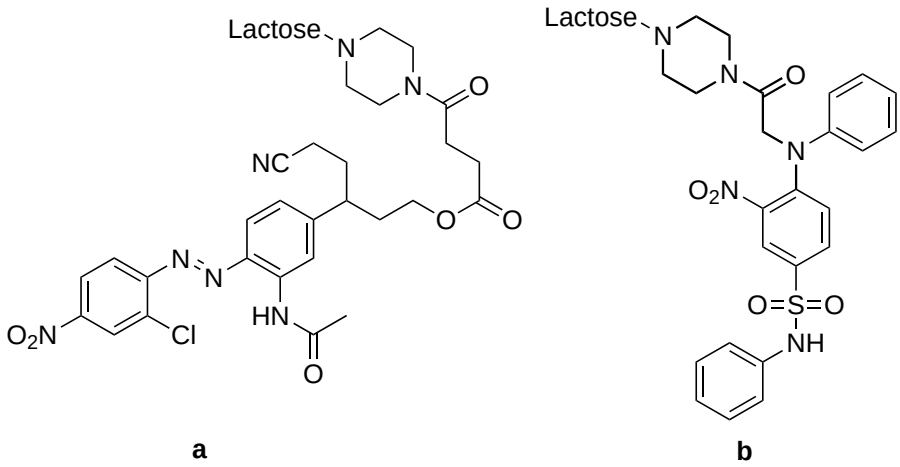


Figure 3.1: Naturalised Red 202 (**a**) and Naturalised Yellow 42 (**b**). *Lactose* is the deprotected sugar residue

compounds the best value in water is 1.5 mg/mL, so it could be still possible to use it to dye polyester. On the other side in MeOH and in DMSO the 2 mg/mL concentration showed clear solutions. Methyl Heck derivative didn't show any solubility in water, while in the two organic solvents the same results of the orther two candidates were reached. The results suggested that **NRC1** and **NRC2** formed stable aggregates in solution clearly visible only after a certain concentration, but it was supposed that at lower concentration they were also present.

3.1 Visble spectra

The first analysis performed on the two naturalised water soluble derivatives were the absorption Visible spectra. It was prevoisly demonstrated that the shape of the absorption profile for other naturalized dyes was different depending on the solvent used. DMSO and MeOH solution represent the model absroption spectra for the totally solubilized situation. For example NR202 spectra show a great difference in absorption profiles passing from water to MeOH and DMSO (Figure 3.2).

Bearing in mind these results, the same analyses were performed on **NRC1**

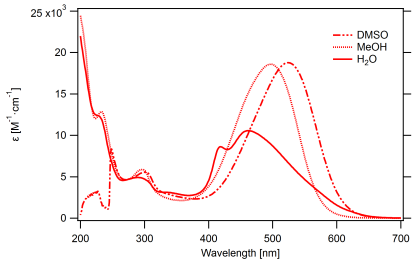


Figure 3.2: UV-Visible spectra of 1 mg/mL solutions of NR202 in H_2O, MeOH and DMSO

and **NRC2** (Figure 3.3). In the first case it was shown that the absorption profiles were slightly different between MeOH and DMSO solutions at 1 mg/mL, while the water solution at the same concentration showed a lower ϵ value and a hypsochromic shift in λ_{max}. The less peaked shape for the water solution is in accordance with the presence of aggregates in solution.

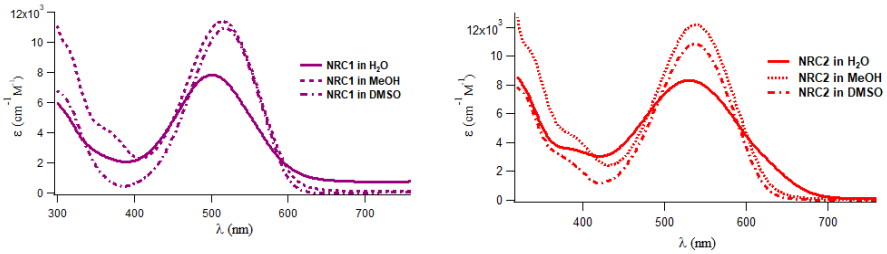


Figure 3.3: Visible spectra in H_2O, MeOH and DMSO for 1 mg/mL solutions of **NRC1** (*left*) and **NRC2** (*right*)

The same behaviour was found for the **NRC2** derivative. Even if it is a mixture of different species in an unknown rate, they still remain undistinguisible from the Visible spectra using both MeOH and DMSO. The broadening of absorption curve for the water solution is in accordance with the result obtained for **NRC1**, even if the hypsochromic shift of λ_{max} is less pronounced than what was observed for **NRC1**.

The 1 mg/mL water solution of **NRC1** was also investigated with increasing amount of the negative charged surfactant Sodium Dodecylsulphate (SDS). It was chosen for the ability to destroy supramolecular aggregates and the pur-

pose was to reproduce a solution with *free* molecules without any interaction. Surfactant concentration was changed in the range between 0.1 and 150 mM, and Visible spectra of these solution were recorded (Figure 3.4).

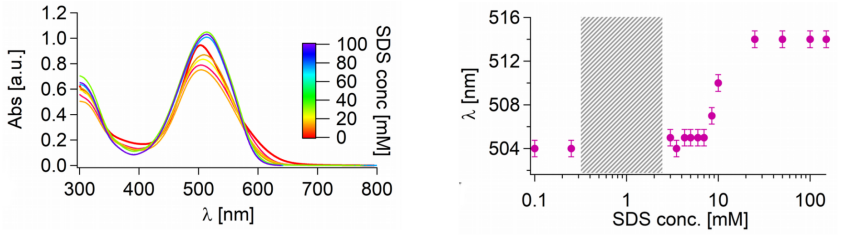


Figure 3.4: **NRC1** 1 mg/mL solution in water with increasing SDS concentration: visible spectra (*left*) and λ_{max} values (*right*)

A slow increse of the λ_{max} was observed at SDS concentration below 7 mM and above 25 mM. Between these two values λ_{max} incresed very fast with an inflection point for the 8.5 mM solution. For the solution in the interval between 0.2 and 2 mM (the grey area in the graphic on the right) it was impossible to register any visible absorption profile because an unexpected phenomenon was recorded (Figure 3.5).

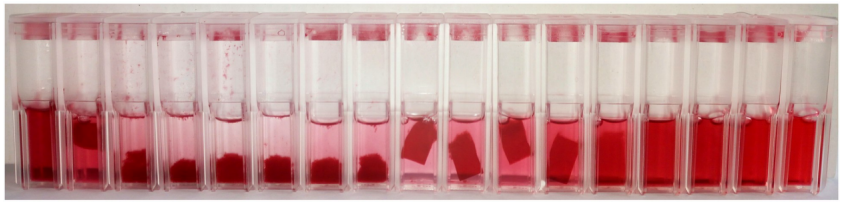


Figure 3.5: **NRC1** 1 mg/mL solution with increasing amount of SDS between 0.1 and 3 mM concentration

The addition of SDS at the 1 mg/mL solution of the dye resulted in an istantaneous precipitation of **NRC1** forming flocculate or gel-like phases. This phenomenon was assigned to a reentrant condensation that happen when the surface charge of the cationic dye is neutralized by the opposite charge of the surfactant. [61,62] This charge neutralization lowers the coulombic repulsion between the positively charged chromophores promoting the aggregation. In

Figure 3.5 the solutions presenting this phenomenon are highlighted. As it is possible to see even with a naked-eye analysis, two different kind of precipitates were found. For SDS concentration above 1 mM the dye precipitate formed flocculate particles landing at the bottom of the cuvette. Above 1 mM concentration, it rapidly formed a gel-like phase floating in the cuvette, as if there were an appreciable amount of water trapped between the supramolecular aggregates. SAXS and AFM measurement will be performed to better understand the shape and the composition of these aggregates.

The solution lying in the interval between 0.1 and 3 mM were studied more in detail with DLS (Figure3.6).

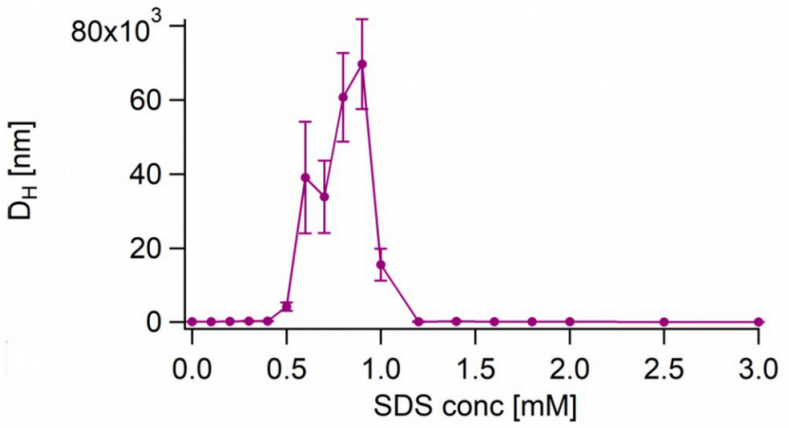


Figure 3.6: **NRC1** 1 mg/mL solution with increasing amount of SDS between 0.1 and 3 mM concentration

Data showed that the hydrodinamic diameter of the aggregates increased passing from 0.3 to 1 mM SDS concentration, but it rapidly decreased until the 1.3 mM was reached. After this value, the original hydrodinamic diameter was restored.

