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MSc in Chemistry

Synthesis of quinoid natural products and analogues

Thesis submitted in fulfillment of the requirements

for the degree of Doctor (PhD) in Applied Biological Sciences:

Chemistry

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List of abbreviations

ADP: Adenoside diphosphate

ATP: Adenoside triphosphate

ATR: Attenuated total reflection

BPO: Dibenzoylperoxide

CAN: Cerium(IV) Ammonium Nitrate

COSY: Correlation Spectroscopy

DIPEA: Diisopropylethylamine

DMF-DMA: *N,N*-dimethylformamide-dimethylacetal

DNA: DeoxyriboNucleic Acid

DEPT: Distortionless Enhancement by Polarization Transfer

EBV-EA: Epstein Barr Virus Early Antigen (activation)

HMBC: Heteronuclear Multiple-Bond Connectivities

HSQC: Heteronuclear Single Quantum Correlation

IC50: Inhibitory Concentration 50% level

IR: Infra Red spectroscopy

LG: Leaving Group

m-CPBA: *meta*-Chloroperbenzoic acid

MIC: Minimum Inhibitory Concentration

NAD: Nicotinamide Adenine Dinucleotide

NADP: Nicotinamide Adenine Dinucleotide Phosphate

NMR: Nuclear Magnetic Resonance

NBS: Nitrogen Bromosuccinimide

NOE: Nuclear Overhauser Effect

MDR-TB: Multidrug Resistant Tuberculosis

MS: Mass Spectroscopy

PIFA: Phenyliodine bis(trifluoroacetate)

PG: Protecting group

PPA: Polyphosphoric acid

PPTS: Pyridinium *para*-toluenesulfonyl

p-Ts: *para*-Toluenesulfonyl

RCM: Ring Closing Metathesis

RNA: Ribo Nucleic Acid

ROS: Reactive Oxygen Species

SOD: Superoxide dismutase

TB: Tuberculosis

TLC: Thin Layer Chromatography

TMS: Tetramethylsilane

TPM: Tripiperidinomethane

UDP: Uridine diphosphate

UV-Vis: UltraViolet -Visual spectroscopy

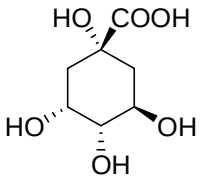
WHO: World Health Organization

Chapter 1: Introduction and goals

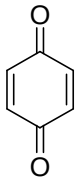
1.1. Introduction

Quinones constitute a valuable class of organic compounds that are non-aromatic but fully conjugated cyclic diketones. Each of these compounds is named after its aromatic analogue. For instance, benzene gives rise to *benzoquinone*, naphthalene to *naphthoquinone*, anthracene to *anthraquinone, etc...* However, the term *quinone* stems etymologically from the native South-America Quechua word *kina-kina*, which can be translated through the Spanish word *quina* meaning *Cinchona* bark.

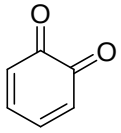
Despite the discovery of 1,4-benzoquinone **2** by the Polish chemist Alexandre Wosrerenski in 1838, quinones rose up in the literature around the mid-nineteenth century with the oxidation of quinic acid **1** (Figure 1-1), which was isolated from *Cinchona* species (Rubiaceae), a genus of medicinal plants native to tropical South-America, to 1,4-benzoquinone **2** (Figure 1-1).[1]



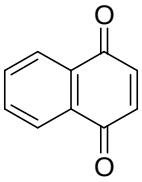
1 quinic acid



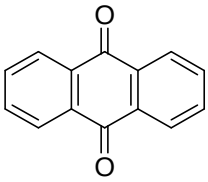
2 1,4-benzoquinone



3 1,2-benzoquinone



4 1,4-naphthoquinone

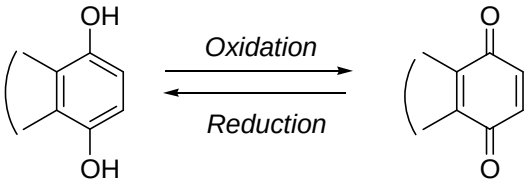


5 9,10-anthraquinone

Figure 1-1. Structure of quinic acid **1** and some simple quinones

The simplest and prototypical examples of the class of quinones are 1,4-benzoquinone **2** and 1,2-benzoquinone **3**. Other relevant members are 1,4-naphthoquinone **4** and 9,10-anthraquinone **5**, which constitute the basic core of many naturally occurring quinones.

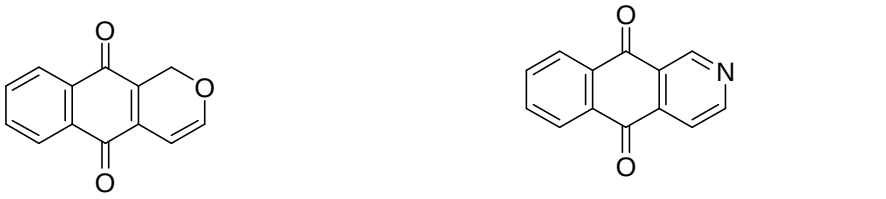
The chemistry of this class of compounds is dominated by the reversible conversion between hydroquinones **6** and quinones **7** (Scheme 1-1), which is of paramount importance to different biological systems, much as the respiratory chain.[2]



6 **7**

Scheme 1-1. *para*-Quinone redox equilibrium

The electron-donating groups present on aromatic compounds **6** increase the electron-density of the aromatic system and contribute to reach the necessary redox potential to break the aromaticity by an oxidation process giving rise to quinones **7**. The latter compounds **7** are electrophilic Michael acceptors, which are stabilized by conjugation and across which addition reactions occur. These addition reactions often result in the formation of the corresponding hydroquinones due to aromatization. In addition, quinones are excellent dienophiles for Diels-Alder reactions.[3]



8 1*H*-pyranonaphthoquinone (pentalongin) **9** 2-azaanthraquinone

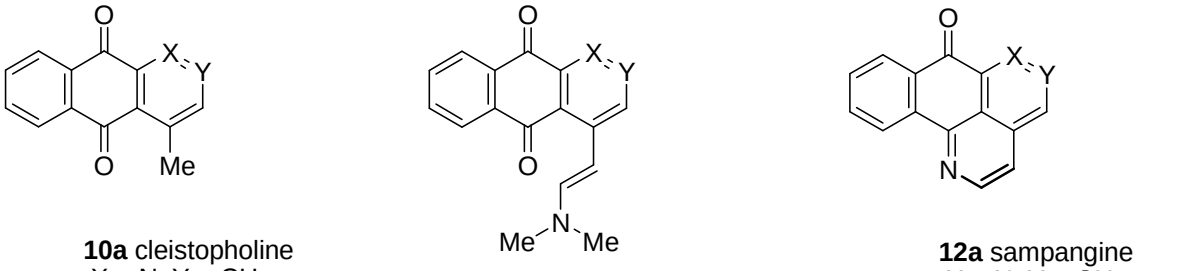
Figure 1-2. Examples of heterocyclic quinones

The class of quinones also includes heterocyclic compounds such as pyranonaphthoquinone **8** and 2-azaanthraquinone **9** (Figure 1-2). The heterocyclic moiety may be constructed selectively starting from either quinone derivatives or their reduced analogues which may be reoxidized in a subsequent step.[4] In case of hydroquinones **6**, this oxidation can be achieved spontanously in the presence of air oxygen.[5] Several other reactions such as rearrangement reactions,[6] the phthalide annulation,[5,7] Friedel-Crafts acylation,[8] palladium catalyzed coupling reactions,[9] Knorr cyclization,[10] *ortho*-lithiation[11] and the dominating hetero Diels-Alder addition[2a,5b] are described in literature to synthesize heterocyclic quinones. The syntheses of 2-azaanthraquinone derivatives as potential new antibiotics against *Mycobacterium* strains are integral parts of the present thesis. Heterocyclic quinones encompass several types of potent biologically active compounds and antibiotics.[12] As a result, they are used as templates in drug discovery and development.

1.2. Goals of the research

The goals for the present reseach were set forth in the three following areas:

(1) Azaanthraquinones **10** and naphthonaphthyridines **12** represent two important related classes of bioactive compounds (Figure 1-3). For instance, cleistopholine **10a** and sampangine **12a** are two strongly related alkaloids which are renowned for their antibiotic activity and which have been initially isolated from the African tropical Annonaceae species *Cleistopholis patens*[13] and the Asian Annonaceae species *Cananga odorata,*[14] respectively. Due to their interesting biological activities, the syntheses of cleistopholine **10a**, sampangine **12a** and their derivatives represent an attractive target for organic chemists.[15] However, their 2-aza analogues, 2-azacleistopholine **10b** and 2-azasampangine **12b** have never been isolated from a natural source nor been synthesized hithertho. In the published synthetic methods of cleistopholine **10a** and sampangine **12a**,[15] the synthesis of cleistopholine **10a** derivatives led to the efficient synthesis of sampangine **12a** derivatives *via* 4-(2-dimethylaminovinyl)benzo[*g*]quinoline-5,10-dione **11a** as the key intermediate, which has been found to exert potent biological activities.[15d] Furthermore, the synthesis of sampangine **12a** can even be accomplished starting from cleistopholine **10a** in a one-pot process without the isolation and purification of the corresponding intermediate **11a**.[15a] Since it is known that 2-azaanthraquinones are more active than the corresponding 1-azaanthraquinones,[15d] the first objective of the present work was to unfold an efficient total synthesis of the hitherto unknown 2-azacleistopholine **10b**, 4-(2-dimethylaminovinyl)-2-azacleistopholine **11b** and 2-azasampangine **12b**.



10a cleistopholine
X = N, Y = CH
10b 2-azacleistopholine
X = CH, Y = N

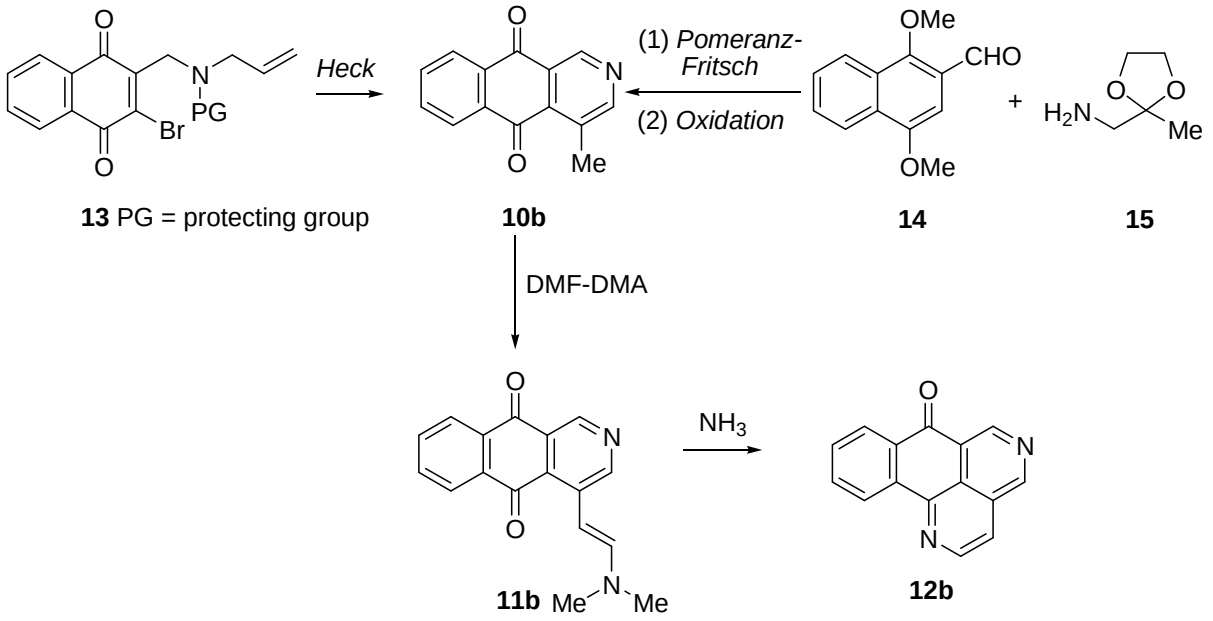
11a X = N, Y = CH
11b X = CH, Y = N

12a sampangine
X = N, Y = CH
12b 2-azasampangine
X = CH, Y = N

Figure 1-3. Structures of 1- and 2-azaanthraquinone lead and target molecules

Two synthetic methodologies will be investigated towards the targeted 2-azacleistopholine **10b**. The Heck reaction of a suitable naphthoquinone **13** and the Pomeranz-Fritsch reaction of 2-formyl-1,4-dimethoxynaphthalene **14** and 2-aminomethyl-2-methyl-1,3-dioxolane **15** will be explored. Once the synthesis of the 2-azacleistopholine **12b** is completed, the synthesis of 2-aza-4-[2-(dimethylamino)vinyl]

cleistopholine **11b** and 2-azasampangine **12b** is envisaged by treatment of 2-azacleistopholine **10b** with DMF-DMA and subsequent reaction with ammonia, respectively (Scheme 1-2).



Scheme 1-2. Synthetic strategies towards the targeted 2-azacleistopholine **10b** and 2-azasampangine **12b**

(2) 2-Azaanthraquinones continue to draw much attention among medicinal chemists since they display a wide spectrum of biological activities. SAR studies established the relevance of the substitution pattern of the *peri*-carbonyl position in increasing biological activities of these molecules.[16] For instance, the presence of a hydroxyl group at the C-1 *peri*-carbonyl position was found to enhance the antibiotic activity.[16] Alternatively, the antifungal activity of naphthoquinonoids also requires the presence of a hydroxyl group at the C-1 *peri*-carbonyl position.[16b] Since the basic chemical structure of azaanthraquinones is a tricyclic aromatic anthracene, another important feature which determines the biological activity is the presence of a covalent bond between two aromatic rings called the biaryl axis.[2a,17] Therefore, the synthesis of 2-azaanthraquinones **16**, **17** and **18**, substituted at the C-1 *peri*-carbonyl position and linked to phenyl groups through a biaryl axis, was devised in order to make a good library of potential pharmaceuticals. More specifically, 3-aryl-2-aza-1-hydroxyanthraquinones **16**, 3-aryl-2-aza-1-methylanthraquinones **17** and 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylanthraquinones **18** will be targeted (Figure 1-4). In addition, the plan was devised to synthesize 3-aryl-2-aza-1-(2-dimethylaminovinyl)anthraquinones **21**. Finally, subsequent ammonia addition would lead to the corresponding sampangine analogues **22** (Scheme 1-3).

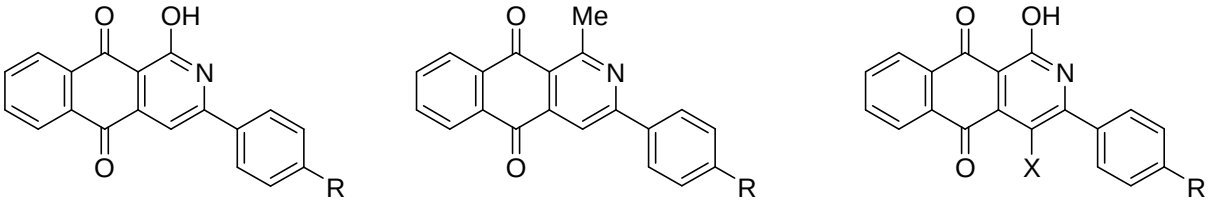
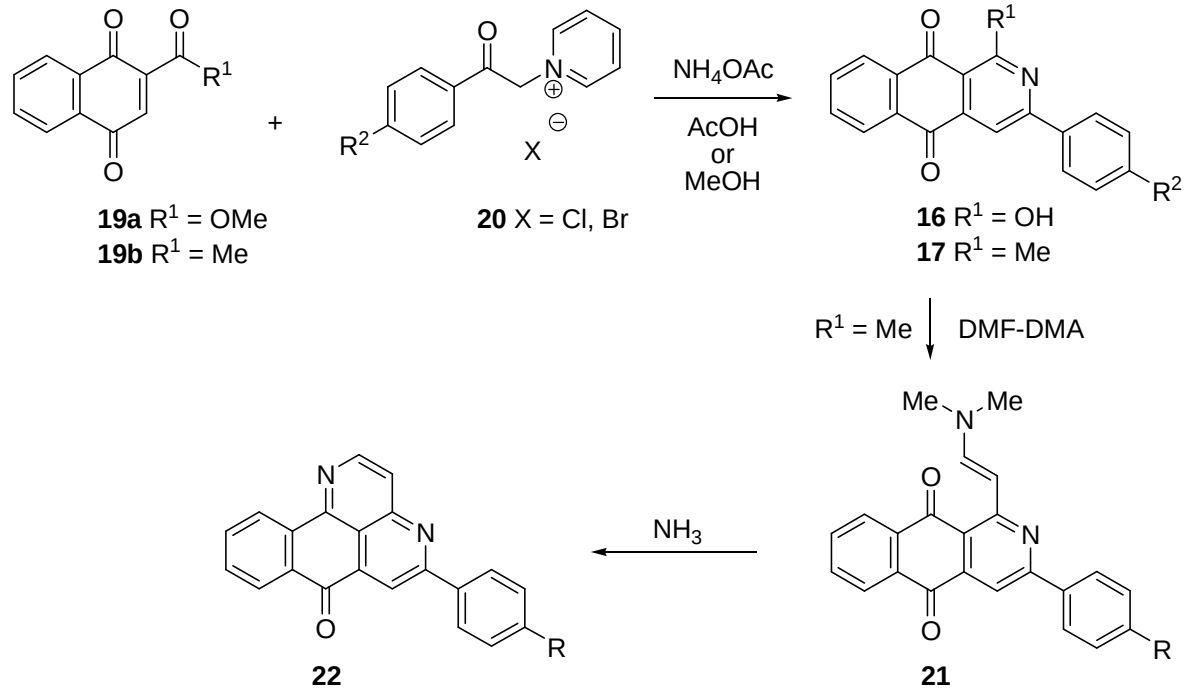


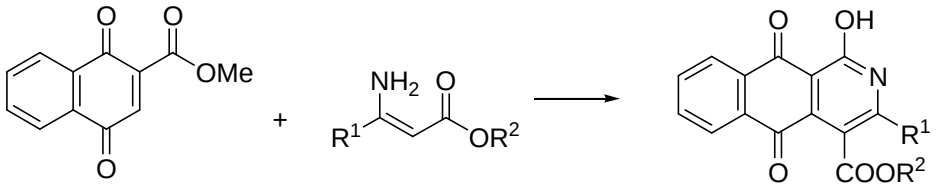
Figure 1-4. Structures of targeted substituted 2-azaanthraquinones **16**-**18**

First, the reaction of different pyridinium salts **20** with activated quinones **19** will be investigated under Kröhnke conditions, which refers to the use of ammonium acetate in methanol or acetic acid. Having the 2-aza-1-methyl-3-arylanthraquinones **17** in hand, the synthesis of 2-aza-1-(2-dimethylaminovinyl)-3-arylanthraquinones **21** will be attempted by using DMF-DMA. Finally, subsequent addition of ammonia would lead to the formation of sampangine analogues **22**.



Scheme 1-3. Synthetic strategy towards substituted 2-azaanthraquinones **16**, **17** and their sampangine analogues **22**

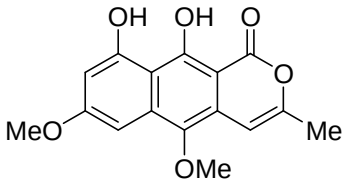
Secondly, the reaction of enaminoesters **23** with the activated naphthoquinone **19a** should give 2-aza-1-hydroxyanthraquinone derivatives **18** upon nucleophilic addition of the enaminoesters **23** and subsequent aza-ring closure, aromatization and oxidation by air oxygen (Scheme 1-4).



19a **23** **18**

Scheme 1-4. Synthetic strategy towards 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylanthraquinones **18**

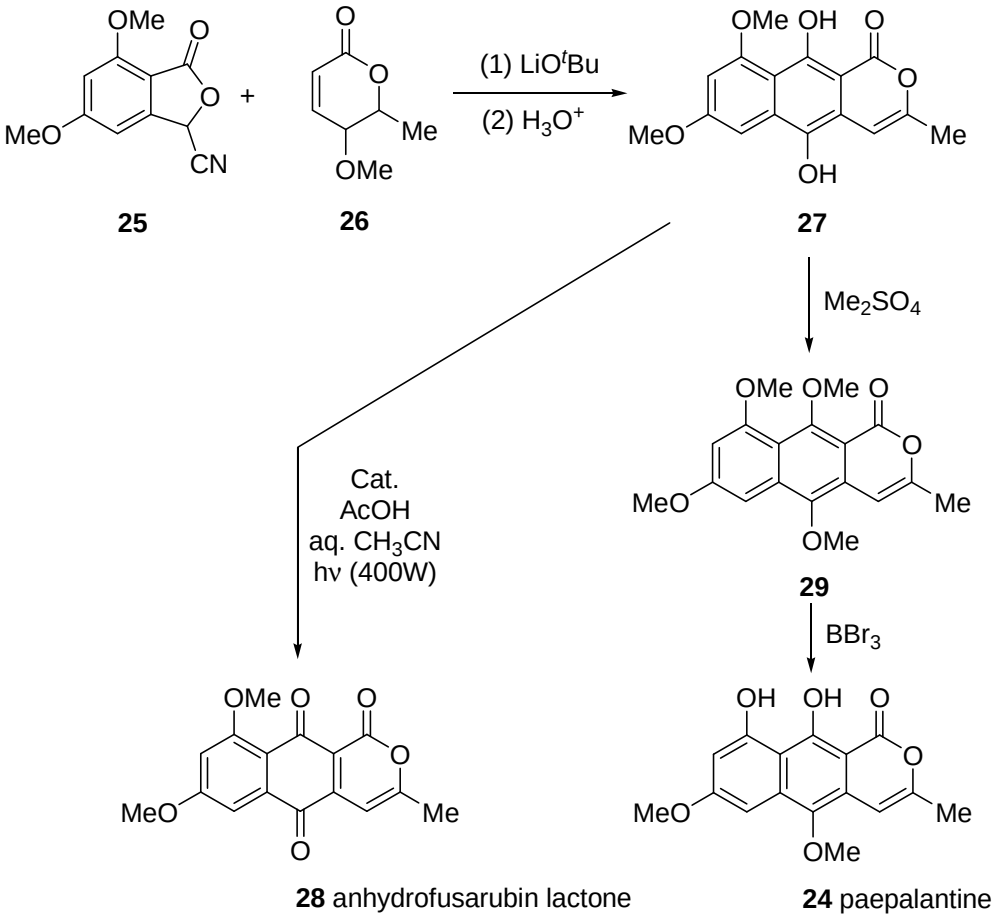
(3) Isocoumarins are secondary metabolites structurally related to the coumarins, but with an inverted lactone ring. These compounds have a wide range of biological activities, including antitumor, antileucemic, antiviral and antimicrobial activities.[18]



24 paepalantine

Figure 1-5. Structure of paepalantine **24**

Paepalantine **24** (Figure 1-5) is the first isocoumarin isolated from *Paepalanthus bromelioides* (Eriocaulaceae),[19] a species widespread and used in traditional medicine in some Brazilian regions. The inhibitory effect on the respiratory burst was reported[20] and it also showed an antimicrobial effect similar to chloramphenicol,[21] and mutagenic and cytotoxic properties.[22] In spite of its biological activity, paepalantine **24** has not been synthesized to date. Therefore, the first synthesis of paepalantine **24** is planned by a phthalide annulation reaction of 3-cyanophthalide **25** and pyran-2-one **26** (Scheme 1-5) for which the synthesis of the unprotected form has been reported in the literature.[23] Acidic workup should give rise to hydroquinone **27** which can be converted to the natural product anhydrofusarubin lactone **28**[24] upon a photochemical oxidation. Alternatively, selective methylation of compound **27** will be investigated and subsequent treatment with boron(III) bromide should give paepalantine **24**.



Scheme 1-5. Synthetic strategy towards paepalantine **24**

Chapter 2: Literature overview

2.1. Modes of actions of quinone biological activities

The detailed mechanism of bioactive quinones in biological systems is not yet fully explored. However, the interaction with biological systems may result from three processes:

(1) A radical-based mechanism generating highly toxic reactive oxygen species (ROS), which trigger oxidative stress, upon interaction with the cellular electron transport system.

(2) An intercalation-based mechanism resulting from quinone insertion between two DNA base pairs causing disturbance of DNA transcription and replication by inhibition of DNA topoisomerases.

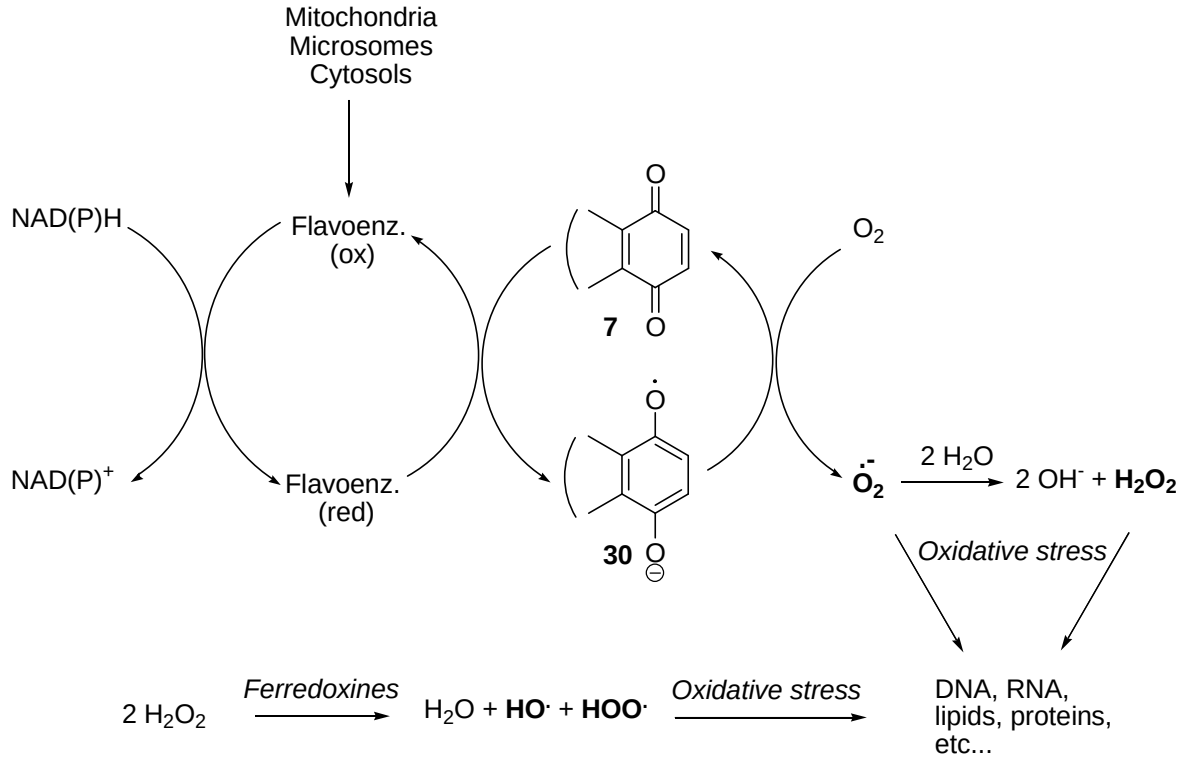
(3) A bioreductive alkylation-based mechanism involving reactions of quinone methides or other electrophilic side chains with vital cell compounds such as DNA, RNA and proteins.

These modes of action are not specific to types of quinones. They may act in synergy for a type of molecule. Thus, the biological activities of benzoquinones, naphthoquinones and pyranonaphthoquinones are generally accepted to be related to a radical-based mechanism and/or bioreductive alkylation while these of anthraquinones are predicted to be an intercalation based mechanism.[25] The biological activities of azaanthraquinones seem to be mediated by DNA intercalation and radical-based mechanisms.[26] In these latter cases, the biological activities are improved by the basic and electron-withdrawing properties of the *N*-heterocyclic ring.[27]

2.1.1. Quinone interaction with the electron transport system. A radical-based mechanism

At the core of many important energy conversion processes in biology are oxidation-reduction reactions in which electrons are transferred through the electron transport system. Famous examples are the photosynthesis and the respiration in green plants, in which carbon dioxide and water combine into glucose and oxygen with energy release ($\Delta G° = -675$ kcal). The electron transport system appears to be particularly stable in some mitochondria where low-content of proteolytic enzymes and a minimum number of respiratory chain-linked dehydrogenases, are present to allow NADH oxidation to NAD^+ by oxygen. Such electron transport system is used by chemotropic and phototropic organisms to allow oxidative phosphorylation of ADP to ATP. The key biological functions of these phenomena are quinone-based couples as electron transfer agents.[28] With regard to these functions, quinones or quinoïd compounds are provided with redox cycling properties, which result in their toxic and therapeutic

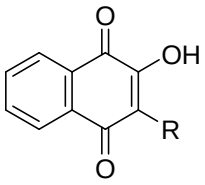
activities. The redox cycling of quinones may be initiated by either a one- or two-electron reduction (Figure 2-1). The one electron reduction of quinones has been suggested to result from the interaction of cellular electron transport systems (containing cytochromes and ferredoxines) to release reactive oxygen species.[29] This process is catalyzed by cellular oxidoreductases (NADH dehydrogenase, NADPH cytochrome P450 reductase and xanthine oxidase)-flavoenzymes which induce one-electron reduction of quinones **7** leading to the formation of semi-quinone anion radicals **30**. These latter compounds react with molecular oxygen to form superoxide, which can be converted to hydrogen peroxide *via* a superoxide dismutase (SOD)-catalyzed reaction, followed by the formation of a hydroxyl radical by the iron-catalyzed reduction of hydrogen peroxide *via* the Fenton-type reaction. The formation of a cascade of reactive oxidative species (superoxide, hydrogen peroxide and hydroxy radicals) triggers the oxidative stress responsible for irresversible cell damage leading to apoptosis or cell death.



Scheme 2-1. Quinone interation with the biological electron transport system

Alternatively, the flavoenzyme DT-diaphorase-mediated two electron reduction of quinones **7** leads to the formation of stable hydroquinones **6**, which are activated *in vivo* to reactive quinone methide species (*vide infra*). These latter compounds are rapidly removed by conjugation with nucleophilic biomolecules such as glutathione, UDP-glucoronic acid, etc. This two electron reduction prossess is catalyzed by the DT-diaphorase that reduces toxic, reactive and unstable quinones shunting the creation of the semiquinone radicals, thus sparing the cell from ROS formation. This process is known to be promoted

by the redox cycling of 2-hydroxy-1,4-naphthoquinones **31** (Figure 2-1) and is considered as a detoxification route for toxic quinones.[30]

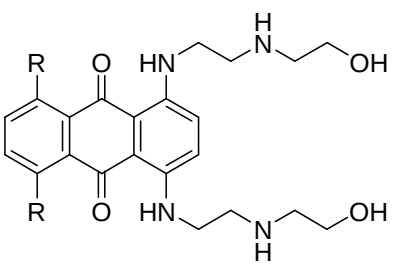


31 R = Alkyl

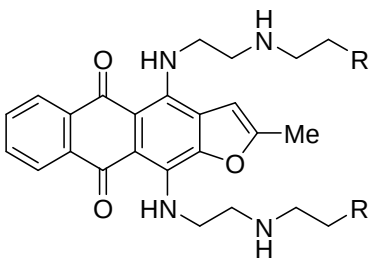
Figure 2-1. Structure of 2-alkyl-3-hydroxy-1,4-naphthoquinones **31**

2.1.2. Quinone intercalation between two DNA-base pairs. Intercalation-based mechanism

DNA intercalation was discovered in 1961 by the American scientist Leonard Lerman who ascribed the mutagenic activity of several compounds to this process.[31] Compounds known to possess biological activities by DNA intercalation have bi- and tricyclic planar aromatic rings that can fit in between adjacent base pairs of uncoiled DNA structure.[32] The presence of cationic and/or electrophilic functionalities on the intercalating molecules plays a necessary role for the genotoxicity.[32c-e] Such intercalating agents may then form hydrogen, covalent or ionic bonds, which increase the residence time inside DNA and thereby inducing sufficient DNA structural modifications that prevent the DNA from regaining its normal helical structure. In this way, such intercalators inhibit DNA topoisomerases I and II efficiently, which rule over DNA replication, transcription and recombination. For instance, derivatives of anthracenediones (mitoxantrone **32a** and ametantrone **32b**) belong to a promising class of new chemotherapeutic agents. Other examples include anthra[2,3-*b*]furan-5,10-diones **33**,[32b] 2-azaanthraquinone **34**,[33] acridones (acronycine **35** and rhodesiacridone **36**),[34] oxoisoaporphines **37**[35] and phenanthrines (fagaronine **38** and ethoxidine **39**).[36] These compounds are not only able to insert between two DNA base pairs but are also able to form chemical bonds leading to irreversible DNA structural modification which causes cell mutagenesis and/or death.



32a mitoxanthrone (R = OH)
32b ametantrone (R = H)



33a (R = OH)
33b (R = NH_2)

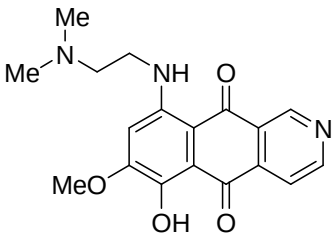


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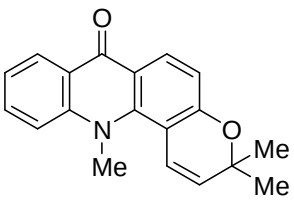
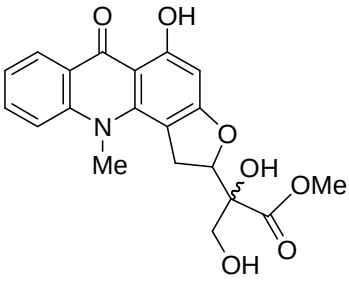
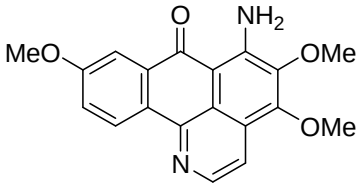
Figure 2-2a. Structures of some DNA intercalating quinones



35 acronycine



36 rhodesiacridone



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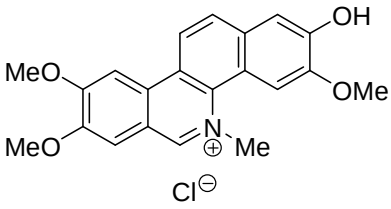
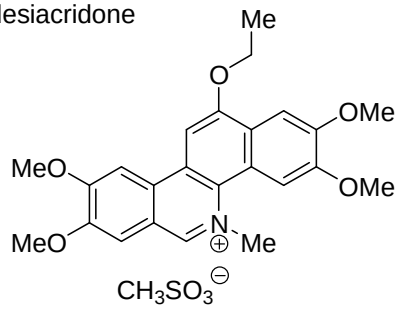


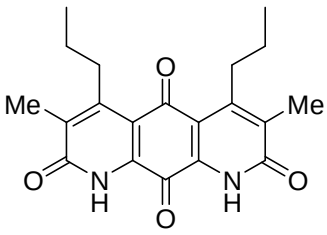
38 fagaronine



39 ethoxidine

Figure 2-2b. Examples of DNA intercalating quinones

In this perspective of forming chemical bonds with and inserting in DNA, Moore and co-workers have predicted that quinones having a nitrogen-heterocyclic ring will intercalate more easily due to the formation of additional hydrogen bonds.[37] Diazaquinomycin A **40** (Figure 2-3), for instance, has been made an attractive lead compound in cancer chemotherapy research.[38]



40 diazaquinomycin A

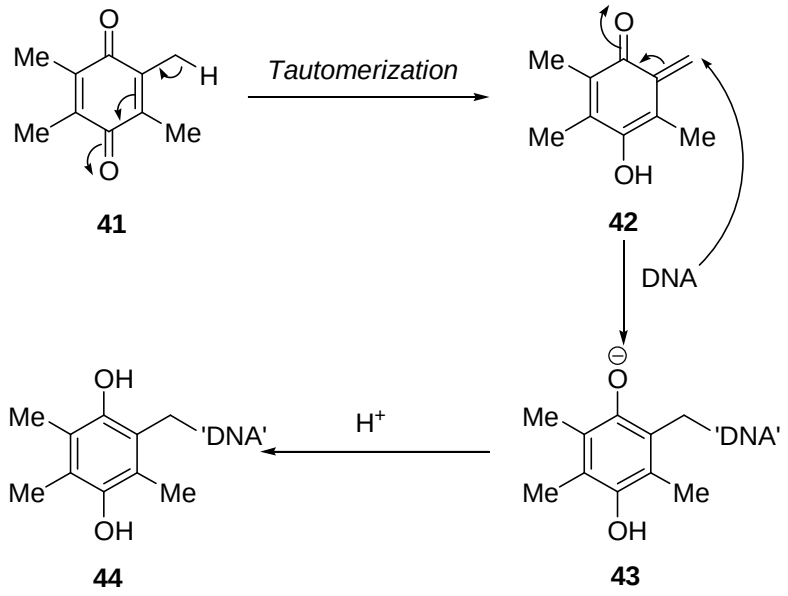
Figure 2-3. Sctructure of diazaquinomycin A **40**

2.1.3. Quinone methide nucleophilic reaction. Bioalkylation mechanism

Quinone bioalkylating agents represent a class of drugs in extensive investigation. They are really pro-drugs which generate *in vivo* simple *ortho*-quinomethides or vinylogous methides.[39] Since these types of quinones generate conjugated unsaturated ketones, which are highly susceptible towards nucleophilic attack, they can alkylate nucleophilic centers in biomolecules such as in DNA, RNA and proteins. The key element of this mechanism implies the formation of a Michael-type acceptor, which may result from a keto-enol tautomerism process or a two-electron reduction of quinones (*vide supra*). The formation of

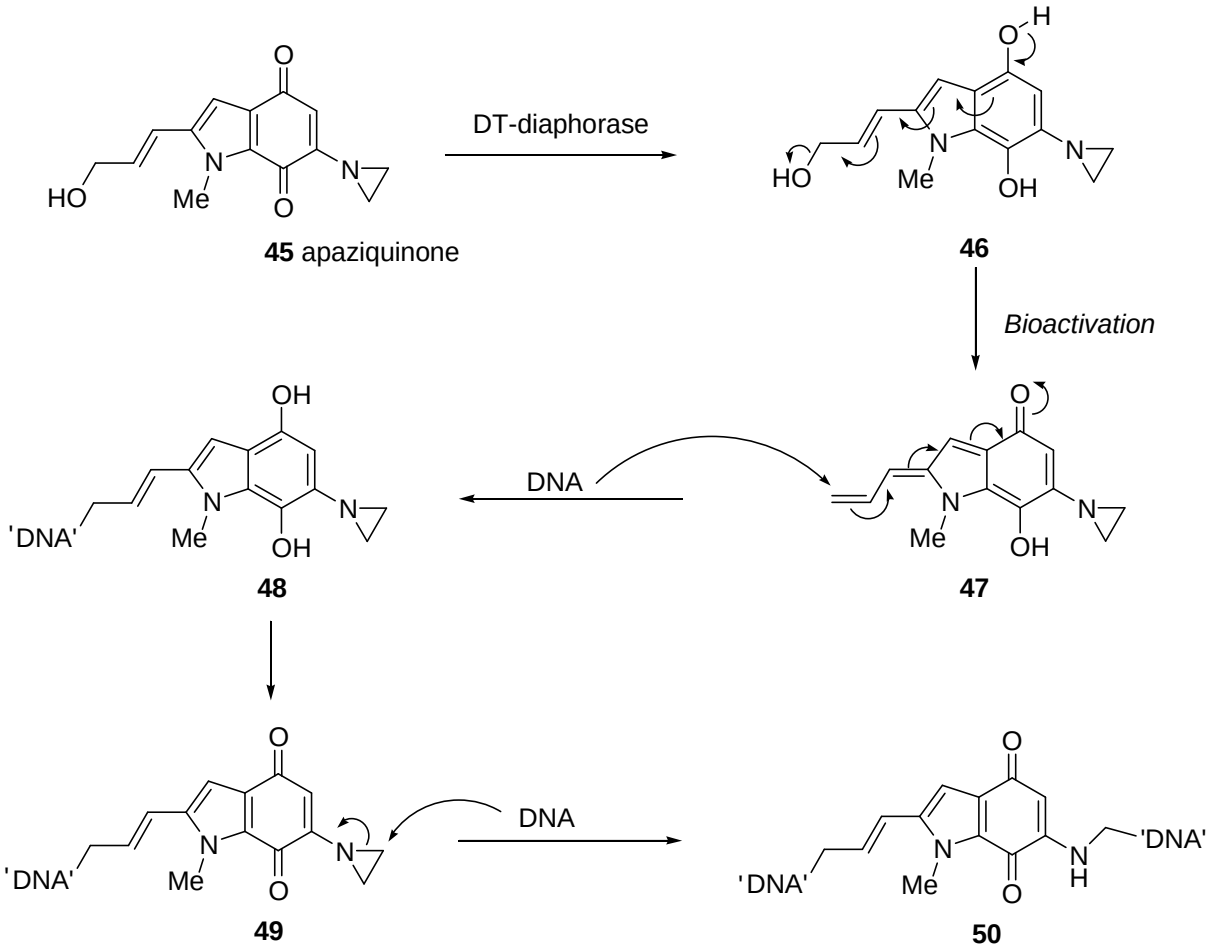
the covalent bond between the activated drug and the DNA can have a variety of damages including irreparable DNA damage and prevention of DNA replication due to strand cross linking.[40]

Duroquinone **41** for instance (Scheme 2-2), can tautomerize *in vivo* to *ortho*-quinomethide **42**.[41] The latter compound can react with a nucleophilic center in one of the DNA strands. This bioactivated alkylation reaction can be repeated with another nucleophilic center in the same or the other DNA strand and thus prevent DNA replication by cross linking causing cell death.