3.2 Circular dichroism and DLS analyses

Circular Dichroism measurements were performed on **NRC1** and **NRC2** in water and MeOH. **NRC1** and **NRC2** activities are shown in figure 3.7. The two graphics are reported with the same θ interval to better understand the

differences in CD activity for the two chromophores.

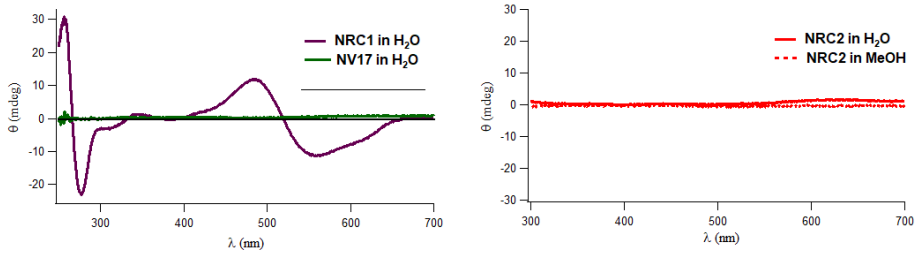


Figure 3.7: CD Spectra of **NRC1** and **NV1** 1 mg/mL solutions in water (*left*) and CD spetctra of **NRC2** 1 mg/mL solutions in water and MeOH

The 1 mg/mL water solution of **NRC1** shows dichroic activity defining the chirality of the supramolecular structures. From the spectrum it was possible to obtain other information about the structures. This a typical spectrum of an exciton-coupled system. There are two couplets: one is centered at 518 nm and the other one at 266 nm. They both aren't at the same value of the λ_{max} of the two absorption peaks **NRC1** has in the 200-800 nm region. They both present a batochromic shift respect to it. The exciton couplet in the Visible region is referred to a system where at least two chromophore units are near in space. Looking at the structure of the dye, it consists of a anthraquinone unit and a lactose residue. The first one is undoubtely a hydrophobic unit, while the sugar is the water soluble side of the molecule. It is reasonable to think that the interaction between dye molecules in the supramolecular aggregates is related to the hydrophobic interactions between the aromatic units, in particular the π-stacking. Dye molecules are stacked one over the other forming H or J aggregates. The negative sign of the exciton couplets suggest the presence of a left handed rotation of the electric dipole transition moment of the stacked chromophores, indicating the presence of a left ended screw aggregation of the dyes. In MeOH it doesn't have any dichroic activity, highlighting the absence of **NRC1** aggregates in this solutions.

There are two hypothesis for the chirility of the molecule, but further investigation is needed. The presence of the sugar unit could influence a particular aggregation. Nine of the ten stereogenic carbon atoms have the same absolute configuration, as it doesn't change in any process of lactose modification. Anyway once the compound goes under deprotection, the ring closure restores the

two anomers with a β/α ratio higher than 1, in accordance with the natural anomers distribution of lactose water solutions. Bearing in mind the bulkyness of the lactose structure, the presence of two anomers doesn't represent a relevant change in the structure of the entire molecule. The presence of chiral aggregates was for this reason assigned to a contribution made by the sugar unit. Anyway the **NRC2** water solution doesn't present any chiral aggregate, indicating that this compound aggregate in a different way.

The analyses of the Circular Dichroism spectra in water for a 1 mg/mL solution of **NRC1** was also studied with an increasing amount of SDS (Figure 3.8)

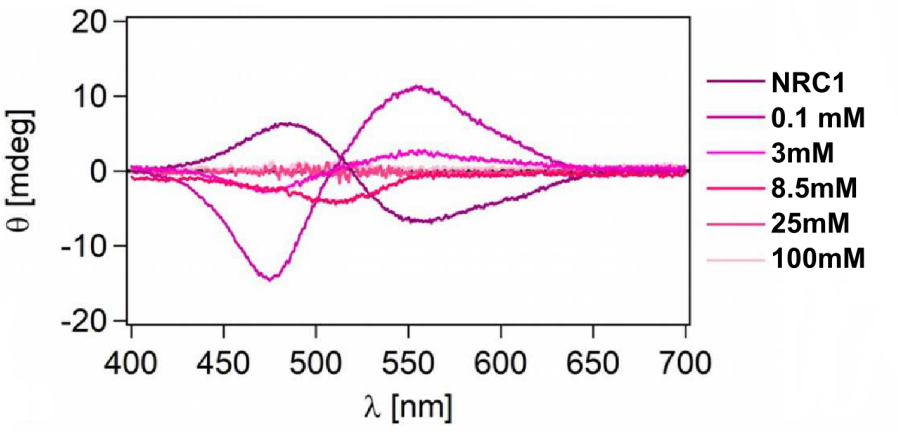


Figure 3.8: CD spectra of a **NRC1** 1 mg/mL solution with increasing amount of SDS

The addition of SDS even at very low concentration (0.1 mM) show an inversion of the absorption profile. This can be assigned to the inversion of the elicity of the aggregates in solution. From these results it was concluded that **NRC1** present at least two forms of aggregates aggregates in solution, and the addition of SDS change the equilibrium ratio among them. Anyway, the decrease of CD activity increasing SDS concentration allows the hypothesis that the surfactant destroys the aggregates, as it was thought from a preliminar analysis of the bathochromic shift of λ_{max} in the Visible spectra at different SDS concentration.

Chapter 4

Matherials and Methods

Procedure A for the synthesis of compounds **6a-6i**

In a 100 mL round-bottom flask $Pd(OAc)_2$ (0.05 mmol) and PPh_3 (0.2 mmol) were dissolved in 30 mL of THF under N_2 atmosphere and stirred for 10 minutes. Then a solution of KOH (2.5 mmol) in 8 mL of water was mixed with THF solution. Anthraquinone **5** (1 mmol) and the boronic acid (1.5 mmol) were added and the solution was left at reflux for 2-12 hours. The solution was cooled at r.t. and transferred in a 500 mL beaker with 300 mL of demineralized H_2O and stirred for 2 hours. Then a 10% v/v HCl solution was added until pH 2 was reached and the suspension obtained was decanted for 20 minutes. The mixture was filtered under vacuum washing with H_2O, toluene and petroleum ether. The solid was dissolved in EtOH and the solution was stirred for 2 hours at room temperature. The mixture was then filtered and washed with EtOH to recover the product.

Procedure B for the synthesis of compounds **10a-10h**

In a 25 mL round-bottom flask $Pd(OAc)_2$ (0.05 mmol) and P(*o*-tolyl)$_3$ (0.2 mmol) were dissolved in 5 mL DMSO under N_2 atmosphere and stirred for 10 minutes. Then compound **5**, NEt_3 and the opportune styrene were added to the reaction mixture and left at 110 °C under N_2 atmosphere overnight. The solution was cooled at r.t and transferred in a 500 mL beaker with 300 mL of demineralized H_2O and stirred for 2 hours. Then a 10% v/v HCl solution was

added until pH 2 was reached and the suspension obtained was decanted for 20 minutes. The mixture was filtered under vacuum washing with H_2O, toluene and petroleum ether. The solid was dissolved in EtOH and the solution was stirred for 2 hours at room temperature. The mixture was then filtered and washed with EtOH to recover the product.

Procedure C for the synthesis of compounds **12a-12f**

In a 25 mL round-bottom flask $Pd(OAc)_2$ (0.05 mmol) and PPh_3 (0.2 mmol) and CuI (0.1 mmol) were dissolved in 5 mL Pyridine under N_2 atmosphere and stirred for 10 minutes. Then compound **5**, NEt_3 () and the opportune styrene were added to the reaction mixture and left at 90 °C under N_2 atmosphere for 1h. The solution was cooled at r.t and transferred in a 500 mL beaker with 300 mL of demineralized H_2O and stirred for 2 hours. Then a 10% v/v HCl solution was added until pH 2 was reached and the suspension obtained was decanted for 20 minutes. The mixture was filtered under vacuum washing with H_2O, toluene and petroleum ether. The solid was dissolved in EtOH and the solution was stirred for 2 hours at room temperature. The mixture was then filtered and washed with EtOH to recover the product.

Experimental Section

Materials for synthesis

Commercially available reagents were purchased from Sigma Aldrich, Fluorochem or TCI and they were used directly. The notation PE refers to the petrol ether fraction boling between 40 and 60 °C. Thin layer cromatography (TLC) analysis was performed using Fluka aluminum foilscoated with 25 mm particle size silica gel matrix F524. TLC development involved either UV (254 and 366 nm) or visible light inspection, followed by either treatment with an acidic solution of *p*-anisaldehyde or a basic solution of $KMnO_4$ and heating. Flash column chromatography was performed on Merck silica gel 60 (particle size 0.040 and 0.063 nm, 230-240 mesh ASTM).

Melting point

Melting points were recorded on a Melting Point Apparatus SMP3-STUART Scientific.

UV-Vis spectroscopy

UV-Visible spectra were recorded on a Cary-4000 Varian spectrophotometer or on a Perkin-Elmer Lambda EZ 201 (Waltham, Massachussetts, USA), using either 1 or 0.1 cm quartz cuvettes.

Infrared spectroscopy

Infrared spectra were recorded in a KBr disk on a Perkin Elmer-Spectrum BX FTIR system.

NMR spectroscopy

^{1}H- and ^{13}C-NMR spectra were recorded at 400 MHz for ^{1}H (100 MHz ^{13}C-C) on a Varian Mercury 400 spectrometer. Spin resonances are reported as chemical shifts (δ) in parts per milliion (ppm) and referenced to the residual peak of the solvent employed, as follows: $CDCl_3$ 7.26 ppm (^{1}H-NMR), 77.0 ppm (^{13}C-NMR, central band), DMSO-d_6 2.50 ppm (^{1}H-NMR, central band), 39.5 ppm (^{13}C-NMR, central band). Spin multiplicity is indicated by s=singlet, d=doublet, m= multiplet, br=braod. Coupling costants J are reported in Herz. MestReNova software was used to elaborate spectra.

Mass spectrometry

Mass spectrometric analysis is quoted in the m/z form. Normal resolution spectra were recorded on a ThermoScientific LCQ-Fleet instrument. HRMS spectra analysis were performed by direct introduction of the samples at a flow rate of 10 μL/min in a Orbitrap high-resolution mass spectrometer (Thermo, Sa José, CA, USA). The instrument was calibrated just before analyses (external calibration). Working conditions were the following: negative polarity, spray voltage - 4 kV, capillary voltage -55 V, capillary temperature 275 °C, yube lens voltage -30 V. The shealth and the auxiliary gas were set, respectively, at 20 (arbitrary units) and 5 (arbitrary units). Xcalibur 2.0 software (Thermo) was

used for spectra acquisition and a nominal resolution (at m/z 400) of 100000 was used.

Elemental analyses

Elemental analyses were recorded on a THERMO FlashEA 1112 Series Elemental Analyzer.

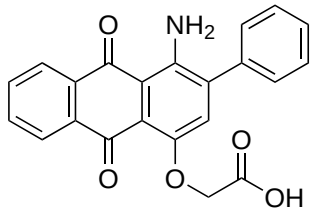
Dynamic light scattering

Dynamic Light Scattering (DLS) measurements were carried out with a Brookheaven Instruments apparatus (BI 9000AT correlator and BI 200 SM goniometer). The light source were a second harmonic ofa diode Nd:YAG laser, $\lambda = 532nm$ Coherent Inova, lineary polarized in the vertical direcion and a HeNe laser, 633 JAS Uniphase, linerly polarized in the vertical direction. The signal was detected by an EMI 9863B/350 photomultiplier.

Circular Dichroism

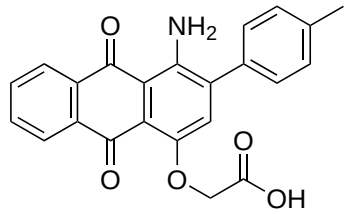
Circular Dichroism measurements were performed on a JASCO J-600 spectropolarimeter, in the 800-200 nm range, using Hellma 1 mm pathlenght quatìrtz cuvettes, scanning speed 50 nm/min, response 1 second, 5 accumulations per sample.

[(4-amino-9,10-dioxo-3-phenyl-9,10-dihydroanthracen-1-yl)-oxy] acetic acid (6a)



Product was synthesized following procedure A. m.p. 218-220 °C. Elem. Anal. Calculated for $C_{22}H_{15}NO_5$: C 70.77% H 4.05% N 3.75%; found C 70.75% H 3.72% N 3.60%; ν_{max}/cm^{-1} 3444, 3064, 1745, 1645, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.19-8.17 (m, 1H), 8.12-8.09 (m, 1H), 7.84-7.79 (m, 2H), 7.57-7.53 (m, 2H), 7.49-7.47 (m, 3H), 7.27 (s, 1H), 4.75 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.0, 181.7, 170.3, 149.8, 145.4, 136.8, 136.3, 133.8, 133.6, 133.3, 133.2, 129.1 (2C), 128.7 (2C), 128.5, 127.8, 125.9 (2C), 120.3, 111.7, 67.4; MS: m/z (rel. int.) 372 (100) [M-]

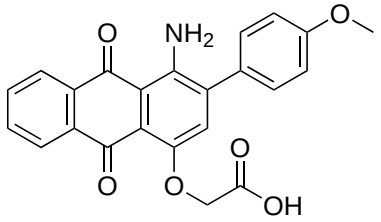
{[4-amino-3-(4-methylphenyl)-9,10-dioxo-9,10-dihydroanthracen-1-yl]oxy}acetic acid (6b)



Product was synthesized following procedure A. m.p 218-220 °C; Elem. Anal. Calculated for $C_{23}H_{17}NO_5$: C 71.31% H 4.42% N 3.62%; found C 71.29% H 4.12% N 3.55%; ν_{max}/cm^{-1} 3461, 3041, 2931, 1735; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.20-8.18 (m, 1H), 8.12-8.10 (m, 1H), 7.87-7.82 (m, 2H), 7.40-7.35 (m, 4H), 7.24 (s, 2H), 4.78 (s, 2H), 2.39 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 181.1, 178.6, 167.4, 146.9, 142.5, 135.1, 133.9, 130.9, 130.6, 130.5, 130.5,

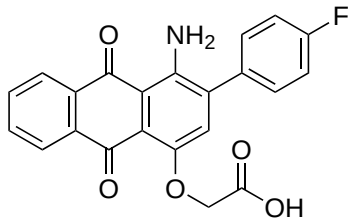
130.4, 126.8 (2C), 125.7 (2C), 124.5, 123.0, 117.0, 108.5, 64.2, 17.8; MS: m/z (rel. int.) 386 (100) [M-], 773 (48) [2M-1]

{[4-amino-3-(4-methoxyphenyl)-9,10-dioxo-9,10-dihydroanthracen-1-yl]oxy}acetic acid (6c)



Product was synthesized following procedure A. m.p. 201-203 °C; Elem. Anal. Calculated for $C_{23}H_{17}NO_6$: C 68.48% H 4.25% N 3.47%; found C 68.48% H 3.81% N 3.14%; ν_{max}/cm^{-1} 3469, 3282, 1743, 1633; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.18-8.16 (m, 1H), 8.09-8.07 (m,1H), 7.83-7.78 (m, 2H), 7.40 (d, J=8 Hz, 2H), 7.14 (s, 1H), 7.08 (d, J=8 Hz, 2H), 4.39 (s, 2H), 3.81 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 183.9, 181.7, 170.2, 159.4, 151.6, 144.7, 137.0, 134.1, 133.6, 133.2 (2C), 130.2 (2C), 128.7, 126.0 (3C), 117.9, 114.6 (2C), 111.2, 68.8, 55.2; MS: m/z (rel. int.) 402 (100) [M-]

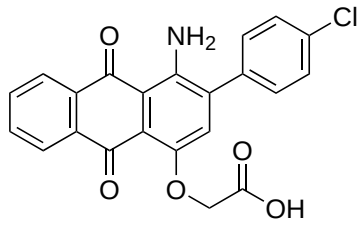
{[4-amino-3-(4-fluorophenyl)-9,10-dioxo-9,10-dihydroanthracen-1-yl]oxy}acetic acid (6d)



Product was synthesized following procedure A. m.p. 230-232 °C; Elem.