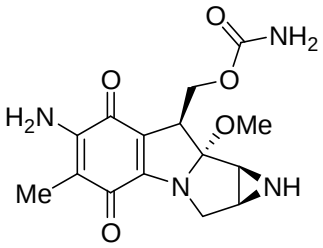


Scheme 2-2. Duroquinone *ortho*-quinomethide reaction with DNA

On the other hand, it is believed that the anticancer drug E09 (apaziquinone) **45**[42] generates its active principle by DT-diaphorase-assisted two-electron reduction to form the hydroquinone **46** (Scheme 2-3), which is activated *in vivo* by forming a vinylogous quinone methide **47**. A subsequent DNA base is then alkylated by this electrophile **43**, resulting in a potent and an effective antitumour drug. The aziridinyl group, present in this molecule, may also be an electrophilic center susceptible to a DNA nucleophilic attack, which would result in ring opening of the aziridinyl substituent. The two possible electrophilic sites may act to create an interstand crosslink between DNA strands, thus preventing DNA replication entailing cell death. The anticancer drug E09 (apaziquinone) **45** was developed as an analogue of mitomycin C **51** (Figure 2-4), with which it shares the same mode of action,[42] and is more active and less toxic than mitomycin C **51** under both oxic and hypoxic conditions. However, the apaziquinone **45** unfortunately failed to pass the complete clinical trials due to unrevealed reasons.[42a,b]



Scheme 2-3. Apaziquinone reaction with DNA



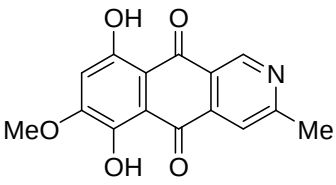
51 mitomycin C

Figure 2-4. Structure of mitomycin C

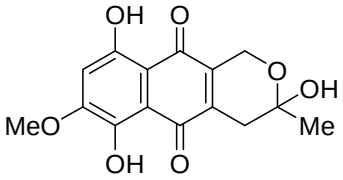
2.2. Biosynthesis of pyranonaphthoquinones and 2-azaanthraquinones

Naturally occurring quinones are synthesized mainly through two biosynthetic pathways from different precursors. They may be formed from phenolic systems generated by either the acetate or shikimate pathway.

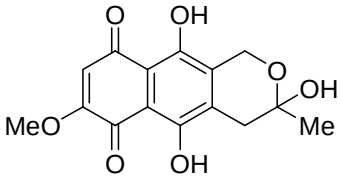
Pyranonaphthoquinones are suggested to be biosynthetic precursors of 2-azaanthraquinones. The 2-aza analogues of pyranonaphthoquinones are formed by ammonia insertion into the pyranonaphthoquinone peripheral carbon chain after reductive amination of the terminal chain carbonyl function.[42] These 2-aza analogues very often aromatize to afford ultimately the corresponding 2-azaanthraquinones. The first 2-azaanthraquinone was isolated in 1953 from *Fusarium bostrycoides* as a red pigment with antibiotic properties and was named bostrycoidin **52**.[43] Like naturally occurring anthraquinones and pyranonaphthoquinones, 2-azaanthraquinones constitute a class of polyketide-derived metabolites, which have been isolated from fungi, lichens and from plants such as *Mitrocarpus scaber* (Rubiaceae).[43] 2-Azaanthraquinones are generally produced *in vivo* as part of a detoxifying process for high ammonia concentrations.[43b] In this way, *in vivo* ammonia incorporation into dihydrofusarubin **53** and fusarubin **54**, is reported to give rise to the naturally occurring 2-azaanthraquinone bostrycoidin **52**.[43b,44]



52 bostrycoidin



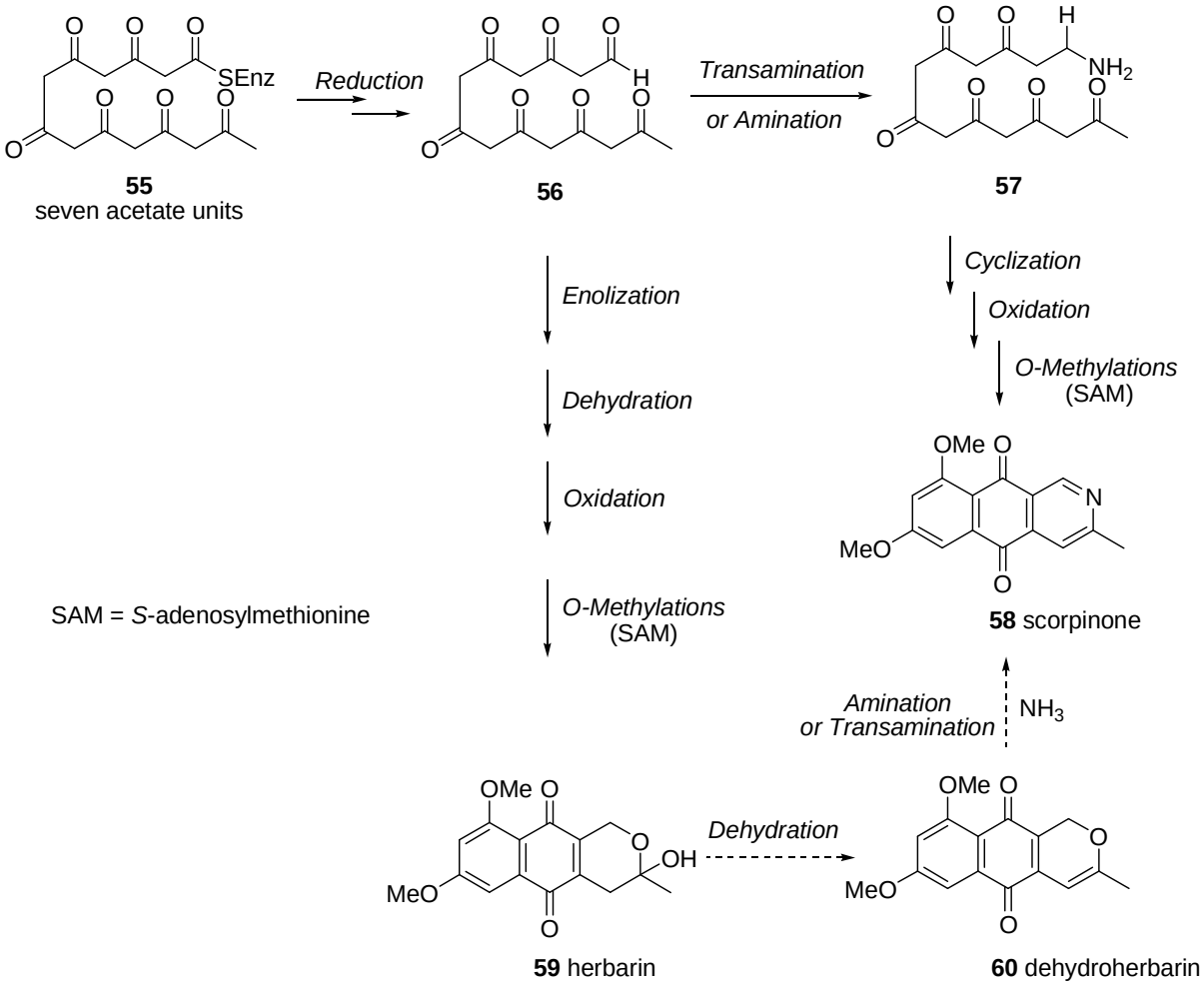
53 dihydrofusarubin



54 fusarubin

Figure 2-5. Structures of bostrycoidin **52**, dihydrofusarubin **53** and fusarubin **54**

Alternatively, the biosynthesis of 2-azaanthraquinones polyketide **55** is reported to be involved in this process.[43,45] The incorporation of the nitrogen atom in these metabolites could derive from either an inorganic nitrogen source or nitrogen-containing organic metabolites. The alternative insertion of the nitrogen atom may be mediated by an amino-transferase from an amino acid.[43] Therefore, a plausible biosynthetic pathway of scorpinone **58** was reported[44] starting from the intermediate **56**, which leads to aminoketone **57** through the action of an aminotransferase or reductive amination. Then, cyclization (dehydration or/and enolization), oxidation and methylation processes give rise to scorpinone **58** (Scheme 2-4).[45] On the other hand, the same intermediate **56** may lead to the pyranonaphthoquinone herbarin **59**, which dehydrates to dehydroherbarin **60**. Subsequently, amination or transamination of dehydroherbarin **60** may occur to produce scorpinone **58**.[6,45]



Scheme 2-4. Biosynthesis of scorpinone **58**, herbarin **59** and dehydroherbarin **60**

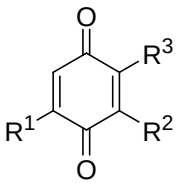
2.3. Naturally occurring quinones from African plants and their biological activities

Africa is famous for the biodiversity of its tropical forests. In such a competitive environment, plant species will protect themselves by producing a vast array of bioactive compounds. African plants have for long been the source of important products with nutritional and therapeutical values. In certain countries, more than 90% of the population still relies on plants as a source of medicines.[46] A variety of quinoid compounds have been among the bioactive compounds isolated from diverse extracts of these plants. They range from simple monomeric quinones to complex oligomeric compounds. Given the richness of the African flora, still a lot of active principles remain to be isolated and identified from medicinal plants. To present an exhaustive list of naturally occurring quinones isolated from African plants in this literature overview will go beyond the scope of the present dissertation. Therefore, this overview will highlight some recently studied naturally occurring quinones and their biological activities.

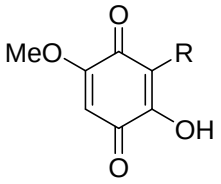
2.3.1. Monomeric quinones

2.3.1.1. Benzoquinones

Simple dimethoxybenzoquinones **61** (Figure 2-6) are often present in trunk extracts of higher plants since they are considered to be the ultimate products of biodegradation of lignin and other phenolic compounds of plant trunks. 2,5-Dimethoxybenzoquinone **61a** has been isolated from several African plants such as *Maesa lanceolata* (Myrsinaceae)[47] and *Cassia obtusifolia* (Caesalpiniaceae).[48] It has been recognized to possess defence stimulant activity[47] and antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*.[48] 2,6-Dimethoxybenzoquinone **61b**, which can cause dermitis and effects on the central nervous system, has been isolated from *Milletia laurentii* (Fabaceae).[49] Finally, 2,3-dimethoxybenzoquinone **61c** was isolated from *Newbouldia laevis* (Bignoniaceae).[50]



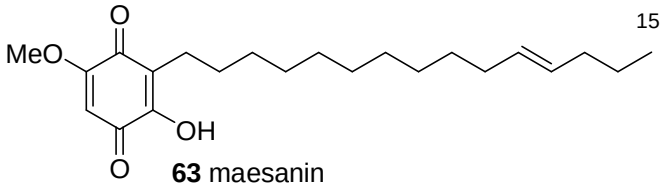
61a R^1 = OMe, R^2 = H, R^3 = OMe
61b R^1 = OMe, R^2 = OMe, R^3 = H
61c R^1 = H, R^2 = OMe, R^3 = OMe



62 R = Alkyl

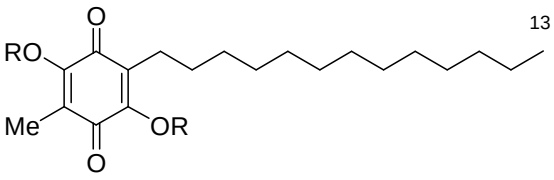
Figure 2-6. Structures of some naturally occurring benzoquinones

In 1988, plants of four genera of the Myrsinaceae family, i.e *Maesa*, *Myrsine*, *Rapanea* and *Embelia* from Kenya, were investigated for their distribution of benzoquinones.[51] The study revealed that the benzoquinones **62** (Figure 2-6) with longer side chains (R = C_{15} - C_{19}) were clearly restricted to *Maesa*, while those with shorter side chains (R = C_{11} - C_{13}) were found in *Myrsine*, *Rapanea*, and *Embelia*. Five years earlier, the isolation and efficient synthesis of maesanin **63** (Figure 2-7), a host defense stimulant and 5-lipoxygenase blocker, isolated from the African medicinal plant *Maesa lanceolata*, was reported.[47,52] More recently, maesamin **63** has been found to possess antiasthmatic activity.[52a] In Central Africa, *M. lanceolata* is used against *Entamoeba histolyca* infections.[52b] In 1999, a reinvestigation of *M. lanceolata* (Myrisinaceae)[53] has revealed the presence of 5-alkylated 2-methylbenzoquinones **64** with different oxygenated substituents (Figure 2-8).

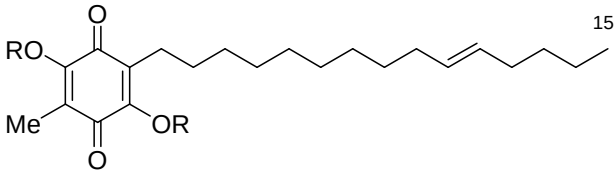


63 maesanin

Figure 2-7. Structure of maesanin **63**



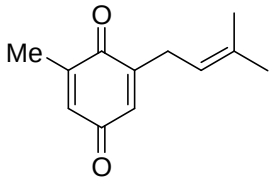
64a R = H, Me, Ac



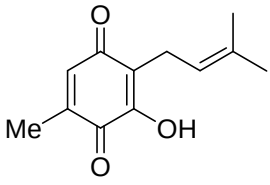
64b R = H, Me, Ac

Figure 2-8. Structures of some 5-alkylated 2-methylbenzoquinones

Recently, two simple prenylated 1,4-benzoquinones **65** (Figure 2-9) have been isolated from the dichloromethane extract of the leaves and stem of the South African *Gunnera perpensa* (Haloragaceae) and were examined for their antimicrobial activities.[54] 2-Methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone **65a** showed significant antimicrobial activity at microgram scale against *Staphylococcus epidermidis*, while 3-hydroxy-5-methyl-2-(3-methyl-2-butenyl)-1,4-benzoquinone **65b** showed no bioactivity.



65a

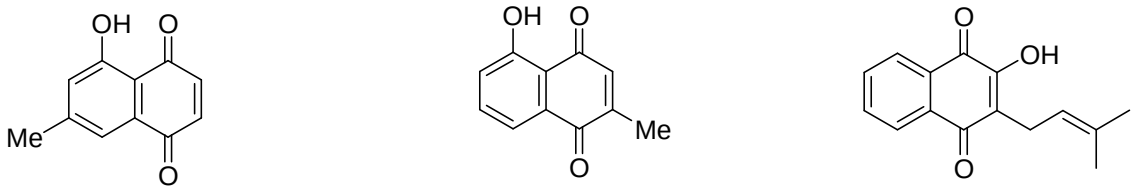


65b

Figure 2-9. Prenylated 1,4-benzoquinones isolated from *Gunnera perpensa* (Haloragaceae)

2.3.1.2. Naphthoquinones

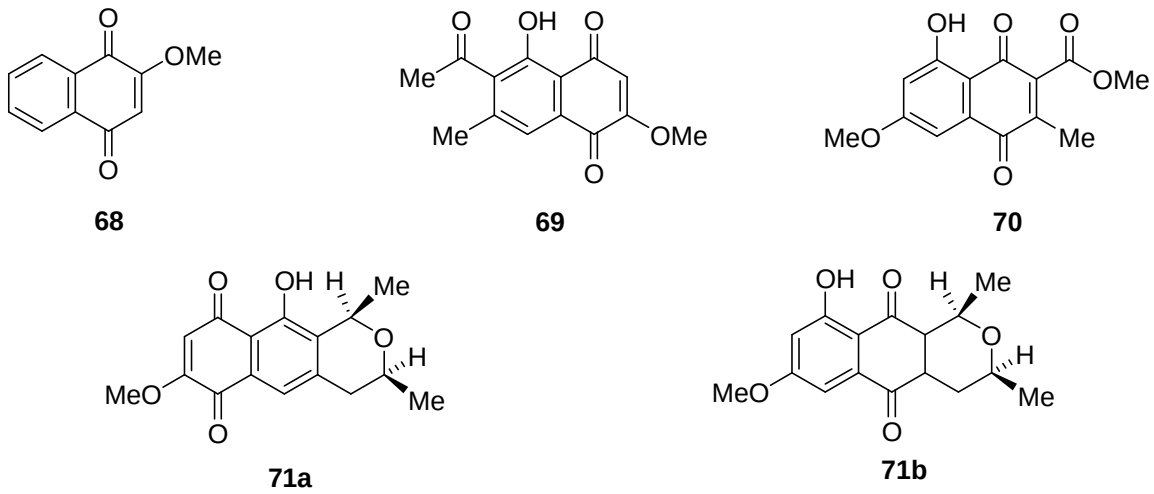
Naphthoquinones are considered as privileged quinones in medicinal chemistry because of their wide occurrence in nature, their biological activities and their structural properties.[55] They serve vitally as links in the electron transport chain in many metabolic pathways. They appear in various families of African plants. Thus, 7-methyljuglone **66a** and plumbagin **66b** (Figure 2-10) are the most representative naphthoquinones isolated from African plants. In 1989, they were found to be ubiquitously present in all the plant organs of the South-African *Drosera* species (Droseracea). *D. capensis* was considered as an interesting natural source of 7-methyljuglone **66a**, while *D. binata* and *D. binata dichotoma* represented good natural sources of plumbagin **66b**.[56] These two naphthoquinones **66a** and **66b** have been found to be active against tuberculosis[57] and trypanosomiasis.[58] Lapachol **67** (Figure 2-10), a prenylated naphthoquinone, which was isolated from African *Kigelia africana* (Bignoniaceae), is widely distributed in the South, Central and West-Africa.[59] A wide spectrum of therapeutic activities has been attributed to lapachol **67** including antileishmanial, antiedemic, anti-inflammatory, antimalarial, antiseptic, antitumor, antiviral, bactericidal, fungicidal, insecticidal, protisticidal, respiradepressant, schistosomicidal, termiticidal and viricidal activities.[6a,60]



66a 7-methyljuglone **66b** plumbagin **67** lapachol

Figure 2-10. Structures of 7-methyljuglone **66a**, plumbagin **66b** and lapachol **67**

Swertia calycina (Gentianaceae) from Rwanda surprisingly revealed the presence of 2-methoxy-1,4-naphthoquinone **68** (Figure 2-11), which is responsible for the antifungal activity of the plant's dichloromethane extract.[61] In 1990, two *Araliorhamnus* species which are endemic to Madagascar, i.e, *A. vaginata* and *A. punctata* (Rhamnaceae), revealed the existence of 6-acetylnaphthoquinone **69** and 2-methoxycarbonylnaphthoquinone **70** with two other interesting heterocyclic quinones **71** (Figure 2-11).[62]



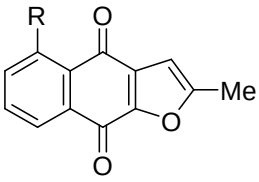
68 **69** **70**

71a **71b**

Figure 2-11. Structures of African naturally occurring naphthoquinones and pyranonaphthoquinones

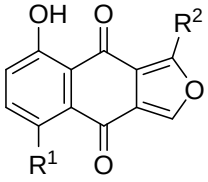
Heterocycles, fused with naphthoquinones, are well represented among heterocyclic quinones isolated from African plants. The two lead compounds of the present research work cleistopholine **10a** and sampangine **12a** (Figure 1-3) have been isolated from *Cleistopholis patens* (Annonaceae), a large tree which occurs in the rain forests of Africa, from Sierra Leone eastward to the Democratic Republic of Congo and Uganda.[63] This plant is used in traditional medicine in Central Africa to fight lung disorders. In addition, its stem bark extract is claimed to be active for infective hepatitis and stomach disorders while its root is used as a vermifuge and its leaves for the treatment of fever.[64] These two compounds **10a** and **12a** are reported to display strong antimycobacterial activity resembling the activity of rifampicine, an important drug in the treatment of tuberculosis.[65]