Anal. Calculated for $C_{22}H_{14}FNO_5$: C 67.52% H 3.61% N 3.58% found C 67.51% H 3.23% N 3.68%; ν_{max}/cm^{-1} 3461, 3280, 3051, 1753, 1650; 1H NMR^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.21-8.18 (m, 1H), 8.12-8.10 (m, 1H), 7.88-7.83 (m, 2H), 7.56-7.52 (m, 2H), 7.41-7.37 (m, 2H), 7.28 (s, 1H), 4.79 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.1, 181.7, 170.4, 162.2 (d, J=122.5 Hz, C-F), 149.7, 145.6, 136.3, 134.3, 134.0, 133.9, 133.8, 131.6, 131.5, 126.4, 116.6, 116.4, 112.2, 67.8; MS: m/z (rel. int.) 390 (100) [M-], 781 (33) [2M-1]

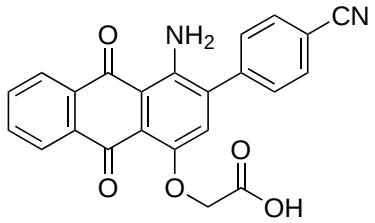
{[4-amino-3-(4-chlorophenyl)-9,10-dioxo-9,10-dihydroanthracen-1-yl]oxy}acetic acid (6e)



Product was synthesized following procedure A. m.p. 234-237 °C; Elem. Anal. Calculated for $C_{22}H_{14}ClNO_2$: C 64.79% H 3.46% N 3.43%; found C 64.67% H 3.45% N 3.33%; ν_{max}/cm^{-1} 3465, 3271, 3062, 1745, 1645; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.20-8.17 (m, 1H), 8.11-8.09 (m, 1H), 7.87-7.82 (m, 2H), 7.63-7.60 (m, 2H), 7.53-7.51 (m, 2H), 7.29 (s, 1H), 4.79 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.6, 170.4, 162.9, 149.7, 145.5, 135.5, 135.2, 133.8, 133.6 (2C), 133.5, 133.4, 138.8 (2C), 129.2 (2C), 127.7, 126.0, 120.5, 111.7, 67.2; MS: m/z (rel. int.) 406 (100) [M-], 813 (33) [2M-1]

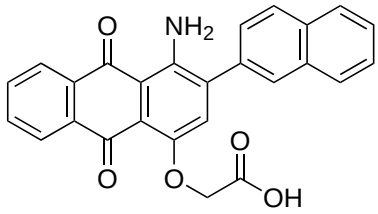
{[4-amino-3-(4-cyanophenyl)-9,10-dioxo-9,10-dihydroanthracen-1-yl]oxy}acetic acid (6f)

Product was synthesized following procedure A. m.p. 260-263 °C; ν_{max}/cm^{-1} 3467, 2225, 1770, 1639; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.18-8.16 (m, 1H), 8.11-8.08(m, 1H), 7.79 (pd, J=8 Hz, 2H), 7.84-7.82 (m, 2H), 7.69 (pd, J=8 Hz, 2H), 4.77 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.7, 170.3, 149.6,



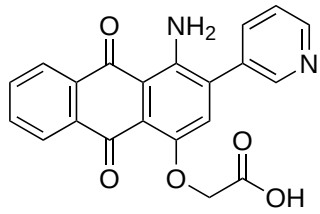
145.2, 141.3, 134.8, 133.8, 133.5 (2C), 133.4, 132.9 (2C), 130.1 (2C), 127.9, 126.0 (2C), 121.1, 118.6, 112.0, 111.2, 67.3; MS: m/z (rel. int.) 397 (100) [M-]; HRMS (ESI-Orbitrap): calculated for $C_{23}H_{13}NO_5$ [M-H]$^-$ 397.0829; found 397.0825

{[4-amino-3-(naphthalen-2-yl)-9,10-dioxo-9,10-dihydroanthracen-1-yl]oxy}acetic acid (6g)



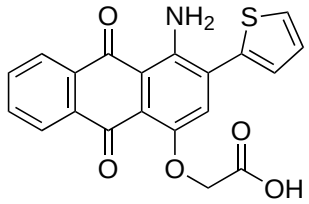
Product was synthesized following procedure A. m.p. 222-225 °C; Elem. Anal. Calculated for $C_{26}H_{17}NO_5$: C 73.75% H 4.05% N 3.31%; found C 73.55% H 4.09% N 3.37%;ν_{max}/cm^{-1} 3467, 3278, 3055, 1757, 1645, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.20-8.17 (m, 1H), 8.13-8.10 (m, 1H), 8.05 (d, J=8.8 Hz, 1H), 8.04 (s, 1H) 7.83-7.81 (m, 2H), 7.59-7.57 (m, 3H), 7.37 (s, 1H), 4.73 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.0, 181.7, 170.5, 150.0, 145.6, 136.8, 133.9 (2C), 133.6, 133.3, 133.2, 133.0, 132.6, 128.6, 128.6, 128.2, 128.1, 127.8, 127.5, 126.6, 126.5 (2C), 126.0, 120.1, 111.7, 67.6; MS: m/z (rel. int.) 422 (100) [M-], 845 (91) [2M-1]

{[4-amino-9,10-dioxo-3-(pyridin-3-yl)-9,10-dihydroanthracen-1-yl] oxy}acetic acid (6h)



Product was synthesized following procedure A. m.p. 217-219 °C; Elem. Anal. Calculated for $C_{22}H_{15}NO_5$: C 67.38% H 3.77% N 7.48%; found C 66.85% H 4.28% N 7.09%; ν_{max}/cm^{-1} 3500-2500, 3473, 3552, 3271, 1747; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.67 (m, 2H) 8.24-8.17 (m, 1H), 8.11-8.09 (m, 1H), 7.91 (dt, J=7.8 Hz, J= 1.6 Hz, 1H), 7.84-7.79 (m, 2H), 7.53 (dd, J=7.8 Hz, J=4.8 Hz), 7.31 (s, 1H), 4.72 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.1, 181.7, 170.3, 149.9, 149.3 (2C), 145.6, 136.6, 133.8, 133.6, 133.3 (2C), 133.2, 132.5, 128.0, 125.9 (2C), 123.8, 120.6, 111.9, 67.5; MS: m/z (rel. int.) 373 (49) [M-], 747 (100) [2M-1]; HRMS (ESI-Orbitrap): calculated for $C_{22}H_{15}NO_5$ [M-H]$^-$ 373.0829; found 373.0825

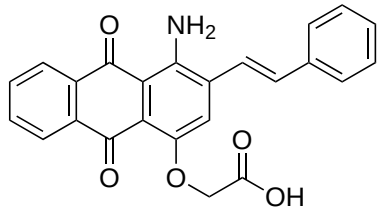
{[4-amino-9,10-dioxo-3-(thiophen-2-yl)-9,10-dihydroanthracen-1-yl]oxy}acetic acid (6i)



Product was synthesized following procedure A. m.p. 225-228 °C; Elem. Anal. Calculated for $C_{20}H_{13}NO_5S$: C 63.32% H 3.45% N 3.69% found C 63.22% H 3.00% N 3.77%; ν_{max}/cm^{-1} 3450, 3272, 3082, 1737, 1633; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.20-8.17 (m,1H), 8.11-8.09 (m, 1H), 7.85-7.83 (m,

2H), 7.78 (dd, J= 5.2 Hz, 1H), 7.62 (dd, J=3.6 Hz, 1H) 7.40 (s, 1H), 7.27 (dd, J= 3.6 Hz, J= 2.4 Hz, 1H), 4.77 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.3, 181.6, 170.4, 149.4, 145.4, 136.9, 133.8, 133.6, 133.5 (2C), 129.1, 128.3 (2C), 128.2 (2C), 128.0 (2C), 127.9 (2C), 126.1 (2C), 126.0 (2C), 120.1, 112.2, 67.3; MS: m/z (rel. int.) 378 (89) [M-], 757 (100) [2M-1]

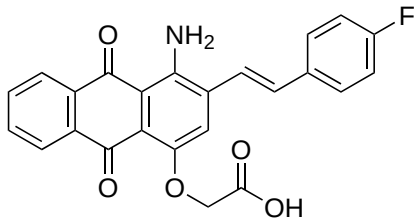
({4-amino-9,10-dioxo-3-[(*E*)-2-phenylethenyl]-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10a)



Product was synthesized following procedure B. m.p. 217-219 °C; Elem. Anal: calculated for $C_{24}H_{17}NO_6$: C 68.90% H 4.10% N 3.37%; found C 68.90% H 4.50% N 3.37%; ν_{max}/cm^{-1} 3452, 3284, 3028, 1755, 1623; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.20-8.17 (m, 1H), 8.10-8.07 (m, 1H), 7.86-7.80 (m, 2H), 7.4 (d, J=8 Hz, 2H), 7.71 (s, 1H), 7.57 (d, J=16 Hz, 1H, Sistema AB), 7.45-7.32 m, 4H), 4.83 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.5, 170.4, 149.8, 146.4, 136.7, 133.9, 133.6 (2C), 133.5, 133.4, 132.8, 128.7 (2C), 128.5, 127.3 (2C), 126.0 (2C), 122.7, 121.7, 120.4, 111.6, 67.3; MS: m/z (rel. int.) 398 (100) [M-], 797 (30) [2M-1]