Plants of the Asphodelaceae family (*Bulbine capitata*, *B. frutescens*, *B. abyssinica*), the extracts of which are used as antibiotics in some countries of eastern, central and southern Africa were investigated.[66] Extract of the aerial parts and roots of these plants revealed the abundance of furanonaphthoquinones **72** and isofuranonaphthoquinones **73** (Figure 2-12).[67] Isofuranonaphthoquinones **73** have been found to have antioxidant and also mild antiplasmodial properties.[68] A particular *Newbouldia laevis* species from Guinea-Conakry was found to present various furan derivatives of lapachone **74b-f** (Figure 2-13) with interesting antifungal activities.[69]



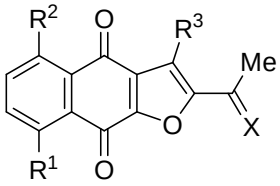
72a R = H

72b R = OH



73a R^1 = OH, R^2 = H

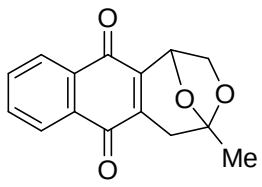
73b R^1 = OMe, R^2 = CH_2OAc



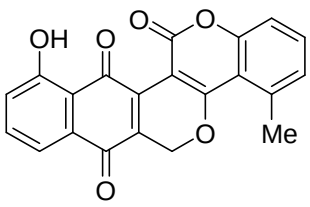
74a R^1 = H, R^2 = H, R^3 = H, X = O
74b R^1 = R^2 = R^3 = H, X = CH_2
74c R^1 = H, R^2 = OH, R^3 = H, X = CH_2
74d R^1 = H, R^2 = OMe, R^3 = H, X = CH_2
74e R^1 = OH, R^2 = R^3 = OH, X = CH_2
74f R^1 = R^2 = H, R^3 = OH, X = CH_2

Figure 2-12. Structures of furanonaphthoquinones and isofuranonaphthoquinones

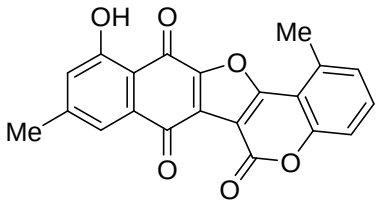
The isolation of pentalongin **8** (Figure 1-2) and isagarin **75** (Figure 2-13) from *Pentas longiflora* (Rubiaceae) has been a landmark to our department.[5a,70] Special attention was attracted in the early nineties to this very promising plant species used in Burundi, Rwanda and Kenya for its medicinal propreties. Synthesis of different pentalongin derivatives has been accomplished in our research group. This applies as well as for their corresponding aza analogues. Pentalongin derivatives and their aza analogues, assorted with their biological activities are extensively described in literature.[5a]



75 isagarin



76 cyclocanaliculatin



77 crassiflorone

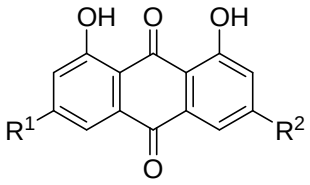
Figure 2-13. Structures of isagarin **75**, cyclocanaliculatin **76** and crassiflorone **77**

Cameroonian medicinal plants have been studied for the relevance of quinone metabolites present in them. In this way, pentacyclic quinones such as cyclocanaliculatin **76** and crassiflorone **77** (Figure 2-13)

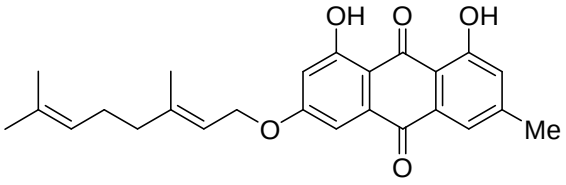
have been isolated from *Diospyros crassiflora* (Ebenaceae).[71] Crassiflorone **77** has been recognized to possess antimicrobial activity.[72]

2.3.1.3. Anthraquinones

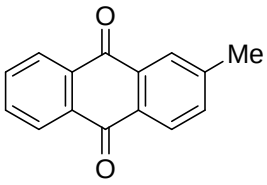
Simple anthraquinones such as chrysophanol **78a** and aloe-emodin **78b** (Figure 2-14) have been isolated from species of the genus *Bulbine.* They have been recognized as DNA-intercalating[73] and antileukemic[74] agents. The anthraquinone emodin **78c** and geranyloxy-6-methyl-1,8-dihydroxyanthraquinone **79** (Figure 2-14) from the ethanolic stem bark extract of the Tanzanian medicinal plant *Vismia orientalis* (Clusiaceae) showed strong antiprotozoal activities against *Trypanosoma rhodesiense*, *T. cruzi*, *Leishmania donovani* and *Plasmodium falciparum. A*loe-emodin **78b,** isolated from the African medicinal shrub *Stephania dinklagei* (Menispermaceae), showed moderate activity against *T. rhodesiense*.[75] Other simple anthraquinones such as 2-methyl-9,10-anthraquinone **80**, 2-hydroxy-3-methoxy-9,10-anthraquinone-1-carbaldehyde **81** (Figure 2-14), have been isolated from *N. laevis* (Bignoniaceae).[76]



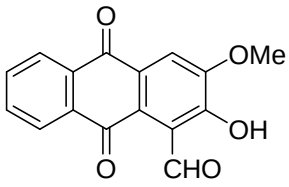
78a chrysophanol R^1 = H, R^2 = Me
78b aloe-emodin R^1 = H, R^2 = CH_2OH
78c emodin R^1 = OH, R^2 = Me



79



80

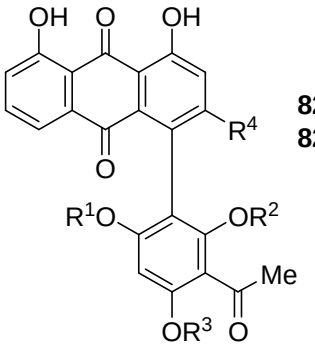


81

Figure 2-14. Structures of some anthraquinones isolated from African medicinal plants

The genus *Bulbine* (Fabaceae) produces a great diversity of 4-arylanthraquinones **82** (Figure 2-15), which have been identified as a class of antiplasmodial substances comparable to the commercial drug chloroquine.[77] Although the first phenylanthraquinone, knipholone **82**, was reported to be isolated from *Kniphofia foliosa,*[78] it has also been isolated from other *Kniphofia*, *Bulbinella,*[79] *Bulbine,*[80] and *Senna* species (Fabaceae).[81] These arylanthraquinones **82b** are constitutionally asymmetrical, stereochemically stable and optically active biaryl compounds. Their pronounced antiplasmodial activity is intrinsically associated with the stereogenic axis of their rings.[77] The substitution patterns on the

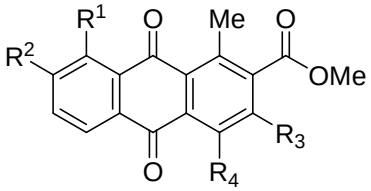
combined anthraquinone and benzene rings increase difference of atropoisomer chemical and physical properties.



82a R^1 = β-Glu, R^2 = H, R^3 = R^4 = Me
82b knipholone R^1 = R^2 = H, R^3 = R^4 = Me

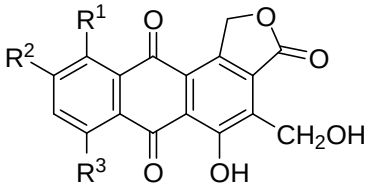
Figure 2-15. Structures of 4-arylanthraquinones **82**

Rhamnaceae species, *Araliorhamnus vaginata* and *A. punctata,* endemic to Madagascar also revealed several other interesting anthraquinones, such as methyl 1-methylanthraquinone-2-carboxylate **83** and anthraquinone lactones **84** (Figure 2-16).[62]



83

R^1 = OH, OMe
R^2 = H, OH, OMe
R^3 = H, OH
R^4 = OH, OMe



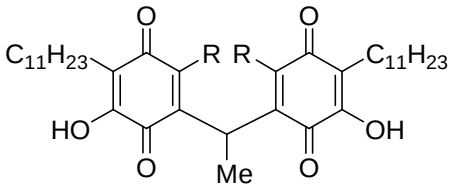
84

R^1 = OH, OMe
R^2 = H, OMe
R^3 = H, OH

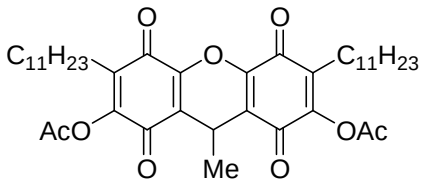
Figure 2-16. Anthraquinones isolated from *Rhamnaceae* species

2.3.2. Dimeric quinones

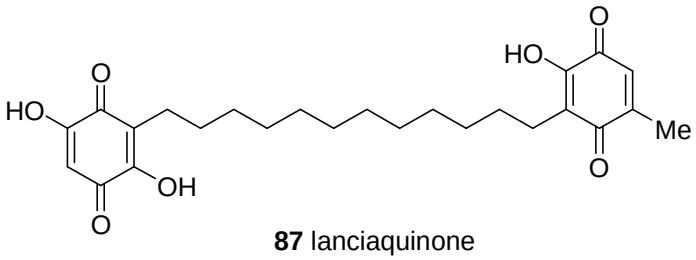
The family Myrsinaceae is characterized by the presence of 2,5-dihydroxy-3-alkylbenzoquinones. In search for further related chemical constituents of these plants, the isolation and the structure determination of the dimeric quinones methylvilangin **85**, methylanhydrovilangin **86**, in addition to the bisbenzoquinone, lanciaquinone **87** have been reported for the first time from *M. lanceolata* and *M. africana* (Figure 2-17).[82]



85 methylvilangin R = alkyl



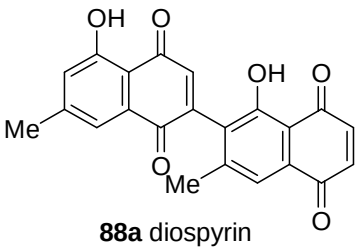
86 methylhydrovilangin



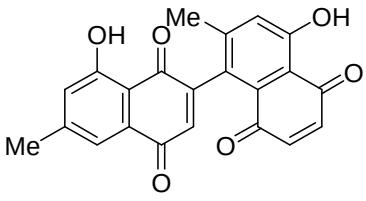
87 lanciaquinone

Figure 2-17. Dimeric benzoquinones isolated from African plants of the *Myrsinaceae* family

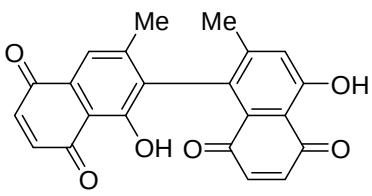
Dimeric naphthoquinones from South African plants were the topic of extensive research in 2006. Bisnaphthoquinones, diospyrin **88a**, neodiospyrin **88b** and isodiospyrin **88c** (Figure 2-18) were isolated in different concentrations from *Euclea* species (Ebenaceae) and have been found to be active against tuberculosis[48] and trypanosomiasis.[49] Diospyrin **88a** and neodiospyrin **88b** have been shown to posses a good tumor inhibitory effect against different cancer cell lines.[83] Isodiospyrin **88c** has been reported as a novel human DNA topoisomerase I inhibitor.[83] Since then, quinonoid compounds have been claimed to constitute a large and an important class of anticancer drugs in treating cancer as well as potential ‘‘lead molecules’’ for novel anticancer drugs.[49a]



88a diospyrin



88b neodiospyrin



88c isodiospyrin

Figure 2-18. Bisnaphthoquinones isolated from *Euclea* species (Ebenaceae)

Two dimeric phenylanthraquinones, namely joziknipholones A **89a** and B **89b** (Figure 2-19), possessing axial and centrochirality, were isolated from the roots of the African plant *Bulbine frutescens* (Asphodelaceae).[84] Joziknipholones A **89a** and B **89b** are the first members of a structurally unique novel class of dimeric phenylanthraquinones. These novel type of metabolites possess good antimalarial activities and are thus potential lead compounds for antimalarial drug discovery.[67c]

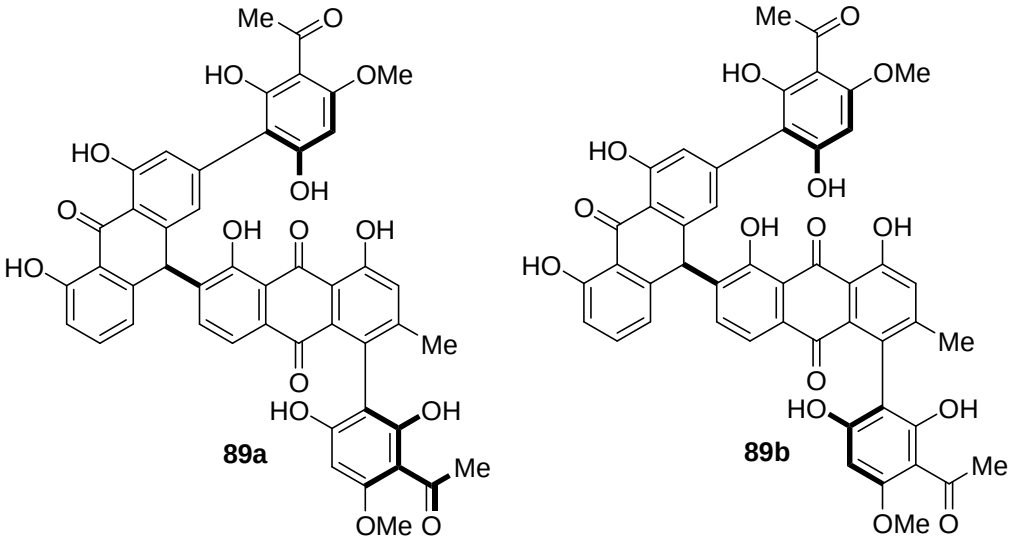
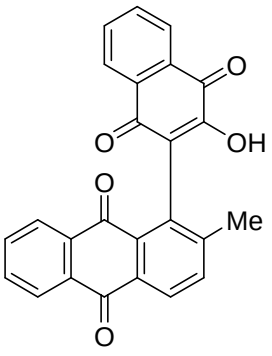


Figure 2-19. Structures of joziknipholones **89**

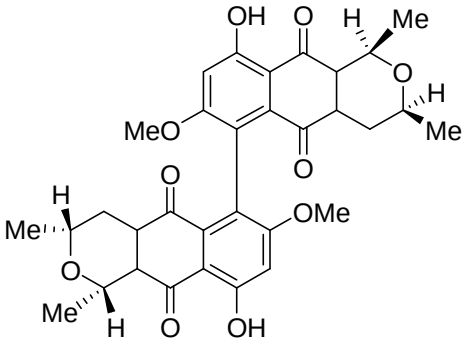
The genus *Newbouldia* (Bignoniaceae) comprises only one species distributed throughout the tropical and sub-tropical zones of Africa. It has been used in African folk medicine as an astringent in diarrhea, dysentery ailments and in the treatment of various diseases such as worms, malaria, sexual transmitted diseases, and in the reduction of dental caries.[84] From this species, a special type of dimeric quinone, namely newbouldiaquinone **90** was isolated (Figure 2-20). The newbouldiaquinone **90** merits focus because it is an unusual quinone with mixed naphthoquinone-anthraquinone coupling monomers, a feature uncommon to naturally occurring dimeric quinones. The presence of this type of quinones in a plant contrasts with the most widespread groups of quinone dimers found in nature[85] which are often bis-benzoquinones, bis-naphthoquinones and bis-anthraquinones. A preliminary study[76c] on biological activities showed that newbouldiaquinone **90** is moderately active against *Bacillus megaterium.*



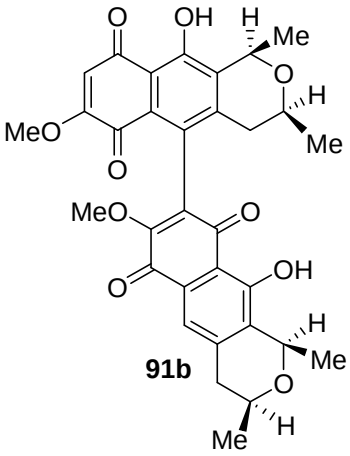
90 newbouldiaquinone

Figure 2-20. Structure of newbouldiaquinone **90**

Rhamnaceae species, *Araliorhamnus vaginata* and *A. punctata* showed the presence of dimeric heterocyclic quinones **91** (Figure 2-21).[62]



91a



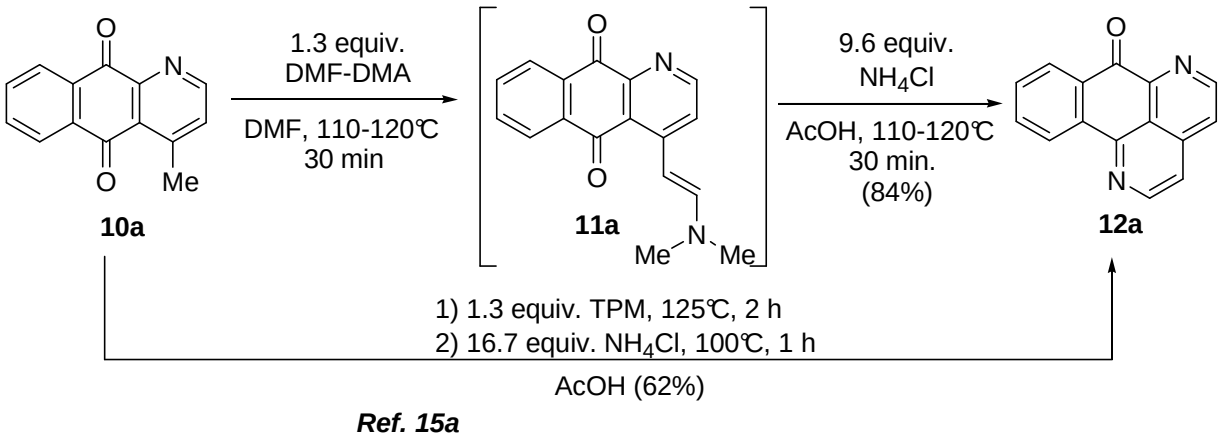
91b

Figure 2-21. Dimeric heterocyclic quinones from African *Rhamnaceae* species

Chapter 3: Results and discussion

3.1. Effort towards a short and efficient synthesis of 2-azacleistopholine 10b and 2-azasampangine 12b

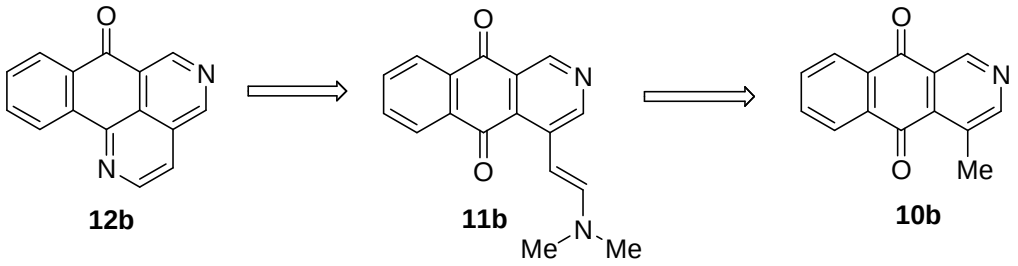
Cleistopholine **10a** and sampangine **12a** are two strongly related polycyclic aromatic alkaloids isolated from different plants belonging to the Annonaceae family with a wide range of interesting biological activities.[86] Cleistopholine **10a** is a tricyclic azaanthraquinone alkaloid isolated from the root bark of *Cleistopholis patens*[13] and sampangine **12a** is a tetratracyclic naphthyridine alkaloid isolated from the stem back of *Cananga odoranta*.[87] Cleistopholine **10a** showed fungitoxic potential against *Candida albicans*, *Cryptococcus neoformans* and *Mycobaterium intracellulare*, which are opportunistic fungi occurring in AIDS patients.[86e] In addition of exhibiting a powerful activity against *Mycobaterium tuberculosis* with a minimum inhibitory concentration (MIC = 0.78 µg/ml) which is lower than the MIC for current anti-TB drugs as rifampicin (MIC = 0.5-0.9 µg/ml) and streptomycin (MIC = 2-8 µg/ml),[65] sampangine **12a** is known to possess strong antifungal activity.[86e] In the literature, a convenient synthesis of sampangine **12a** was reported starting from cleistopholine **10a** (Scheme 3-1).[15a]