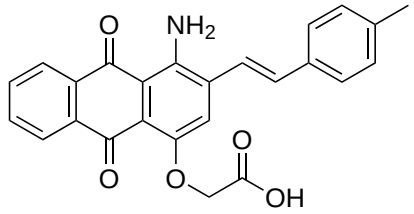
({4-amino-3-[(E)-2-(4-chlorophenyl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10b)

Product was synthesized following procedure B. m.p. 240-243 °C; Elem. Anal: calculated for $C_{25}H_{19}NO_6$: C 69.53% H 4.20% N 3.24%; found: C 69.14% H 3.81% N 3.47%; ν_{max}/cm^{-1}: 3467, 3286, 3065, 1751, 1623, 1588, 1536 ; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.18-8.16 (m, 1H), 8.09-8.07 (m, 1H), 7.86-7.80 (m, 2H), 7.75 (d, J=8Hz, 2H), 7.71 (s, 1H), 7.58 (d, J=16 Hz, 1H), 7.49 (d, J=8



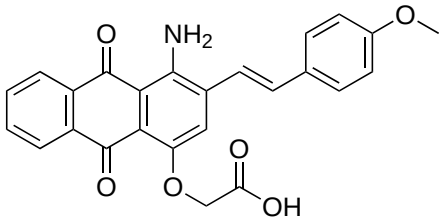
Hz, 2H), 7.36 (d, J=16 Hz, 1H); ^{13}C-NMR (DMSO-d_6) δ 184.2, 181.5, 170.4, 149.8, 146.4, 135.7, 133.8, 133.6, 133.5, 133.4, 132.8, 132.4, 132.2, 128.9 (2C), 128.7 (2C), 126.0 (2C), 122.8, 122.5, 120.6, 111.7, 67.3; MS: m/z (rel. int.) 432 (100) [M-]

({4-amino-3-[(E)-2-(4-methylphenyl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10c)



Product was synthesized following procedure B. m.p. 238-240 °C; Elem. Anal: calculated for $C_{25}H_{19}NO_5$: C 69.44% H 4.43% N 3.24%; found: C 69.43% H 4.67% N 3.37%; ν_{max}/cm^{-1} 3444, 3280, 3022, 1747, 1622; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.19-8.17 (m, 1H), 8.10-8.07 (m, 1H), 7.84-7.80 (m, 2H), 7.70 (s, 1H), 7.63 (d, J=8 Hz, 2H), 7.51 (d, J=16 Hz, 1H Sistema AB), 7.33 (d, J=16 Hz, Sistema AB), 7.24 (d, J=8 Hz), 4.3 (s, 2H), 2.33 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.4, 170.4, 149.9, 146.3, 138.1, 134.0, 133.9, 133.6 (2C), 133.4, 133.3, 133.0, 129.3 (2C), 127.3 (2C), 126.0 (2C), 122.4, 120.5, 120.1, 111.6, 67.3, 20.9; MS: m/z (rel. int.) 412 (100) [M-], 825 (26) [2M-1], 847 (62) [2M-1+Na]

({4-amino-3-[(E)-2-(4-methoxyphenyl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10d)



Product was synthesized following procedure B. m.p. 229-231 °C; Elem. Anal: calculated for $C_{25}H_{19}NO_6$: C 69.92%, H 4.46%, N 3.26%; found: C 69.86%, H 4.62%, N 3.30%; ν_{max}/cm^{-1} 3434, 3276, 2931, 1745, 1622; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.21-8.18 (m, 1H), 8.11-8.09 (m,1H), 7.85-7.83 (m, 2H), 7.69 (d, J=8Hz, 2H), 7.68 (s, 1H), 7.43 (d, J=16 Hz, 1H), 7.33 (d, J=16 Hz, 1H), 7.01 (d, J= 8.4 Hz, 2H), 4.83 (s, 2H), 3.81 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.4, 170.5, 159.7, 150.1, 146.3, 133.9, 133.6, 133.4 (2C), 133.3 (2C), 129.4, 128.8 (2C), 126.0, 125.9, 122.0, 119.8, 119.2, 114.2 (2C), 111.5, 67.4, 55.3; MS: m/z (rel. int.) 428 (100) [M-]

({4-amino-3-[(E)-2-(4-aminophenyl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10e)

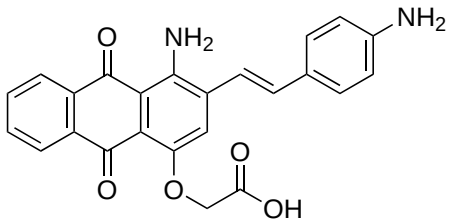
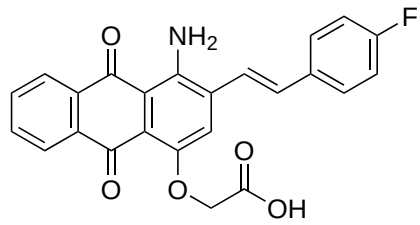


Figure 4.1: attraversamento

Product was synthesized following procedure B. m.p. 245-247 °C; Elem.

Anal: calculated for $C_{24}H_{18}N_2O_5$: C 66.51% H 4.19% N 6.46%; found C 66.50% H 4.41 N 6.81%; ν_{max}/cm^{-1} 3417, 3008, 2358, 1747, 1604; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.20-8.17 (m, 1H), 8.10-8.08 (m, 1H), 7.85-7.80 (m, 2H), 7.61 (s, 1H), 7.44 (d, J=8 Hz, 2H), 7.23 (s, 2H), 6.60 (d, J=8 Hz, 2H), 4.82 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.1, 181.2, 170.5, 150.3, 149.8, 146.3, 134.8, 134.2, 134.0, 133.7, 133.3 (2C), 128.9 (2C), 126.0, 125.9, 124.4, 121.0, 119.0, 115.3, 113.7 (3C), 111.3, 67.3; MS: m/z (rel. int.) 413 (100) [M-]

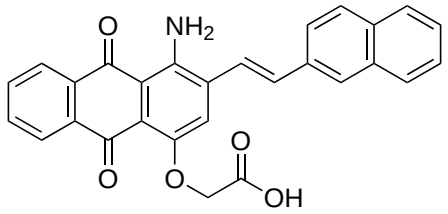
({4-amino-3-[(E)-2-(4-fluorophenyl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10f)



Product was synthesized following procedure B. m.p. 244-246 °C; Elem. Anal: calculated for $C_{24}H_{16}FNO_5$: C 69.06%, H 3.86%, N 3.86%; found: C 68.95%, H 3.55%, N 4.11%; ν_{max}/cm^{-1} 3452, 3286, 3068, 1753, 1625; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.18-8.15 (m, 1H), 8.08-8.06 (m, 1H), 7.83-7.76 (m, 4H) 7.68 (s, 1H) 7.50 (d, J=16 Hz, Sistema AB, 1H), 7.35 (d, J= 16 Hz, Sistema AB, 1H), 7.28-7.24 (m, 2H,), 4.82 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.6, 181.9, 170.9, 162.6 (d, J=245 Hz, C-F), 150.3, 146.8, 134.3, 134.0, 133.9, 133.8, 133.1, 132.8, 129.7 (d, J=9 Hz, C-F), 126.4, 123.1, 122.0, 120.8, 116.1 (d, J= 22 Hz), 112.1, 67.8; MS: m/z (rel. int.) 416 (100) [M-]

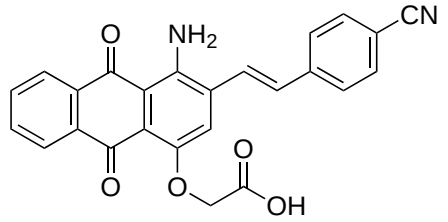
({4-amino-3-[(E)-2-(naphtalen-2-yl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10g)

Product was synthesized following procedure B. m.p. 241-243 °C; Elem. Anal: calculated for $C_{25}H_{19}NO_5$: C 71.79%, H 4.08%, N 2.99%; found C 71.78%, H 4.47% N 2.90%; ν_{max}/cm^{-1} 3438, 3286, 3053, 2356, 1747, 1622; ^{1}H-NMR (400



MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.17-8.15 (m, 1H), 8.08-8.07 (m, 2H), 8.03 (d, J=9 Hz, 1H, Sistema AB), 7.93 (d, J=9 Hz, 1H, Sistema AB) 7.92-7.90 (m, 2H), 7.81-7.79 (m, 2H), 7.75 (s, 1H), 7.68 (d, J=15.6 Hz, 1H, Sistema AB), 7.53-7.49 (m, 3H), 4.86 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.5, 170.4, 149.6, 146.5, 141.4, 133.8, 133.5 (2C), 133.4 (2C), 132.6 (3C), 131.6 (2C), 127.9 (3C), 126.0 (2C), 125.3, 123.2 (2C), 121.2, 118.9, 111.9, 110.2, 67.4; MS: m/z (rel. int.) 448 (100) [M-], 897 (23) [2M-1]

({4-amino-3-[(E)-2-(4-cyanophenyl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yl}oxy)acetic acid (10h)



Product was synthesized following procedure B. m.p. 248-250 °C; Elem. Anal: calculated for $C_{25}H_{16}N_2O_5$: C 67.72% H 3.64%, N 6.32%; found C 67.71% H 4.03% N 6.24%; ν_{max}/cm^{-1} 3438, 3288, 3062, 2225, 1747, 1625; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.20-8.17 (m, 1-H), 8.09-8.06 (m, 1H), 7.91-7.86 (m, 2H), 7.84-7.81 M, 2H), 7.75 (s, 1H), 7.73 (d, J=16 Hz, 1H, Sistema AB), 7.43 (d, J=16Hz, 1H, Sistema AB), 4.82 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.5, 170.3, 149.6, 146.5, 141.3, 133.8, 133.5 (2C), 133.4, 132.6 (2C), 131.6 (2C), 127.9 (2C), 126.0 (2C), 125.3, 123.2, 121.1, 118.9, 111.9, 110.2, 67.4; MS: m/z (rel. int.) 423 (100) [M-]

[4-amino-9,10-dioxo-3-(phenylethynyl)-9,10-dihydroanthracen-1-yl] oxyacetic acid (12a)

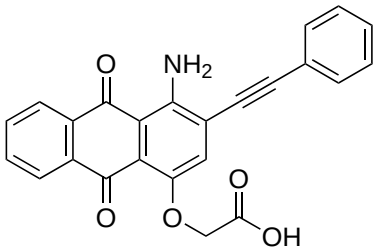
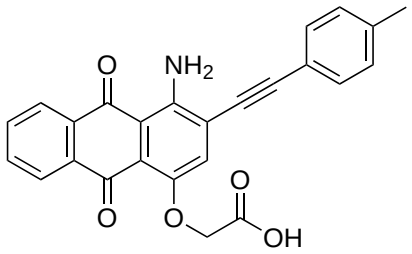


Figure 4.2: attraversamento

Product was synthesized following procedure A. m.p. 218-220 °C. Elem. Anal. Calculated for $C_{24}H_{15}NO_5$: C 72.54% H 3.80% N 3.51%; found C 72.75% H 3.51% N 3.60%; ν_{max}/cm^{-1} 3438, 3290, 2200, 1740, 1631, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.19-8.17 (m, 1H), 8.10-8.08 (m, 1H), 7.85-7.83 (m, 2H), 7.74-7.63 (m, 2H), 7.63 (s, 1H), 7.48-7.47 (m, 3H), 4.78 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.4, 170.3, 149.1, 147.4, 133.9, 133.6 (2C), 133.2 (2C), 131.8 (2C), 129.5, 128.9, 128.6 (2C), 126.1, 126.0 (2C), 121.5, 116.8, 111.8, 99.1, 84.2, 67.1; MS: m/z (rel. int.) 396 (100) [M-]

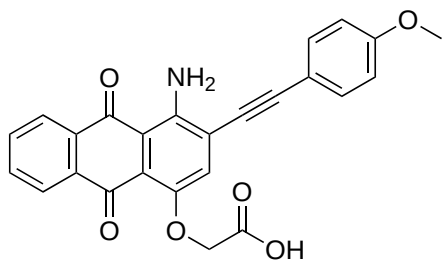
(4-amino-3-[(4-methylphenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yloxy)acetic acid (12b)



Product was synthesized following procedure A. m.p. 218-220 °C. Elem. Anal. Calculated for $C_{22}H_{15}NO_5$: C 72.99% H 4.16% N 3.40%; found C 72.45%

H 4.21% N 3.60%; ν_{max}/cm^{-1} 3460, 3305, 3064, 2197, 1776, 1749, 1637, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.19-8.17 (m, 1H), 8.11-8.07 (m, 1H), 7.63-7.60 (3, 2H), 7.28-7.26 (m, 2H), 4.77 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.2, 181.4, 170.2, 149.1, 147.3, 139.4, 133.8, 133.5 (2C), 133.2, 131.7 (2C), 129.2 (2C), 129.1 (2C), 128.7, 126.0, 125.9, 121.3, 118.4, 117.1, 111.7, 67.4, 21.1; MS: m/z (rel. int.) 372 (100) [M-]

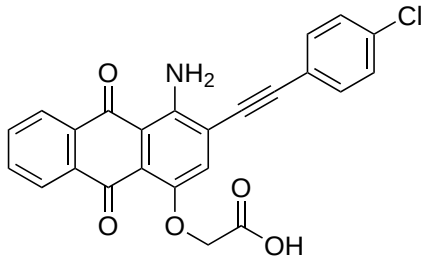
(4-amino-3-[(4-methoxyphenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yloxy)acetic acid(12c)



Product was synthesized following procedure A. m.p. 218-220 °C. Elem. Anal. Calculated for $C_{25}H_{17}NO_6$: C 70.25% H 4.01% N 3.28%; found C 70.55% H 3.82% N 3.52%; ν_{max}/cm^{-1} 3444, 3305, 3066, 2197, 1749, 1633, 1604, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.19-8.17 (m, 1H), 8.10-8.08 (m, 1H), 7.84-7.83 (m, 3H), 7.54-7.52 (m, 2H), 6.74-6.72 (m, 2H), 4.76 (s, 2H), 2.99 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.7, 181.8, 160.6 (2C), 149.8, 147.7, 134.4, 134.0 (3C), 133.7, 129.3, 126.5 (2C), 126.4, 121.5, 117.9, 114.8 (3C), 113.8, 112.1, 100.2, 83.6, 55.8; MS: m/z (rel. int.) 426 (100) [M-]

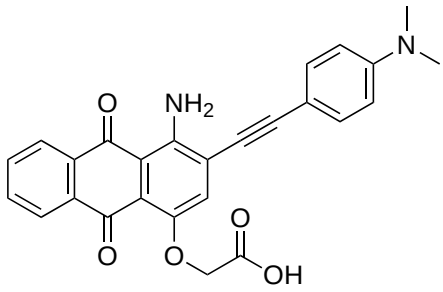
(4-amino-3-[(4-chlorophenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yloxy)acetic acid(12d)

Product was synthesized following procedure A. m.p. 218-220 °C. Elem. Anal. Calculated for $C_{22}H_{15}NO_5$: C 70.77% H 4.05% N 3.75%; found C 70.75% H 3.72% N 3.60%; ν_{max}/cm^{-1} 3458, 3306, 3064, 2200, 1749, 1603, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.18-8.16 (m, 1H), 8.09-8.07 (m, 1H), 7.86-7.84 (m,



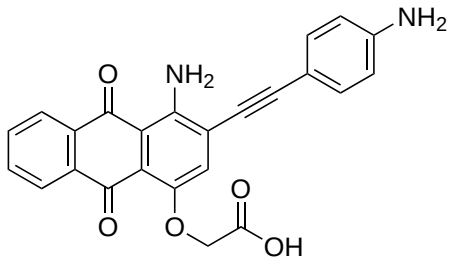
3H), 7.86-7.84 (m, 3H), 7.78-7.76 (m, 3H), 7.56-7.54 (s, 2H), 4.78 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.0, 181.7, 170.3, 149.8, 145.4, 136.8, 136.3, 133.8, 133.6, 133.3, 133.2, 129.1 (2C), 128.7 (2C), 128.5, 127.8, 125.9 (2C), 120.3, 111.7, 67.4; MS: m/z (rel. int.) 430 (100) [M-]

(4-amino-3-((4-dimethylaminophenyl)ethynyl)-9,10-dioxo-9,10-dihydroanthracen-1-yl)oxy)acetic acid (12e)



Product was synthesized following procedure A. m.p. 218-220 °C. Elem. Anal. Calculated for $C_{22}H_{15}NO_5$: C 70.77% H 4.05% N 3.75%; found C 70.75% H 3.72% N 3.60%; ν_{max}/cm^{-1} 3458, 3306, 3064, 2183, 1749, 1633, 1604, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.19-8.17 (m, 1H), 8.12-8.09 (m, 1H), 7.84-7.79 (m, 2H), 7.57-7.53 (m, 2H), 7.49-7.47 (m, 3H), 7.27 (s, 1H), 4.75 (s, 2H), 2.9 (m, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.5, 181.7, 171.3, 150.3, 147.4, 146.5, 133.9, 133.3, 133.2 (2C), 133.1, 127.4 (2C), 126.2 (2C), 125.7, 120.5, 117.9 (2C), 111.4, 107.2, 102.4, 82.5, 67.6, 41.3; MS: m/z (rel. int.) 439 (100) [M-]

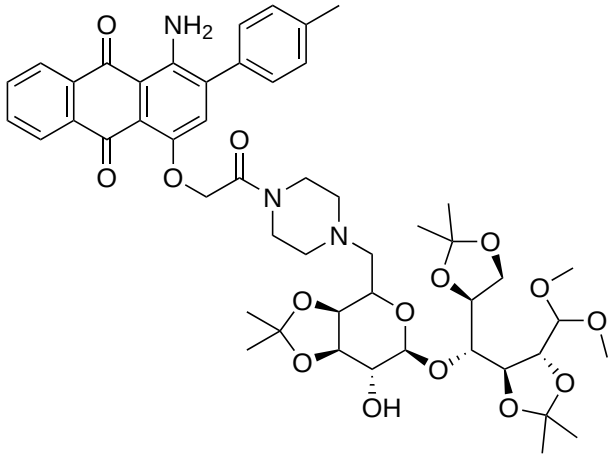
(4-amino-3-[(4-aminophenyl)ethynyl]-9,10-dioxo-9,10-dihydroanthracen-1-yloxy)acetic acid(12f)



Product was synthesized following procedure A. m.p. 218-220 °C. Elem. Anal. Calculated for $C_{24}H_{16}N_2O_5$: C 69.90% H 3.91% N 6.76%; found C 70.25% H 4.12% N 6.60%; ν_{max}/cm^{-1} 3458, 3371, 3305, 2185, 1747, 1633, 1604, 1589; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.19-8.17 (m, 1H), 8.10-8.08 (m, 1H), 7.84-7.82 (m, 2H), 7.49 (s, 1H), 7.40-7.38 (m, 2H), 6.60-6.58 (m, 2H), 4.775 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 184.1, 181.2, 170.3, 150.3, 149.4, 146.9, 133.9, 133.4, 133.3 (2C), 133.2, 127.4 (2C), 126.0 (2C), 125.9, 120.2, 118.5 (2C), 111.3, 106.9, 102.5, 82.2, 67.1; MS: m/z (rel. int.) 411 (100) [M-]

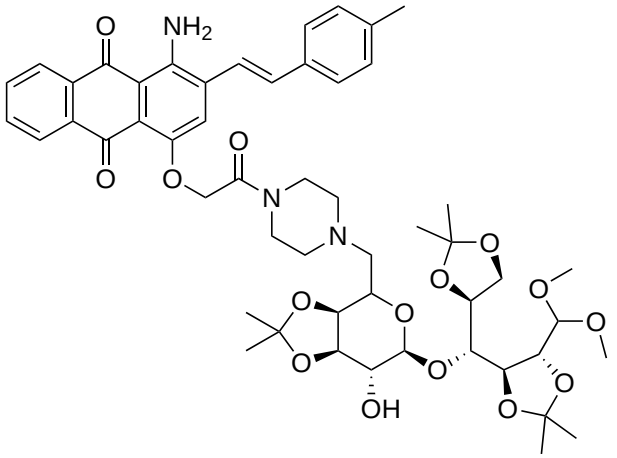
1-amino-4-[2-(4-[(3aS,4R,6S,7R,7aR)-6-{(R)-[(4S,5R)-5-(dimethoxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl][(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-7-hydroxy-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl]methylpiperazin-1-yl)-2-oxoethoxy]-2-(4-methylphenyl)anthracene-9,10-dione (16)

In a 50 ml round-bottom flask compound **6a** (1mmol) and compound **15**1 (1.2 mmol) were dissolved in 20 mL THF under N_2 atmosphere and stirred for 7 h at 50 °C. Then 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium chloride (DMTMM, 1.2 mmol) was added and the mixture was left o/n in the same conditions. Then the solution was cooled at r.t. and THF was evaporated. The slurry was diluted with 50 mL AcOEt and washed with water (2 x 10 mL) and brine (1 x 20 mL). The organic phase was evaporated, and the crude was purified with chromatography on silica gel with DCM/THF 10:1 as eluent.



A red powder is obtained; m.p. 107-109 °C; Elem. Anal. Calculated for $C_{50}H_{63}N3O15$ C 63.48% H 6.71% N 4.44%; found C 63.37% H 6.60% N 4.29%; ν_{max}/cm^{-1} 3477, 2985, 2935, 2358, 2935, 2358, 2341, 1660; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.28-8.26 (m, 1H), 8.22-8.20 (m, 1H), 7.76-7.70 (m, 2H), 7.33-7.31 (m, 5H), 4.82 (s, 2H), 4.38-4.15 (m, 6H), 4.04-3.95 (m, 4H), 3.90-3.65 (m, 4H), 3.58-3.43 (m, 9H), 2.73-2.49 (m, 3H), 2.43 (s, 3H), 1.68 (s, 3H), 1.49 (s, 6H), 1.43 (s, 2H), 1.38 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 185.2, 182.8, 166.5, 150.3, 145.8, 138.9, 137.5, 134.4, 134.1, 133.4, 133.3, 133.1,130.1, 128.7, 128.0, 126.5 , 125.5, 121.6, 113.0, 110.3, 109.9, 108.3, 106.1, 103.9, 78.9, 78.0, 77.9, 76.4, 75.9, 74.6, 74.3, 71.7, 70.6, 64.7, 58.3, 56.8, 54.6, 54.1, 53.3, 45.5, 42.2, 34.2, 30.3, 28.2, 27.3, 26.5, 26.3, 25.7, 24.6, 21.3; MS: m/z (rel. int.) 946 (11) [M^+], 968 (24) [M+Na^+], 1914 (100) [2M+Na^+]

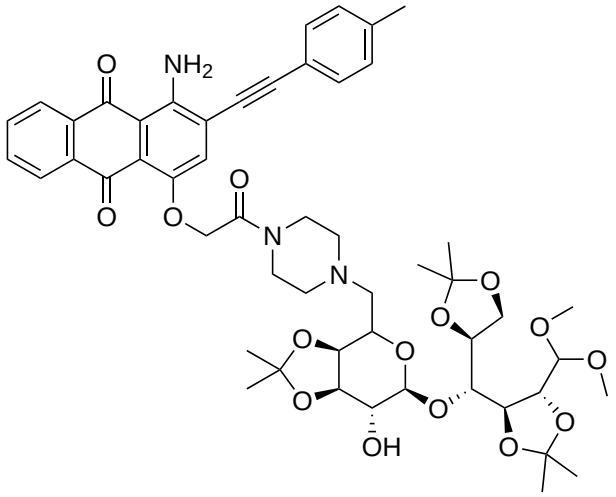
1-amino-4-[2-(4-{[(3aS,4R,6S,7R,7aR)-6-(R)-[(4S,5R)-5-(dimethoxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl][(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-7-hydroxy-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl]methylpiperazin-1-yl)-2-oxoethoxy]-2-[(4-methylphenyl)ethenyl]anthracene-9,10-dione (17)



In a 50 ml round-bottom flask compound **10a** (1 mmol) and compound **15** (1.2 mmol) were dissolved in 20 mL THF under N_2 atmosphere and stirred for 7 h at 50 °C. Then 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium chloride (DMTMM, 1.2 mmol) was added and the mixture was left o/n in the same conditions. Then the solution was cooled at r.t. and THF was evaporated. The slurry was diluted with 50 mL AcOEt and washed with water (2 x 10 mL) and brine (1 x 20 mL). The organic phase was evaporated, and the crude was purified with chromatography on silica gel with DCM/THF 10:1 as eluent. A deep purple powder is obtained; m.p. 110-112 °C; Elem. Anal: calculated for $C_{52}H_{65}N_3O_{15}$: C 64.25% H 6.74% N 4.32%; found C 64.39% H 6.56% N 4.68%; ν_{max}/cm^{-1} 3461, 2985, 2933, 1658;^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.27-8.25 (m, 1H), 8.20-8.18 (m, 1H), 7.75-7.69 (m, 2H), 7.58 (m, 2H), 7.44 (d, J=8 Hz, 2H), 7.28 (s, 1H), 7.19 (d, J=8 Hz, 2H), 7.19 (d, J=16 Hz, 1H, Sistema AB), 7.06 (d, J=16 Hz, 1H, Sistema AB), 4.87 (s, 2H), 4.39-4.36 (m, 2H), 4.30-4.24