Ref. 15a

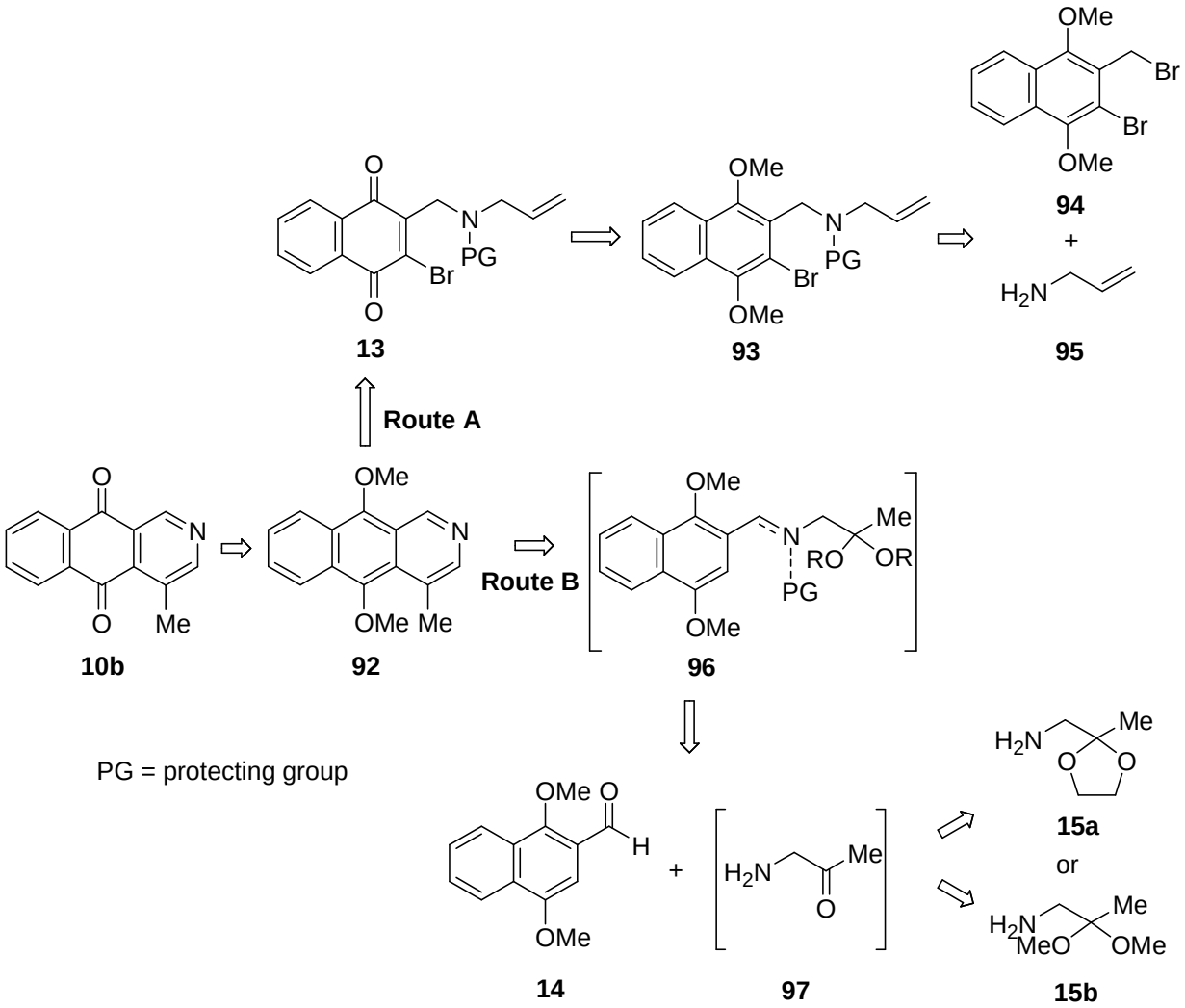
Scheme 3-1. Synthesis of sampangine **12a** starting from cleistopholine **10a**

Since it is known that 2-azaanthraquinones are more bioactive than their corresponding 1-aza analogues,[16a] a short and efficient synthesis of 2-azacleistopholine **10b** and 2-azasampangine **12b** was envisaged. This synthesis is based on the above presented literature reports of the synthesis of cleistopholine **10a** and sampangine **12a**. The strategy, which will be followed, is depicted retrosynthetically in the following scheme (Scheme 3-2).



Scheme 3-2. Retrosynthetic analysis of 2-azasampangine **12b**

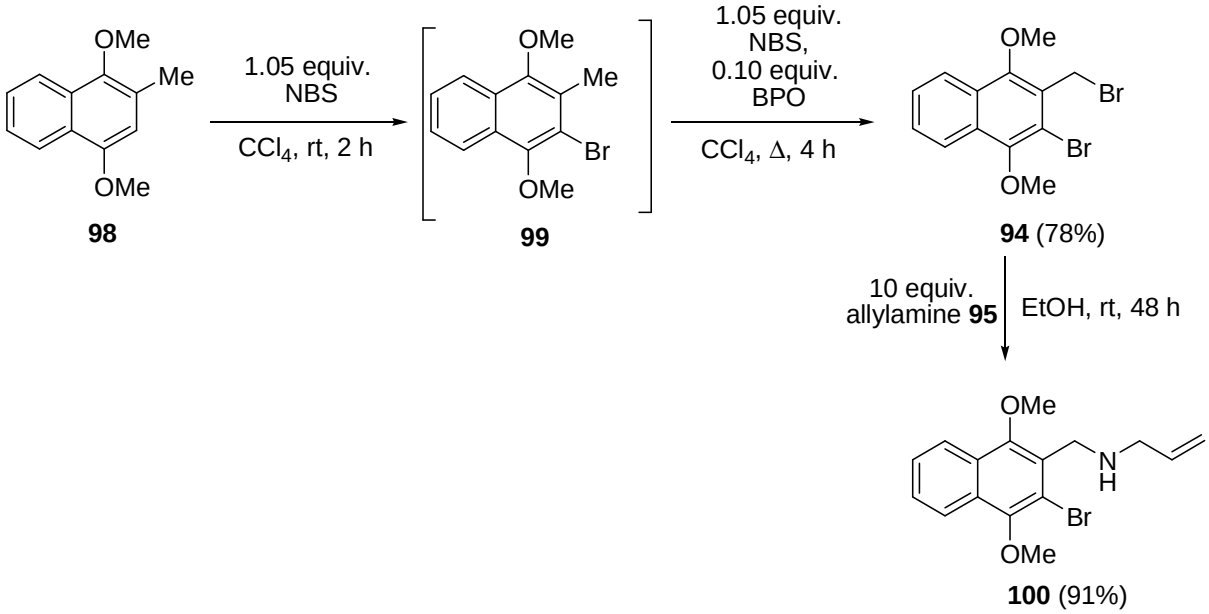
2-Azacleistopholine **10b** may be obtained by either an intramolecular palladium-catalyzed coupling reaction (Heck reaction, route A) or an acid-promoted intramolecular condensation (Pomeranz-Fritsch reaction, route B) as described in scheme 3-3. In the first reaction route, the key step consists of an intramolecular coupling reaction of the *N*-protected 1-bromo-2-(allylaminomethyl)-1,4-naphthoquinone **13**, which could be obtained upon reaction of 2-bromo-3-bromomethyl-1,4-dimethoxynaphthalene **94** with allylamine **95**, followed by protection of the nitrogen and an oxidative demethylation reaction of the hydroquinone methyl ether **93**. In an alternative pathway, an acid-promoted intramolecular cyclization might be performed using compound **96**. This compound could bear either an amino or imino moiety and could be prepared by a condensation reaction of 2-formyl-1,4-dimethoxynaphthalene **14** and α-aminoacetone **97**. However, since α-aminoacetone **97** is prone to self-condensation, the synthesis of 2-aminomethyl-2-methyl-1,3-dioxolane **15a** or aminoacetone acetal **15b** was envisaged.



Scheme 3-3. Retrosynthetic analysis of 2-azacleistopholine **10b**

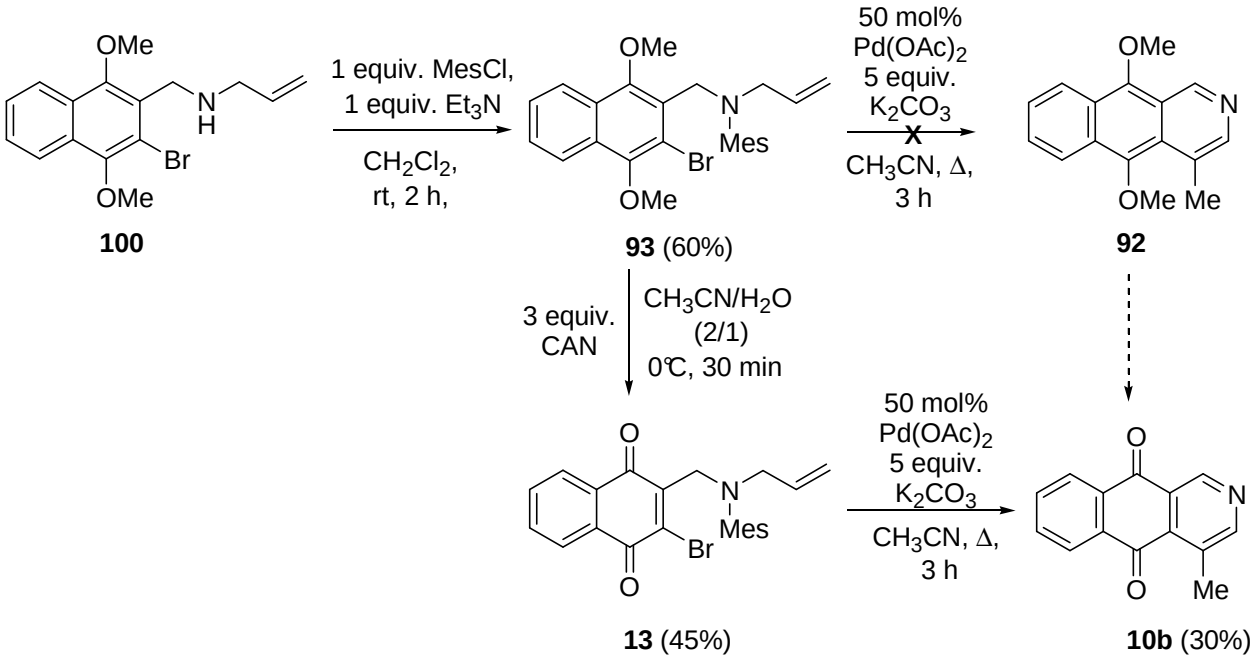
3.1.1. Synthesis of 2-azacleistopholine 10b with the Heck reaction in key step

The Heck reaction is a palladium-catalyzed coupling of olefins with aryl or alkenyl halides or triflates.[88] It is one of the prime tools for building carbon-carbon bond formation in organic synthesis and as a result this reaction is of paramount importance. Usually, the Heck reaction is carried out with 1-5 mol% of a palladium catalyst along with a phosphine ligand in the presence of a suitable base.[89] Numerous nitrogen heterocycles have been prepared by intramolecular Heck cyclization.[90] In order to prepare 2-azacleistopholine **10b** by the Heck reaction, the appropriate substrate **13** needed to be synthesized. In this way, 2-bromo-3-bromomethyl-1,4-dimethoxynaphthalene **94**, which was obtained according to the literature procedure from 1,4-dimethoxy-2-methylnaphthalene **98** *via* selective bromination,[91,92] was reacted at room temperature for 48 hours with an excess of allylamine **95** in absolute ethanol to afford 2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **100** in 91% yield (Scheme 3-4).



Scheme 3-4. Synthesis of 2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **100**[92]

The 2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **100** was converted to *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **93** in 60% yield by reaction with methanesulfonyl chloride in dichloromethane in the presence of triethylamine. The oxidative demethylation of this first Heck reaction substrate **93** with CAN gave rise to the corresponding naphthoquinone **13**. Different phosphine ligands and bases (amongst which the standard Heck reaction conditions) were screened for the intramolecular palladium-catalyzed cyclization of *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **93** and *N*-methanesulfonyl 2-(allylaminomethyl)-3-bromo-1,4-naphthoquinone **13** in a previous synthetic study of our department.[92] Next, different ligand-free conditions were tested (Table 1) since it was reported that $Pd(OAc)_2$ in combination with K_3PO_4 as a base and *N*,*N*-dimethylacetamide (DMA) as a solvent can be used as suitable reactions conditions for the Heck reaction of both activated and deactivated aryl bromides.[93]



Scheme 3-5. Synthesis of 2-azacleistopholine **10b** using the Heck reaction in the key step

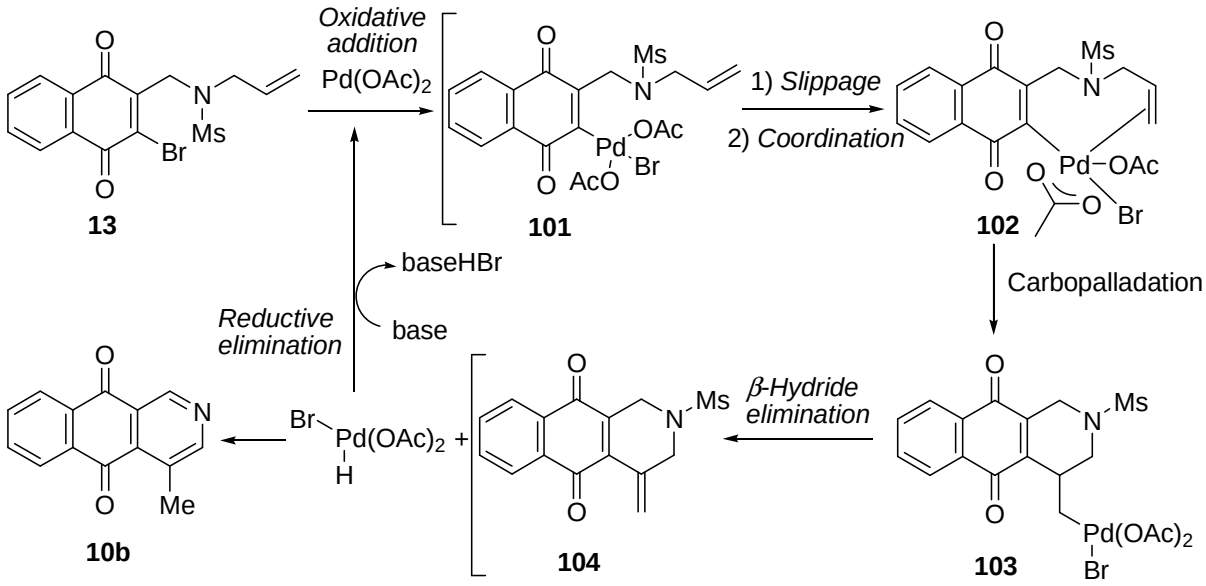
Table 1: Reaction conditions used in the Heck reaction to convert *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-naphthoquinone **13** to 2-azacleistopholine **10b**

Entry	$Pd(OAc)_2$ (mol%)	Solvent	Base (equiv.)	Temperature (°C)	Reaction time (h)	Product **10b** yield (%)[a]	(%)[b]
1	0.1	DMA	K_3PO_4 (1.4)	Rt	4	0	-
2	1.0	DMA	K_3PO_4 (1.4)	80	4	35	-
3	1.0	DMA	K_3PO_4 (1.4)	140	19	34	-
4	10	DMA	K_3PO_4 (3.5)	140	19	35	-
5	50	CH_3CN	K_2CO_3 (5)	Reflux	3	45	30

[a]presence of compound **10b** in reaction crude judged upon LC-MS. [b]isolated yield.

Unfortunately, starting from *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **93**, these reaction conditions failed to give intramolecular ring closure and complex reaction mixtures were retrieved. This result is attributed to the fact that electron-rich aromatics are relatively unreactive to oxidative addition.[94] Since none of these test reactions gave the Heck cyclization product **92**, *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-naphthoquinone **13** was tested as a substrate

towards the direct synthesis of 2-azacleistopholine **10b** (Table 1). To this end, upon reflux naphthoquinone **13** for 3 hours in acetonitrile in the presence of 50 mol% $Pd(OAc)_2$ and 5 equivalents of K_2CO_3, 2-azacleistopholine **10b** was obtained in an isolated yield of 30%. Although the exact mechanism to explain the formation of 2-azacleistopholine **10b** was not established, the expected mechanism involves the formation of compound **101** (Scheme 3-6) by the oxidative addition across the carbon-bromide bond of substrate **13**. Slippage would afford intermediate **102** after which carbopalladation would form the cyclized compound **103**. *β*-Hydride elimination would break the intermediate **103** into compound **104**. Base promoted-reductive elimination would regenerate the catalytic palladium(II) acetate, while the intermediate **104** would aromatize to 2-azacleistopholine **10b**.

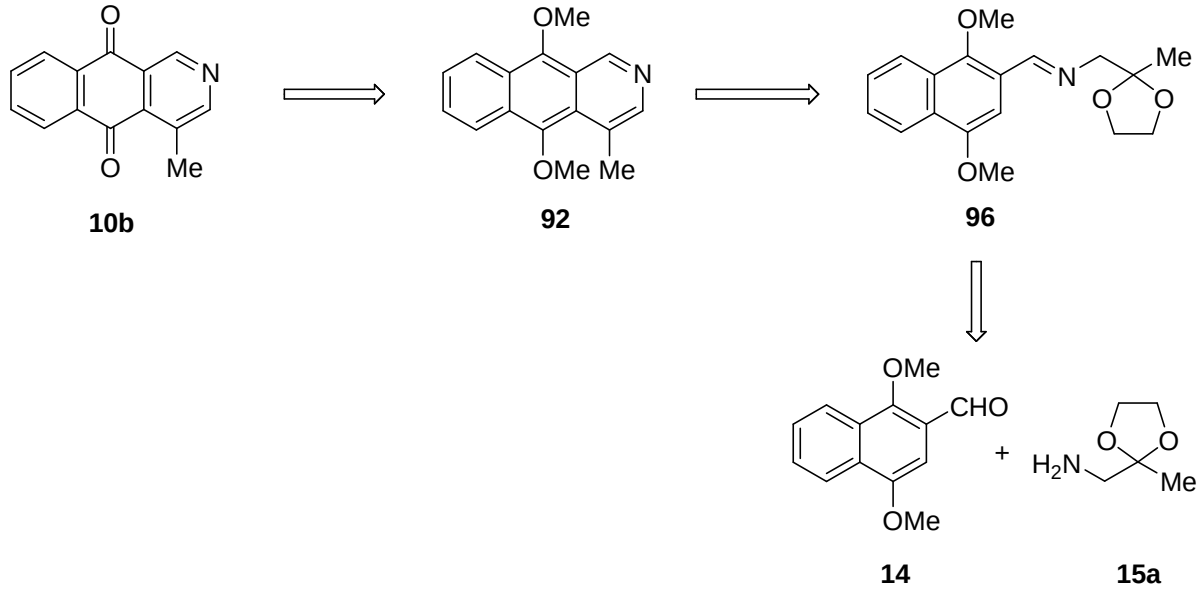


Scheme 3-6. Reaction mechanism of the intramolecular Heck reaction

An attempt to scale-up the Heck reaction on substrate **13** from 250 mg (0.65 mmole) to 500 mg (1.30 mmoles) under the same reaction conditions failed to reproduce the abovementioned isolated yield. These low yields reflect the relative instability of quinones to rigorous reaction conditions and the interaction of the palladium metal with the quinone function, thereby reducing the catalytic activity of $Pd(OAc)_2$ reoxidation of Pd(0). The low yields, harsh reaction conditions, high catalyst load and tedious scale-up severely plagued this linear synthesis and as a result, an alternative pathway to 2-azacleistopholine **10b** was investigated.

3.1.2. Synthesis of 2-azacleistopholine 10b by acid-promoted intramolecular condensation-Pomeranz-Fritsch reaction in the key step

Retrosynthetic analysis of 2-azacleistopholine **10b** by this alternative route gave 2-formyl-1,4-dimethoxynaphthalene **14** and protected aminoacetone **15a** as synthetic precursors (Scheme 3-7). Imination of 2-formyl-1,4-dimethoxynaphthoquinone **14** would occur by nucleophilic attack of the amino group of the aminoacetal **15a** across the aldehyde function of 2-formyl-1,4-dimethoxynaphthoquinone **14** to give the imine **96** after elimination of water. A subsequent acid-promoted intramolecular condensation of imine **96** under water-free conditions, would afford 2-aza-9,10-dimethoxy-4-methylanthracene **92**, which can be converted to 4-methylbenzo[*g*]isoquinoline-5,10-dione **10b** upon oxidative demethylation.

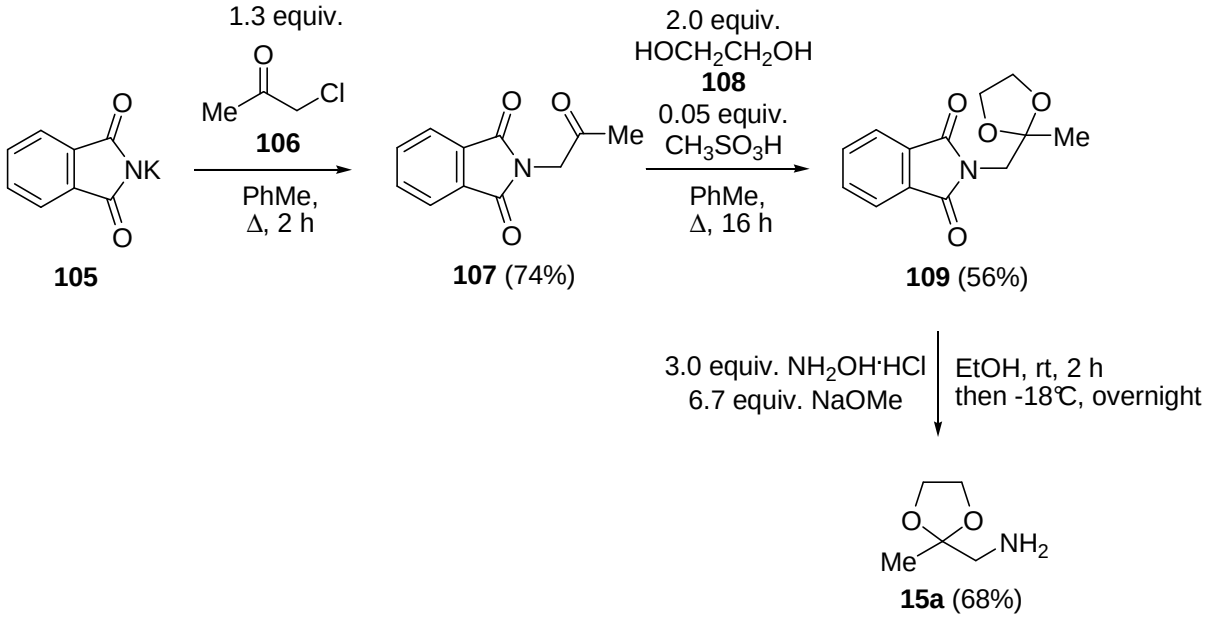


10b **92** **96**

14 **15a**

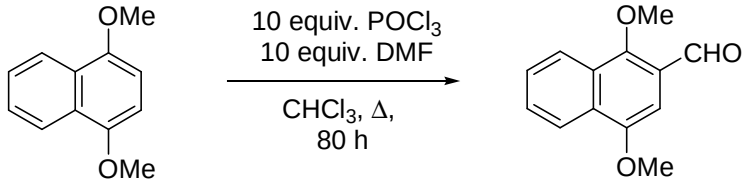
Scheme 3-7. Retrosynthetic analysis of 2-cleistopholine **10b** using the Pomeranz-Fritsch reaction

Synthesis of 2-aminomethyl-2-methyl-1,3-dioxolane **15a** was carried out according to a literature procedure (Scheme 3-8).[95] It commenced with a Gabriel synthesis using potassium phthalimide **105** and α-chloroacetone **106**. These starting materials were reacted in boiling toluene for 2 hours to form the *N*-acetonylphthalimide **107** in 74% yield. The reaction of *N*-acetonylphthalimide **107** with ethylene glycol **108** in boiling toluene for 16 hours in the presence of methanesulfonic acid as catalyst afforded the dioxolanyl protected ketone **109** in a yield of 56%. Subsequently, the imide function was cleaved by hydroxylamine in ethanol to afford 2-aminomethyl-2-methyl-1,3-dioxolane **15a** in 68% yield.



Scheme 3-8. Synthesis of 2-aminomethyl-2-methyl-1,3-dioxolane **15a**[95]

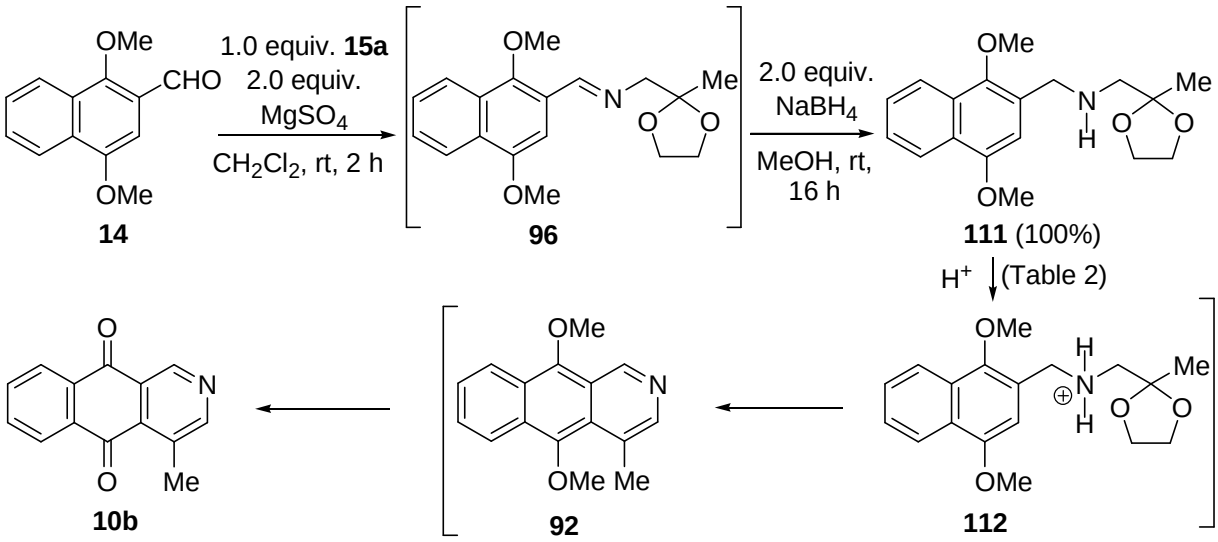
The second precursor, 2-formyl-1,4-dimethoxynaphthalene **14**, was obtained in 75% yield through a Vilsmeier formylation of 1,4-dimethoxynaphthalene **110** in boiling chloroform for 80 hours under nitrogen atmosphere (Scheme 3-9).[96]



Scheme 3-9. Synthesis of 2-formyl-1,4-dimethoxynaphthalene **14**[96]

The condensation reaction of 2-formyl-1,4-dimethoxynaphthalene **14** and 2-aminomethyl-2-methyl-1,3-dioxolane **15a** occurred smoothly in anhydrous dichloromethane in the presence of magnesium(II) sulfate at room temperature furnishing the intermediate imine **96**, which was reduced quantitatively to the corresponding amine **111** by two equivalents of sodium borohydride in methanol at room temperature for 16 hours. Different reaction conditions were tested to induce the intramolecular cyclization of the amine **111** using different acids to 4-methyl-9,10-dimethoxyanthracene **92** (Table 2, page 34). Mild acidic conditions proved to produce no reaction (entries 1-5) due most likely to the relative stability of the dioxolane ring while rigorous conditions led to complex mixtures containing minor amounts of 2-azacleistopholine **10b** (entries 10 and 12). The use of gaseous HCl or diluted H_2SO_4 led to the formation of ammonium salt **112** (entries 11 and 14). The conversion to 2-azacleistopholine **10b**

could be carried out by treating the amine **111** with H_3PO_4 (entry 6) or H_2SO_4 in dichloromethane (entries 7 and 8) for a relatively short reaction time.



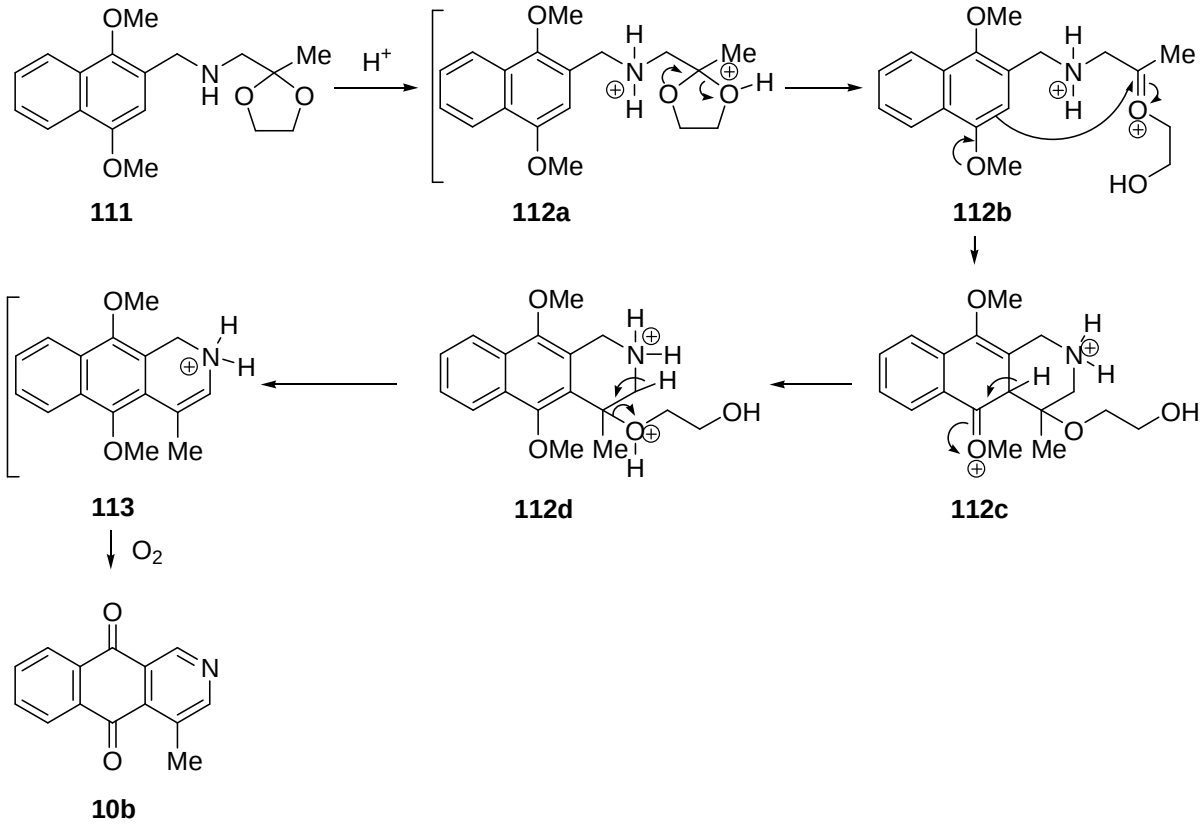
Scheme 3-10. Synthesis of 2-azacleistopholine **10b** using the Pomeranz-Fritsch reaction

In this way, 2-azacleistopholine **10b** was obtained directly in yield of 50% upon reaction of amine **111** for 2 days in a mixture of sulfuric acid and dichloromethane (2/1) at room temperature (Table 2, entry 8). It is important to note that the yield of this Pomeranz-Fritsch process is affected by the acid-base character of the workup because of the simutanous presence of a fairly acidic benzylic proton and basic isoquinoline nitrogen in 2-azacleistopholine **10b**. Therefore the neutrality of the aqueous phase is required for an optimumal extraction.

Table 2: Optimization process of the acid mediated conversion of amine **111** to 2-azacleistopholine **10b**

Entry	Reaction conditions	Results	Yield (%)
1	AcOH, H_2SO_4 (cat), 1 h at rt to 4 h of reflux	No reaction	-
2	10 equiv. PPA, EtOH, 1 h at rt to 4 h of reflux	No reaction	-
3	6 M HCl, THF, 1 h at rt to 4 h of reflux	No reaction	-
4	2 equiv. *p*-TsOH, PhMe, 1 h at rt to 3 h of reflux	No reaction	-
5	2 equiv. PPTS, PhMe, 1 h at rt to 3 h of reflux	No reaction	-
6	98% H_3PO_4, 130 °C, 3 h	Compound **10b**	10
7	H_2SO_4 (conc.): CH_2Cl_2 (2:1), rt, 60 h (2.5 d)	Compound **10b**	35
8	**H_2SO_4 (conc.): CH_2Cl_2 (2:1), rt, 48 h (2 d)**	**Compound 10b**	**50**
9	H_2SO_4 (conc.), rt, 3 h	No reaction	-
1 0	H_2SO_4 (conc.), rt, 48 h	Complex mixture	-
11	HCl(g), dry Et_2O, rt, 1 h	Formation of **112**	-
12	10 equiv. $ClSO_3H$, CH_2Cl_2, rt, 1 h	Complex mixture	-
13	10 equiv. $ClSO_3H$, CH_2Cl_2, -5°C to Δ, 10 min.	Complex mixture	-
14	15% H_2SO_4, CH_2Cl_2 (1:1)-SiO_2, rt, 2 h	Formation of **112**	-

The mechanism of this multistep transformation implies an acid-catalyzed deprotection of compound **111** in the presence of excess of strong acid to form simutaneously the ammonium and the oxonium centers to allow subsequent cyclization and oxidative demethylation as visualized in the accompanying scheme (Scheme 3-11).

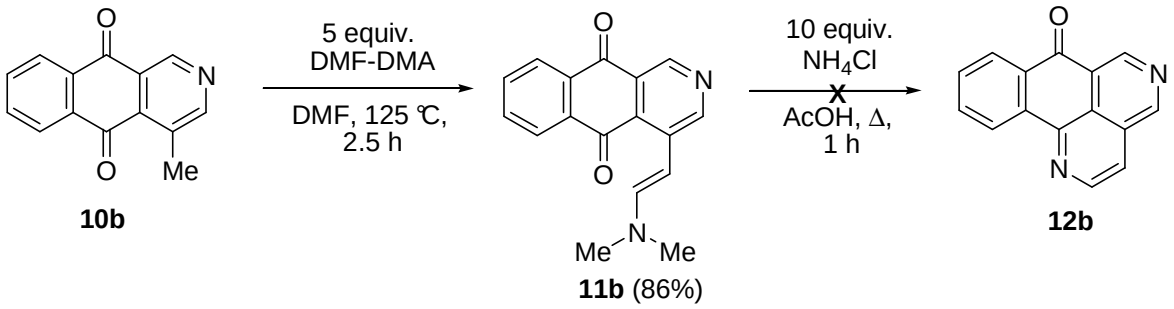


Scheme 3-11. Reaction mechanism of the Pomeranz-Fritsch reaction

3.1.3. Synthesis of 4-[2-(dimethyl)aminovinyl]benzo[*g*]isoquinoline 11b starting from 2-azacleistopholine 10b and effort towards the synthesis of 2-azasampangine 12b

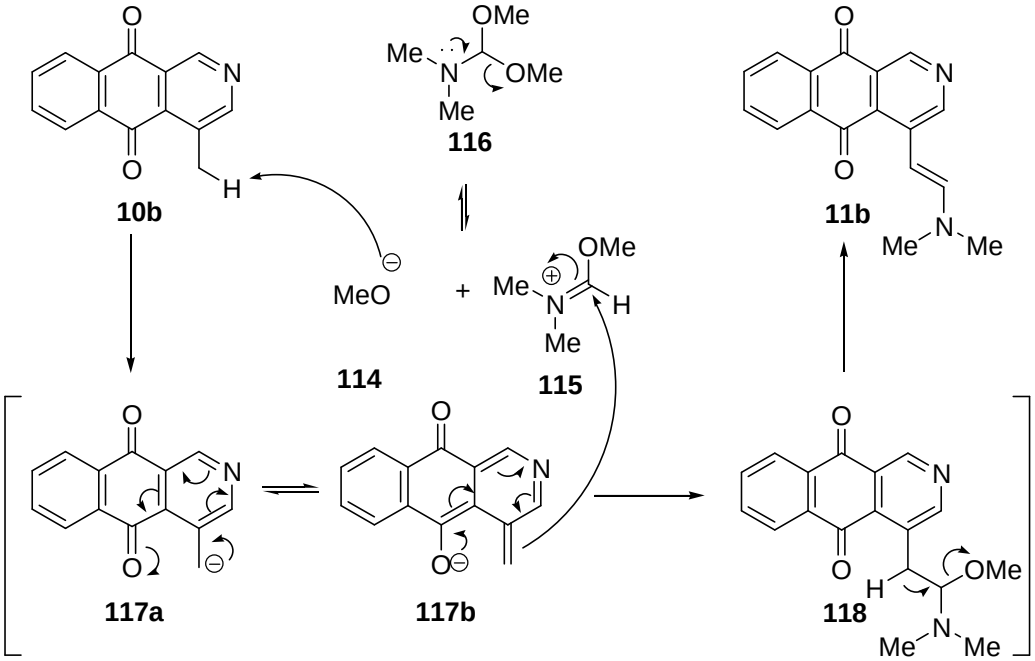
Having 2-azacleistopholine **10b** in hand, the synthesis of 2-azasampangine **12b** was envisaged parallel to the literature report on the synthesis of sampangine **12a** (Scheme 3-1).[15a] In this way, (*E*)-4-[2-(dimethylaminovinyl]benzo[*g*]isoquinoline-5,10-dione **11b** was obtained in 86% yield upon reacting 5 equivalents of DMF-DMA with 2-azacleistopholine **10b** in DMF at 125°C under a nitrogen atmosphere. The reaction was followed up by thin layer chromatography and was run to completion upon 2.5 hours, after which the workup resulted in the isolation of compound **11b** in high purity (Scheme 3-12).

Then, the latter enamine **11b** was introduced in a reaction with an excess of ammonium chloride in boiling acetic acid. The idea was that this would induce transamination of the enamine function of 2-azaanthraquinone **11b**, after which a spontaneous aza-ring closure across the quinone group would afford the targeted 2-azasampangine **12b**. However, in practice these reaction conditions only resulted in the formation of intractable complex reaction mixtures and as a result, the synthesis of 2-azasampangine **12b** still remains a challenge.



Scheme 3-12. Attempt to synthesize 2-azasampangine **12b** from 2-azacleistopholine **10b**

The mechanism of this DMF-DMA-assisted synthesis of (*E*)-4-[2-(dimethylamino)-vinyl]benzo[*g*]isoquinoline-5,10-dione **11b** (Scheme 3-13) can be explained by a deprotonation of the 2-azacleistopholine **10b** at the benzylic position by a methoxide anion **114** which is eliminated from the DMF-DMA. The resulting intermediate anion **117** then reacts with the iminium salt **115** to form a hemiaminal intermediate **118**. This latter transient species eliminates methanol due to the presence of an acidic benzylic proton to generate the enamine function of **11b**.

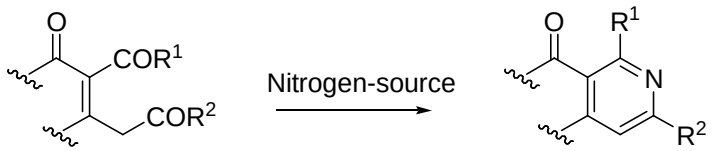


Scheme 3-13. Reaction mechanism for the synthesis of (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **11b**

3.2. Synthesis of 3-aryl-1-hydroxybenzo[g]isoquinoline-5,10-diones 16, 3-aryl-1-methyl benzo[g]isoquinoline-5,10-diones 17 and methyl 3-aryl-1-hydroxybenzo[g]isoquinoline-5,10-dione-4-carboxylates 18

2-Azaanthraquinones bearing a hydroxy substituent at the C-1 *peri*-carbonyl position such as 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-diones **16**, methyl 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-dione-4-carboxylates **18** (Figure 1-4) are interesting targets to synthetic organic chemists due to their promising biological activities as stated in the introduction of this dissertation. It has been shown that the presence of a hydroxyl group at the C-1 *peri*-carbonyl position on 2-azaanthraquinones enhances their antimicrobial activity.[16a] Moreover, 2-azaanthraquinones with an aryl group fixed at C-1 inhibit the proliferation of MT-4 cells at micromolar concentrations,[97] while the antifungal activity of 1,4-naphthoquinone epoxide was shown to require the presence of a hydroxyl group at the C-1 *peri*-carbonyl position.[16b] In a perspective of building a library of 1-substituted 2-aza-3-arylanthraquinones for biological activity tests, the hydroxyl group and its isostere, the methyl group, were considered in order to develop potential lead molecules in the search for new antibiotics. The presence of a methyl group at the *peri*-carbonyl position is expected to eliminate any hydrogen bond formation in comparison with the hydroxyl group and will increase the lipophilicity of these compounds, as well as their membrane permeability. Therefore, syntheses of 3-aryl-2-aza-1-hydroxyanthraquinones **16**, 3-aryl-2-aza-1-methylanthraquinones **17** and 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylanthraquinones **18** became interesting research targets from both synthetic and medicinal points of view.

Compounds **120** bearing a substituent at the C-1 *peri*-carbonyl position, can be prepared starting from substrates **119**, bearing a 1,5-dicarbonyl functionality, and a source of nitrogen such as ammonia, hydroxylamine or ammonium salts (Scheme 3-14). Submitting the appropriate substrate **119** to a nitrogen source would form a pyridone ring, which would tautomerize to the hydroxypyridine ring **120** (R^1 = OH). Actually, the hydroxypyridine tautomer is more stable than the pyridone form[98] because of the hydrogen bond that is formed between the carbonyl and hydroxyl groups and because of the aromaticity of the compound.