(m, 2H), 4.16-3.98 (m, 6H), 3.94-3.50 (m, 8H), 3.42 (s, 6H), 2.27-2.67 (m, 2H), 2.57 (s, 3H), 2.37 (s, 3H), 2.27 (s, 1H), 1.49 (s, 6H), 1.38 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 185.5, 182.6, 166.6, 150.7, 145.7, 139.0, 135.7, 135.4, 134.4, 134.0, 133.8, 133.5, 133.2, 129.6, 127.0, 126.5, 125.5, 124.2, 121.6, 120.2, 113.5, 110.3, 109.9, 108.3, 106.1, 103.9, 78.9, 78.1, 77.9, 76.4, 75.9, 74.6, 74.3, 71.7, 70.7, 64.7, 58.3, 56.8, 54.6, 54.1, 53.3, 45.5, 42.2, 34.2, 30.3, 28.2, 27.3, 26.5, 26.3, 25.7, 24.6, 21.4; MS: m/z (rel. int.) 972 (53) [M$^+$], 994 (100) [M+Na$^+$]

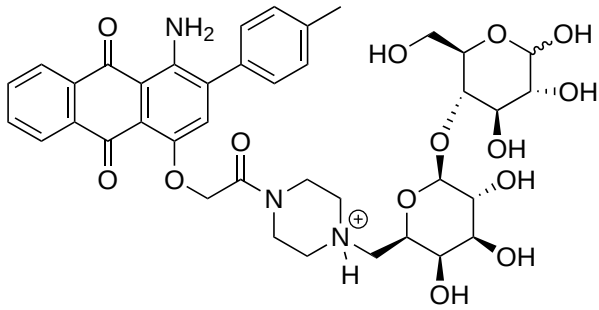
1-amino-4-[2-(4-{[(3aS,4R,6S,7R,7aR)-6-(R)-[(4S,5R)-5-(dimethoxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl][(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-7-hydroxy-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl]methylpiperazin-1-yl)-2-oxoethoxy]-2-[(E)-2-(4-methylphenyl)ethinyl]anthracene-9,10-dione (18)



In a 50 ml round-bottom flask compound **12a** (1 mmol) and compound **15** (1.2 mmol) were dissolved in 20 mL THF under N_2 atmosphere and stirred for 7 h at 50 °C. Then 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium

chloride (DMTMM, 1.2 mmol) was added and the mixture was left o/n in the same conditions. Then the solution was cooled at r.t. and THF was evaporated. The slurry was diluted with 50 mL AcOEt and washed with water (2 x 10 mL) and brine (1 x 20 mL). The organic phase was evaporated, and the crude was purified with chromatography on silica gel with DCM/THF 10:1 as eluent. A dark red powder was obtained; m.p. 108-110 °C; Elem. Anal: calculated for $C_{52}H_{65}N_3O_{15}$: C 64.38% H 6.55% N 4.33%; found C 64.12% H 6.86% N 4.70%; ν_{max}/cm^{-1} 3436, 2985, 2933, 1656;^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.27-8.25 (m, 1H), 8.20-8.18 (m, 1H), 7.74-7.70 (m, 2H), 7.55 (m, 2H), 7.43 (d, J=8 Hz, 2H), 7.27 (s, 1H), 7.19 (d, J=8 Hz, 2H), 4.87 (s, 2H), 4.39-4.36 (m, 2H), 4.30-4.24 (m, 2H), 4.16-3.98 (m, 6H), 3.94-3.50 (m, 8H), 3.42 (s, 6H), 3.25-2.67 (m, 2H), 2.50 (s, 3H), 2.35 (s, 3H), 2.21 (s, 1H), 1.45 (s, 6H), 1.37 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 185.5, 182.6, 166.6, 150.7, 145.7, 139.0, 135.7, 135.4, 134.4, 134.0, 133.8, 133.5, 133.2, 129.6, 127.0, 126.5, 125.5, 124.2, 121.6, 120.2, 113.5, 110.3, 109.9, 108.3, 106.1, 103.9, 78.9, 78.1, 77.9, 76.4, 75.9, 74.6, 74.3, 71.7, 70.7, 64.7, 58.3, 56.8, 54.6, 54.1, 53.3, 45.5, 42.2, 34.2, 30.3, 28.2, 27.3, 26.5, 26.3, 25.7, 24.6, 21.4; MS: m/z (rel. int.) 970 (53) [M$^+$], 992 (100) [M+Na$^+$]

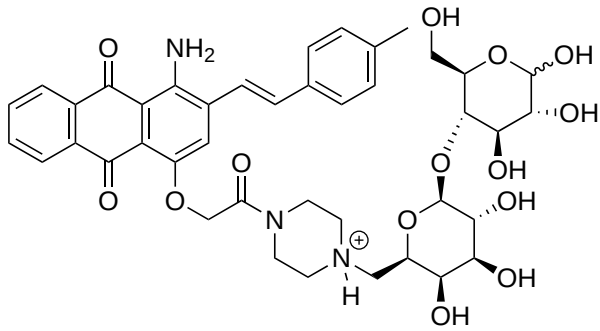
4-O-[6-(4-{[(4-amino-9,10-dioxo-3-phenyl-9,10-dihydroanthracen-1-yl)oxy]acetyl}piperazin-1-ium-1-yl)-6-deoxy-b-D-galactopyranosyl]-D-xylo-hexopyranose (19)



Iin a 25 mL round-bottom flask compound **16** (0.5 mmol) was dissolved in 5 mL acetone and cooled to 0 °C under magnetic stirring. Then a solution of HCl

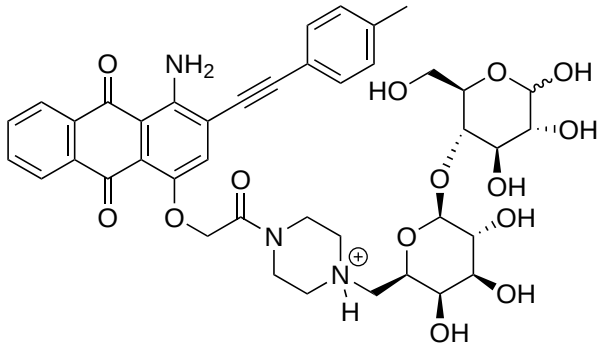
conc. (37% w/w, 109 μL) in H2O (2 mL) was added dropwise and the solution was heated to r.t. and left o/n. Finally, the mixture was diluted with acetone and it was filtered under vacuum washing with acetone. Compounds 14 and 15 were was then dried to eliminate any water residual. MS: m/z (rel. int.) 802 (100) [M+Na^+], 816 [M+OCH2+Na^+]; HRMS (ESI-Orbitrap): calculated for $C_{39}H_{46}N_3O_{14}$ [M-H]: 780.2974; found 780.2964

4-O-{6-[4-([4-amino-3-(4-methylphenyl)-9,10-dioxo-9,10-dihydroanthracen-1-yl]oxy}acetyl)piperazin-1-ium-1-yl]-6-deoxy-b-D-galactopyranosyl-D-glucopyranose(20)



In a 25 mL round-bottom flask compound **17** (0.5 mmol) was dissolved in 5 mL acetone and cooled to 0 °C under magnetic stirring. Then a solution of HCl conc. (37% w/w, 109 μL) in H2O (2 mL) was added dropwise and the solution was heated to r.t. and left o/n. Finally, the mixture was diluted with acetone and it was filtered under vacuum washing with acetone. Compound **15** were then dried to eliminate any water residual. MS: m/z (rel. int.) 828 (100) [M+Na^+], 842 [M+OCH2+Na^+]; HRMS (ESI-Orbitrap): calculated for $C_{41}H_{48}N_3O_{14}$ [M-H]: 806.3130; found 806.3128

4-O-(6-4-[({4-amino-3-[(E)-2-(4-methylphenyl)ethenyl]-9,10-dioxo-9,10-dihydroanthracen-1-yloxy)acetyl]piperazin-1-ium-1-yl}-6-deoxy-b-D-galactopyranosyl)-D-glucopyranose (21)



in a 25 mL round-bottom flask compound **18** (0.5 mmol) was dissolved in 5 mL acetone and cooled to 0 °C under magnetic stirring. Then a solution of HCl conc. (37% w/w, 109 μL) in H2O (2 mL) was added dropwise and the solution was heated to r.t. and left o/n. Finally, the mixture was diluted with acetone and it was filtered under vacuum washing with acetone. Compound **15** were then dried to eliminate any water residual. MS: m/z (rel. int.) 826 (100) [M+Na^+], 840 [M+OCH2+Na^+]; HRMS (ESI-Orbitrap): calculated for $C_{41}H_{48}N_3O_{14}$ [M-H]: 804.3125; found 804.3139

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