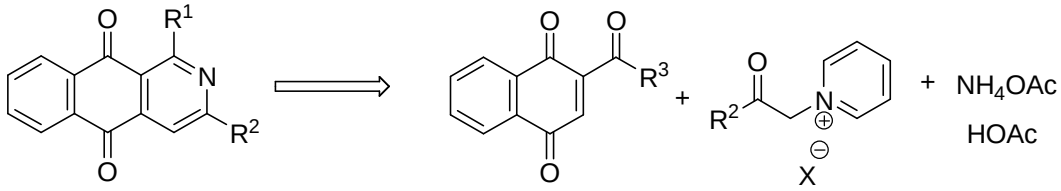


119
R^1 = H, OH, OR, alkyl or aryl
R^2 = H, alkyl, aryl

120
R^1 = H, OH, alkyl or aryl
R^2 = H, alkyl, aryl

Scheme 3-14. Preparation of *peri*-carbonyl substituted compounds **120**

Since pyridinium ylids already proved to be very useful to introduce acetonyl side chains onto quinone moieties,[99] the reaction of 2-methoxycarbonyl-1,4-naphthoquinone **19a** and 2-acetyl-1,4-naphthoquinone **19b** with different pyridinium ylids **20** and ammonia, which would be produced *in situ* from ammonium acetate **121a** in acetic acid and are known as Kröhnke conditions,[99b] were envisaged (Scheme 3-15).



16 R^1 = OH, R^2 = aryl
17 R^1 = Me, R^2 = aryl

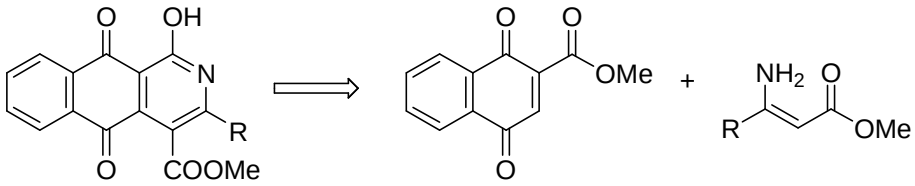
19a R^3 = OMe
19b R^3 = Me

20 R^2 = aryl
X = Cl, Br

121a

Scheme 3-15. Retrosynthetic analysis of 1-substituted-2-azaanthraquinones **16** and **17**

The presence of a methoxycarbonyl group at position C-4 on the third type of targeted 2-azaanthraquinones **18** requires an adjustment of starting materials to achieve their synthesis (Scheme 3-16). Therefore, enaminoesters **23** will be reacted with 2-methoxycarbonyl-1,4-naphthoquinone **19a**, replacing both pyridinium salts **20** and ammonium acetate **121a**.



18 R = Ar

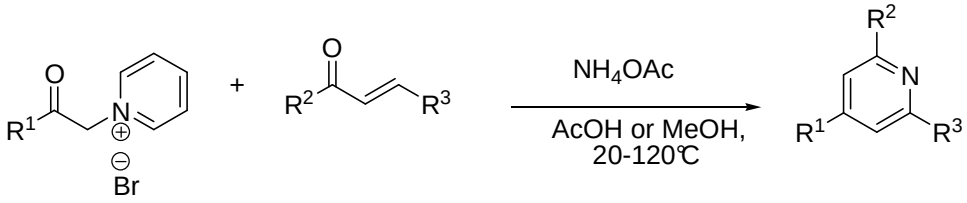
19a

23 R = aryl

Scheme 3-16. Retrosynthetic analysis of methyl 3-aryl-1-hydroxybenzo[g]isoquinoline-5,10-dione-4-carboxylates **18**

3.2.1. Synthesis of 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-diones 16

The synthesis of 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-diones **16** under Kröhnke conditions called upon *N*-phenacylpyridinium salts **20**. These salts can be easily converted to highly reactive *N*-methylenepyridinium ylids by deprotonation with an appropriate base such as hydroxide, ammonia, triethylamine, DABCO, DBU, etc. The rates of the deprotonation reactions of *N*-phenacylpyridinium salts **20** are substituent and solvent dependent.[100] Moreover, Kröhnke pyridines **123** are traditionally synthesized in excellent yields through the reaction of *N*-phenacylpyridinium salts **20** with *α,β*-unsaturated carbonyl compounds **122** (Michael acceptors) in the presence of ammonium acetate **121a** in acetic acid or methanol[99] which are referred to as Kröhnke conditions (Figure 3-17).[99k]



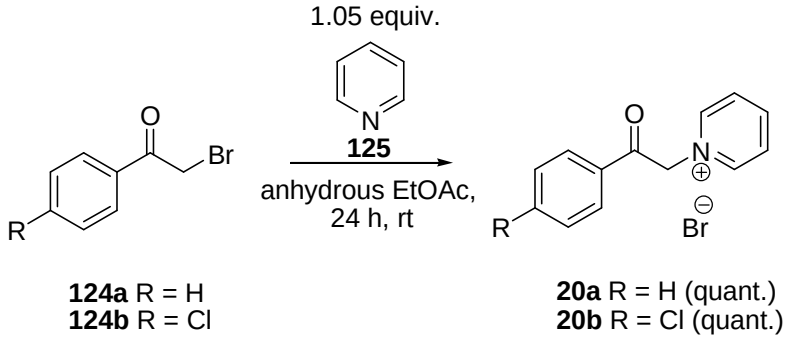
20 **122** **123**

$R^1 = R^2 = R^3$ = H, alkyl, aryl

Scheme 3-17. Synthesis of Kröhnke pyridines **123**[99k]

Analogously, a one-step synthesis of 3-aryl-1-hydroxybenz[*g*]isoquinoline-5,10-diones **16** required the presence of a *α,β*-unsaturated ketone system (found in 2-methoxycarbonyl-1,4-naphthoquinone **19a**) onto which phenacyl groups (originating from the pyridinium salts **20**) could be added to create a 5-oxoester system. The azacyclization of this 5-oxoester system and tautomerization would afford the fused 1-hydroxypyridine ring of the targeted compounds **16**.

In continuation of previous studies in the reseach group[101] and according to the goals set for the PhD research, it was envisaged to use *N*-phenacylpyridinium salts **20c**,**d** (Scheme 3-19) with electron-withdrawing substituents (4'-NO_2, 2',4'-di-Cl) attached to the acetophenone moiety and unsubstituted *N*-phenacylpyridinium salt **20a** as a reference compound. Indeed, the pyridinium salts **20a**,**b** were obtained nearly in quantitative yield according to the procedure described in the literature[102] by the reaction of α-bromoacetophenones **124a**,**b** with 1.05 equivalents of pyridine **125** in anhydrous ethyl acetate at room temperature for 24 hours.

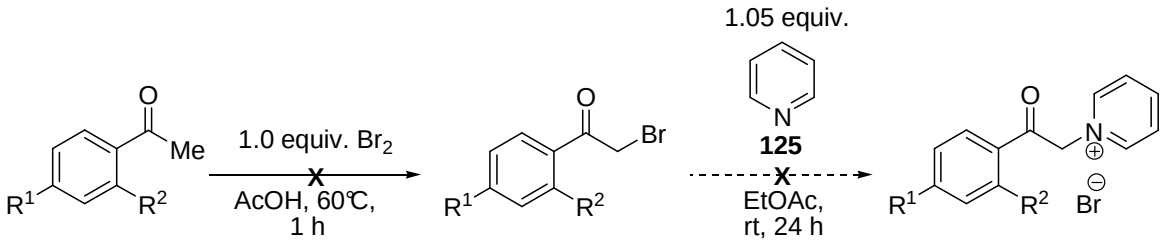


124a R = H
124b R = Cl

20a R = H (quant.)
20b R = Cl (quant.)

Scheme 3-18. Preparation of pyridinium salts **20a** and **20b**

The preparation of α-bromoacetophenones **124c**,**d** were attempted by the usual acid-catalyzed bromination of commercially available acetophenones **126c**,**d** (Scheme 3-19).[103] Although α-bromoacetophenones **124c**,**d** are known, literature procedures for their synthesis were not affording pure products in our hands. Under these typical conditions (bromine in acetic acid at 60°C for one hour), the corresponding α-bromoacetophenones **126c**,**d** could not be obtained with acceptable purity to be used in the subsequent step.



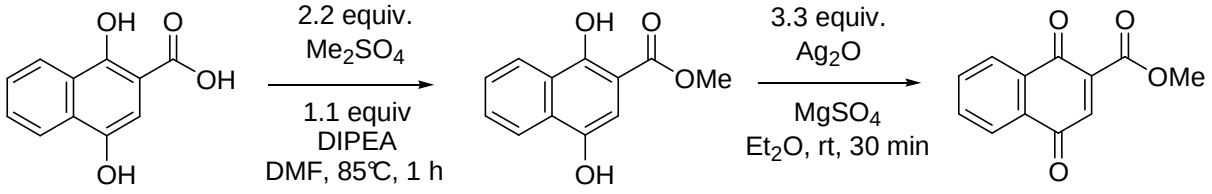
126c R^1 = NO_2, R^2 = H
126d R^1 = Cl, R^2 = Cl

124c R^1 = NO_2, R^2 = H
124d R^1 = Cl, R^2 = Cl

20c R^1 = NO_2, R^2 = H
20d R^1 = Cl, R^2 = Cl

Scheme 3-19. Attempt to prepare α-bromoacetophenones **124c** and **124d**

The synthesis of 2-methoxycarbonyl-1,4-naphthoquinone **19a** was achieved by a successful large scale protocol established in our group (Scheme 3-20),[101,104] the protocol of which implied treatment of the commercially available 1,4-dihydroxy-2-naphthoic acid **127** with 1.1 equivalents of diisopropylethylamine as base and 2.2 equivalents of dimethyl sulfate in *N,N*-dimethylformamide at 85 °C for 1 h, after which methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** was isolated in 84% yield. Finally, silver(I) oxide mediated oxidation of the methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** afforded 2-methoxycarbonyl-1,4-naphthoquinone **19a** in 98% yield.

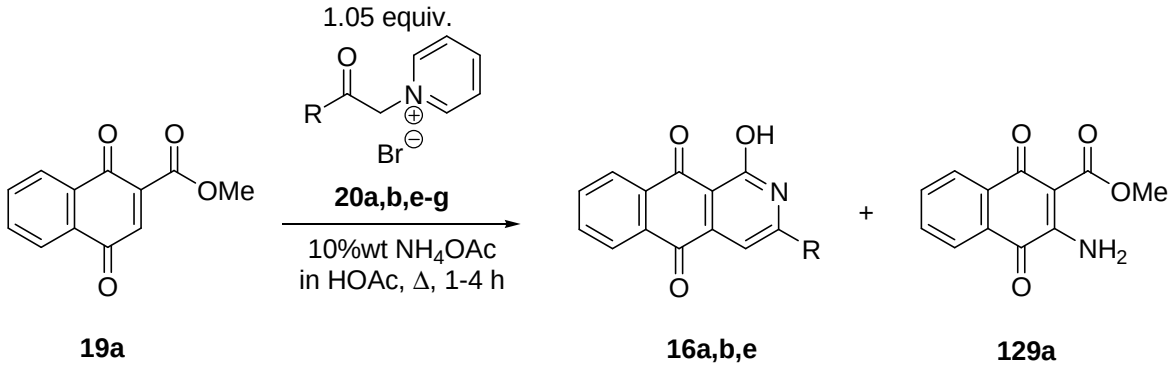


127 **128** (84%) **19a** (98%)

Scheme 3-20. Preparation of 2-methoxycarbonyl-1,4-naphthoquinone **19a**[101,104]

Having in hands both the appropriate Michael acceptor **19a** and the *N*-phenacylpyridinium bromides **20a**,**b** for Kröhnke conditions, these substrates were subsequently reacted in a 10 wt% solution of ammonium acetate in acetic acid[104] and the targeted 3-aryl-1-hydroxybenz[*g*]isoquinoline-5,10-diones **16a**,**b** were isolated in 44 and 75% yield, respectively (Table 3, entries 1 and 2). The reaction with the electron-deficient *N*-phenacylpyridinium bromide **20b** finished after 1 hour while it took 4 hours for the more electron-rich *N*-phenacylpyridinium bromide **20a**. The reaction was affected by the electron-withdrawing effects of the chlorine of *N*-phenacylpyridinium bromide **20a**. To have a clear view on these electronic effects, the activated quinone **19a** was later treated with pyridinium salts **20e-g** (Table 3, entries 3-5), which were previously prepared in our group, after checking their quality using ^{1}H NMR spectroscopy. The formation of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** as a side product was observed in 15-20% yield next to a mixture of unidentified material. The electron-withdrawing effects of the substituents on *N*-phenacylpyridinium salts **20** were best delineated by treating the activated 2-methoxycarbonyl-1,4-naphthoquinone **19a** with pyridinium salts **20f**,**g**, in which these effects are completely absent. Indeed, under Kröhnke conditions, there exists a competition between the addition of the pyridinium ylids and the direct addition of ammonia across the activated naphthoquinone **19a**. It was found that under these conditions, the *in situ* production of *N*-pyridinium acetate ylid and *N*-pyridinium acetamide ylid was not sufficient enough to add across the activated naphthoquinone **19a**. Probably, the ammonia produced *in situ* is not strong enough to deprotonate these pyridinium salts **20f**,**g** to produce their corresponding ylids.[105] Therefore, the formation of the targeted products **16f**,**g** was prevented, while the formation of the competitive side product **129a** was promoted.

Table 3: Synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **16** under Kröhnke conditions

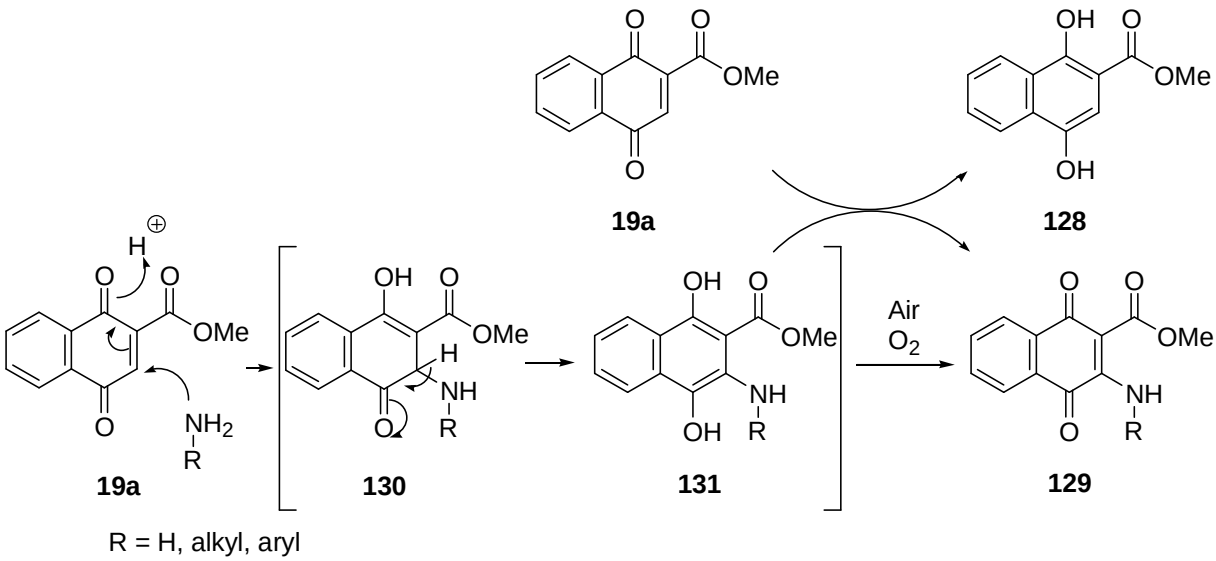


19a **16a,b,e** **129a**

Entry	Compound **20**	R	Reaction time (h)	Compound **16** (%)	Compound **129a** (%)
1	**20a**	C_6H_5	4	**16a** (44)	-
2	**20b**	*p*-Cl-C_6H_4	1	**16b** (75)	-
3	**20e**	*t*-Bu	4	**16e** (40)	15
4	**20f**	EtO	4	-	20
5	**20g**	NH_2	4	-	18

The reaction of 2-methoxycarbonyl-1,4-naphthoquinone **19a** with ammonium acetate in boiling acetic acid was conducted in the absence of *N*-pyridinium salts **20**. 3-Amino-2-methoxycarbonyl-1,4-naphthoquinone derivative **129a** was smoothly formed in 72% yield after 4 hours.

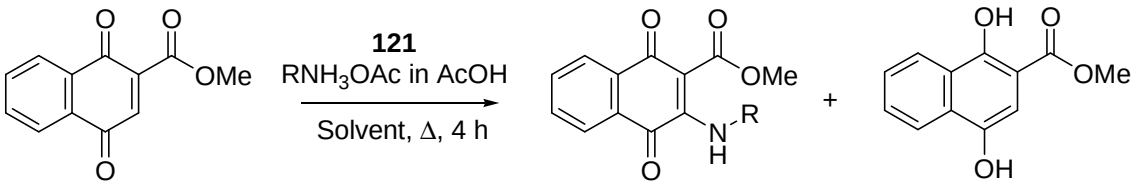
The reaction mechanism involved in the formation of the side-product 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** (Scheme 3-21) implies a conjugate addition of ammonia across the activated naphthoquinone **19a** to form the intermediate **130**, which tautomerizes to 3-amino-1,4-dihydroxy-2-methoxycarbonylnaphthalene **131**, which is oxidized by air and affords the corresponding naphthoquinone **129a**.



Scheme 3-21. Synthesis of 3-amino- and 3-alkylamino-2-methoxycarbonyl-1,4-naphthoquinones **129**

Alkylammonium and arylammonium acetates **121b**,**c** and **121d** were also reacted with the activated naphthoquinone **19a** in boiling mixture of toluene and acetic acid (5/1) for 4 hours to add more insight to this reaction. It resulted in the synthesis 2-methoxycarbonyl-3-(*n*-propylamino)-, 2-methoxycarbonyl-3-(*n*-butylamino)- and 2-methoxycarbonyl-3-phenylamino-1,4-naphthoquinones **129b-d** in 69-87% yields and different small amounts of methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** (Table 4). Although the exact source of the reductant has not been identified, the formation of compound **128** can be explained by the autooxido-reduction cycle of the starting material **19a** and the hydroquinone form of alkylaminonaphthoquinone **131**.

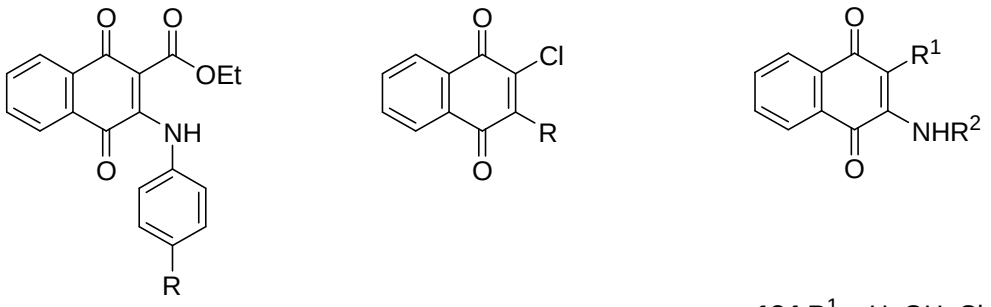
Table 4: Reaction of 2-methoxycarbonyl-1,4-naphthoquinone **19a** with ammonium acetate salts **121** for 4 hours



19a **129** **128**

Entry	Ammonium salt	R	Equiv.	Solvent	Compound **129** (%)	Compound **128** (%)
1	**121a**	H	28	AcOH	**129a** (72)	12
2	**121b**	*n*-Pr	4	PhMe/AcOH (5/1)	**129b** (87)	-
3	**121c**	*n*-Bu	4	PhMe/AcOH (5/1)	**129c** (75)	-
4	**121d**	Ph	4	PhMe/AcOH (5/1)	**129d** (69)	-

In view of the potential biological activity of aminonaphthoquinones **129** and their use in human medicine, 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** was reported to prevent intestinal carcinogenesis.[106] 3-Anilino-2-ethoxycarbonyl-1,4-naphthoquinones **132** (Figure 3-1) were prepared in order to exhibit bacteriostatic activity against *Mycobacterium tuberculosis*.[107] *N*-Substituted 3-amino-2-chloro-1,4-naphthoquinones **133** (Figure 3-1) are reported to possess significantly enhanced antimalarial activity making these compounds a novel type of antiplasmodial agents.[108] Finally, 2-amino-1,4-naphthoquinone derivatives **134** (Figure 3-1) have been found to possess some level of haemolytic activity and nephrotoxicity.[109]



132 R = Br, COOH, COOEt, SO_2NH_2

133 R = NH_2, C_6H_5NH (also pyrrolidino, morpholino)

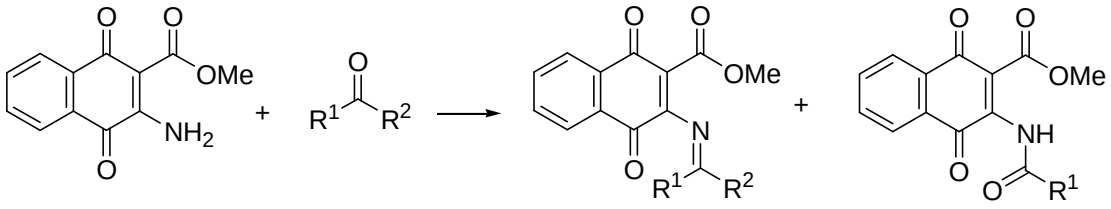
134 R^1 = H, OH, Cl; R^2 = H, Me, Ph

Figure 3-1. Examples of 3-alkyl- and 3-arylamino-1,4-naphthoquinones in the literature

Different attempts were performed to react 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** with common carbonyl electrophiles **135** such as ethyl acetoacetate **135a**, benzaldehyde **135b**, acetic anhydride **135c** and acetyl chloride **135d** (Table 5) under mild neutral, basic and acid conditions. The electrophiles **135** were reacted according to the increasing order of their chemical reactivity.

All the reactions in Table 5 were performed at room temperature and checked by TLC analysis. Since TLC only showed the presence of the starting materials, the reaction mixture was boiled under reflux and followed up by TLC analysis up to 4 hours. Ethyl acetoacetate **135a** was the first compound to be used in the reaction because of the double electrophile, i.e the ester and the ketone functionality, present in the compound. The acidic condition was tested to improve the formation of the corresponding adduct treating 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** with 10 mol% of *p*-toluenesulfonic acid and 1.05 equivalents of ethyl acetoacetate **135a** under Dean-Stark conditions. After boiling the reaction mixture for 4 hours, no sign of the adduct formation was observed and only starting materials were retrieved. Since the ester and ketone functionality failed to react with 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a**, benzaldehyde **135b** was attempted as an electrophile. Therefore, 1.5 equivalents of $MgSO_4$ in boiling dichloromethane or benzene were used. Unfortunately, after 4 hours of reaction time, only the starting materials were observed upon TLC analysis and retrieved from the reaction mixture. Subsequently, it was attempted to acetylate 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** under different conditions. All the acetylating reactions failed to afford the acetylated product **137**.

Table 5: Reaction of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** with electrophiles **135**

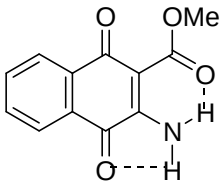


129a **135** **136** **137**

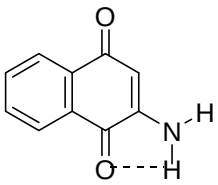
Entry	Electrophile	R^1	R^2	Reaction conditions	Expected product	Result
1	**135a**	Me	CH_2COOEt	(1) 0.1 equiv. *p*-TsOH.H_2O, PhH, Δ, 4 h.	**136**	No reaction
				(2) 0.1 equiv. *p*-TsOH.H_2O, PhMe, Δ, 4 h.	**136**	No reaction
2	**135b**	Ph	H	(1) 1.5 equiv. $MgSO_4$, CH_2Cl_2, Δ, 2 h	**136**	No reaction
				(2) 1.5 equiv. $MgSO_4$, PhH, Δ, 4 h	**136**	No reaction
3	**135c**	Me	OAc	(1) 4.0 equiv. K_2CO_3, PhMe, Δ, 4 h	**137**	No reaction
				(2) 2 drops H_2SO_4, PhMe, Δ, 24 h	**137**	Tar formation
4	**135d**	Me	Cl	(1) 1.0 equiv. Et_3N, PhMe, Δ, 4 h	**137**	No reaction
				(2) 1.0 equiv. DMAP, PhMe, Δ, 4 h	**137**	No reaction

In contrast to the amino group in 2-amino-1,4-naphthoquinone **138** (Figure 3-2), which is somehow reactive towards electrophiles, and is found in many heteroannulation reactions,[109] the amino group of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** was found to be less reactive. This chemical inactivity might be rationalized by the formation of intramolecular hydrogen bonds between the amino group hydrogens and the oxygen atoms of the 2-methoxycarbonyl and the quinone function. A second reason may be found in the vinylogous amide character of the 3-amino group.[110] However, the reaction with acetic anhydride occurred when a catalytic amount of sulfuric acid was used in boiling toluene, but

prolonging the reaction time to 24 hours caused the degradation of starting materials (Table 5, entry 3). Since the synthesis of 1-azaanthraquinones was not a goal for this research work, the chemical reactivity of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** under acid conditions was not investigated further.



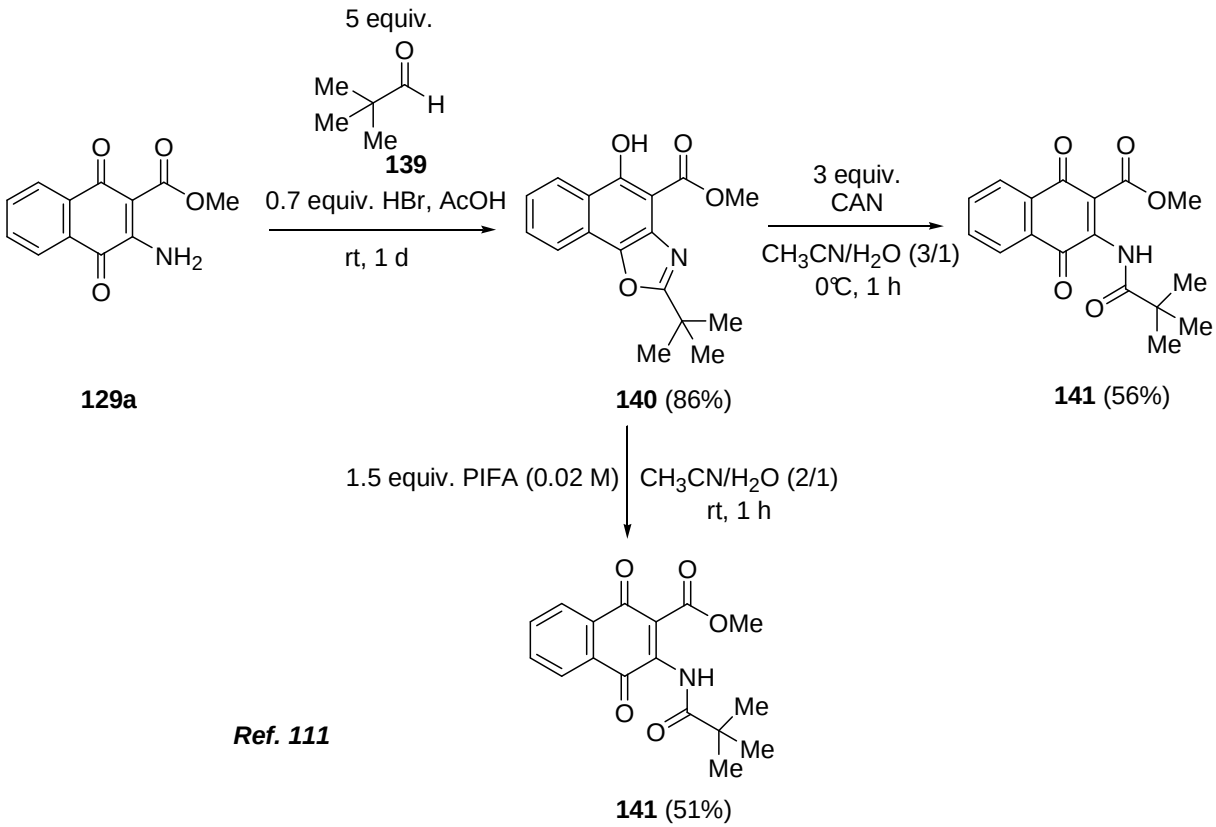
129a



138

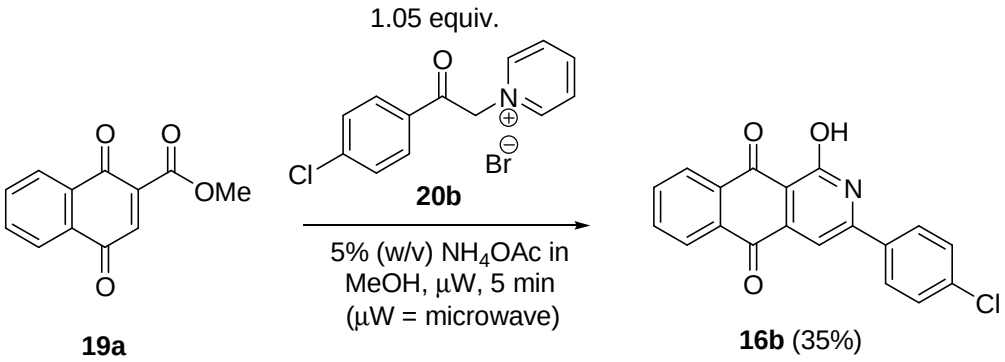
Figure 3-2. Hydrogen bond formation in aminonaphthoquinones **129a** and **138**

Nevertheless, the unexpected reaction of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** with pivaloylaldehyde **139** in hydrobromic acid and acetic acid (scheme 3-22) as a new entry to the synthesis of 2-methoxycarbonyl-3-(pivaloylamine)-1,4-naphthoquinone **141** in 56 and 51% yield, respectively, *via* CAN- and PIFA-mediated oxidation of the intermediate 2-*tert*-butyl-5-hydroxy-4-methoxycarbonylnaphtho[2,1-*d*]oxazole **140** has been reported recently.[111] Perhaps, the reaction conditions used in this article can be used in the future to produce the desired *N*-acylated 3-amino-2-methoxycarbonyl-1,4-naphthoquinones **137**.



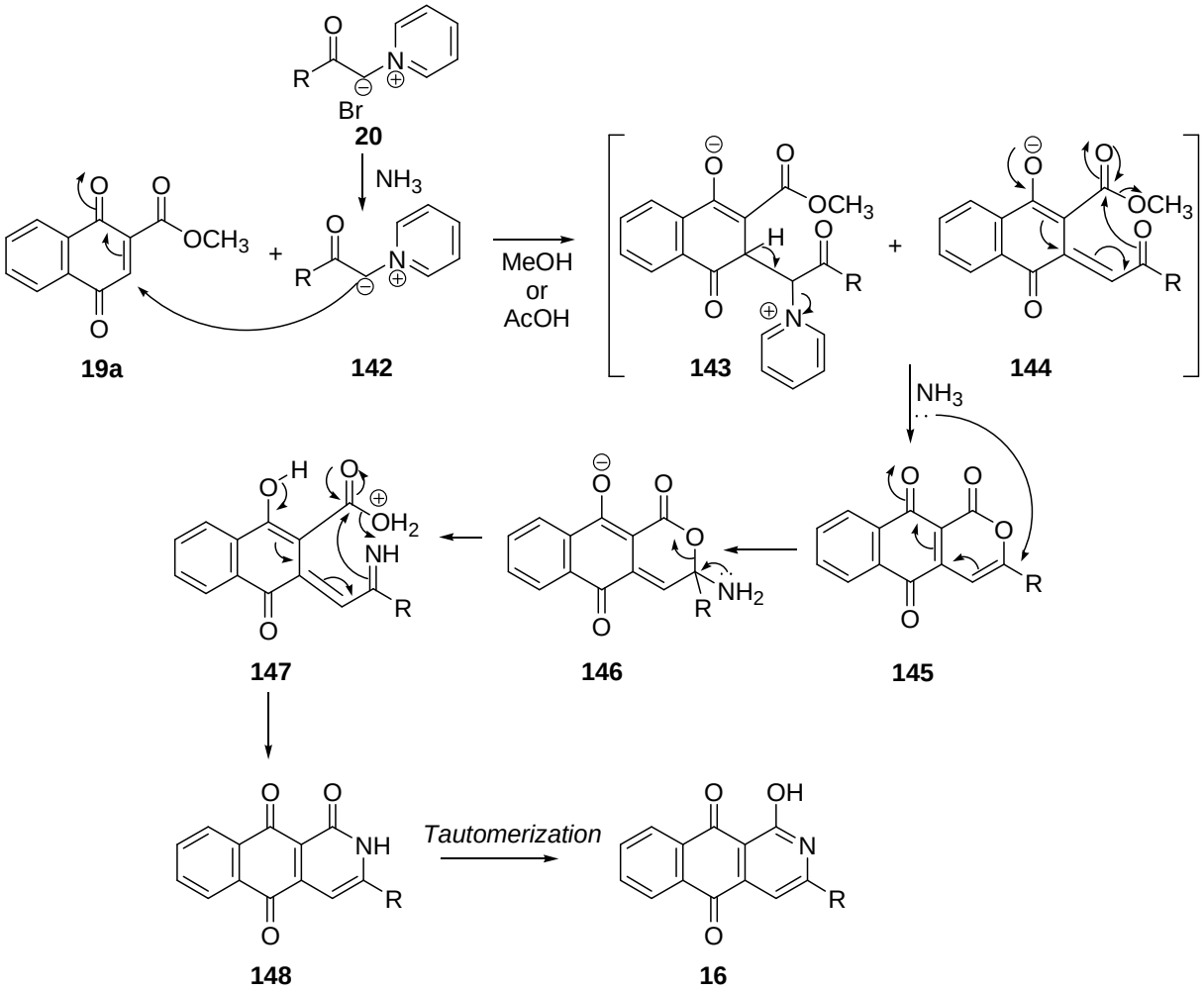
Scheme 3-22. Synthesis of 2-methoxycarbonyl-3-(pivaloylamine)-1,4-naphthoquinone **141**

In need of an optimized synthesis of 3-aryl-2-aza-1-hydroxyanthraquinones **16** under Kröhnke conditions, the competing formation of the side product 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** should be minimized. The synthesis of the targeted 3-aryl-2-aza-1-hydroxyanthraquinones **16** should be achieved shortly, efficiently and with an easy workup. Nowadays, microwave-mediated multicomponent reactions constitute an attractive synthetic strategy for rapid and efficient production of libraries of chemicals with cleaner products and simple manipulation.[112] Therefore, conditions established previously in our group[101b,104] were used and, in this way, quinone **19a** was reacted with 4-chlorophenacylpyridinium bromide **20b** under Kröhnke conditions using microwave irradiation in a 5 wt% solution of ammonium acetate in methanol at 115°C for 5 min (Scheme 3-23). Methanol was used instead of acetic acid since methanol behaves better as solvent (i.e has a higher absorption) under microwave conditions compared to acetic acid.[112a,113] Morever, the target compound **16b** crystallized after cooling down the reaction mixture to room temperature. Therefore, the target compound **16b** could then be easily recovered by filtration. After washing with ice-cold methanol, pure 3-(4-chlorophenyl)-1-hydroxybenz[*g*]isoquinoline-5,10-dione **16b** was isolated in 35% yield.



Scheme 3-23. Synthesis of 1-hydroxy-2-azaanthraquinone **16b** using a microwave reactor

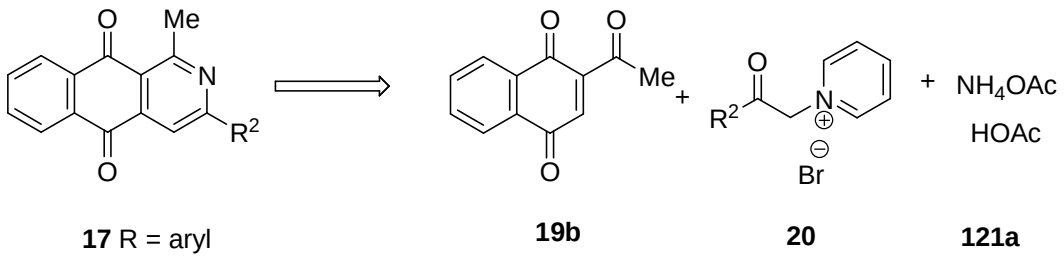
The reaction mechanism involved in this short and efficient synthesis of 1-hydroxybenz[*g*]isoquinoline-5,10-diones **16** might be explained as follows (Figure 3-24). After conjugate addition of the pyridinium ylid **142**, which is formed *in situ* by deprotonation of the corresponding pyridinium salt **20b**, onto the activated naphthoquinone **19a**, the pyridinium moiety is eliminated in a 1,2-fashion from the intermediate **143** thanks to the presence of an acidic α-hydrogen. Subsequently, cyclization occurred to form 1-oxo-3,4-dehydropyranonaphthoquinone **145**, which contains a novel Michael acceptor, to allow the addition of ammonia. Next, the pyran moiety in **146** undergoes ring opening, which leads to the formation of the intermediate imine **147**. Acid-catalyzed ring closure of the intermediate **147** forms lactam **148**, which tautomerizes to the targeted 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones **16**.[104]



Scheme 3-24. Reaction mechanism for the formation of 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-diones **16**

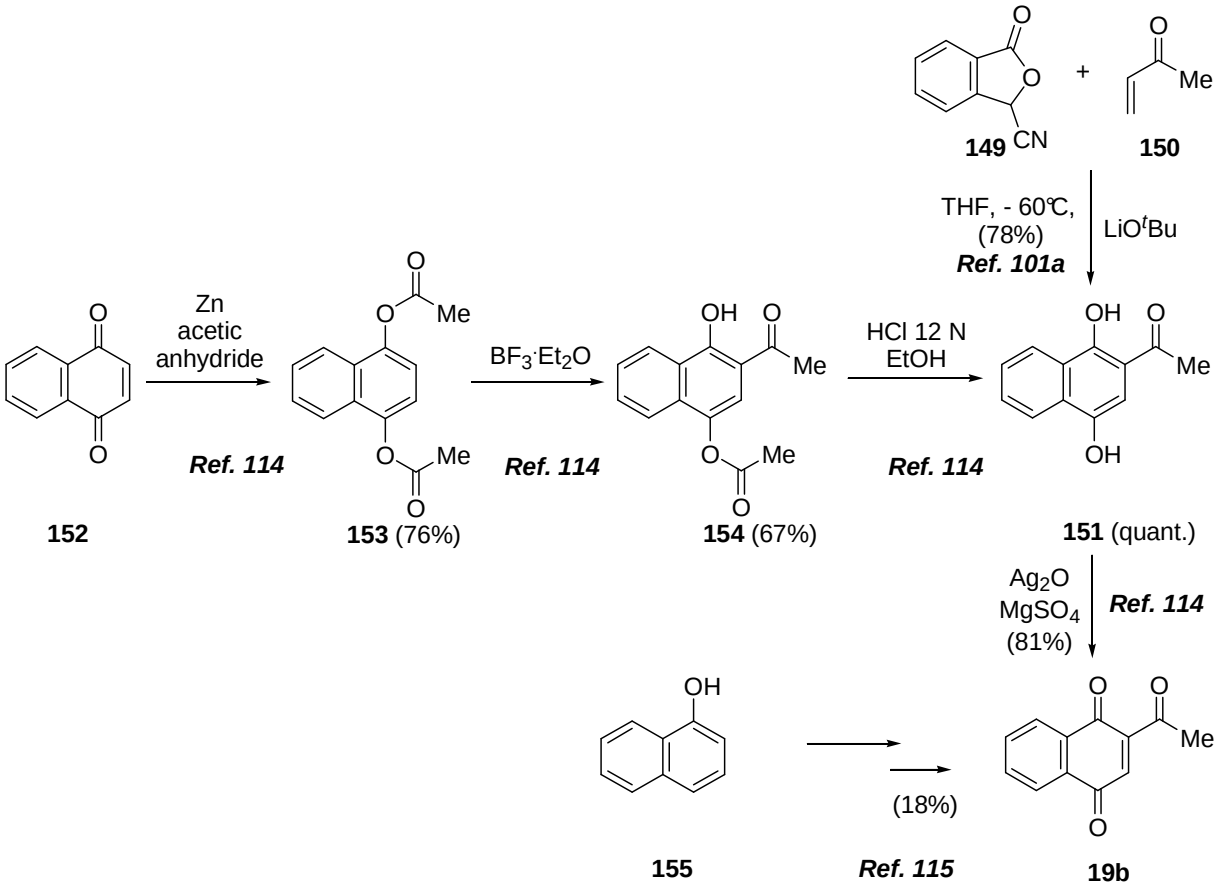
3.2.2. Synthesis of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones 17

The synthesis of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17**, requires 2-acetyl-1,4-naphthoquinone **19b** and pyridinium salts **20** as key intermediates as depicted in the following retrosynthetic scheme (Scheme 3-25).



Scheme 3-25. Retrosynthetic analysis of 1-methylbenzogisoquinoline-5,10-diones **17**

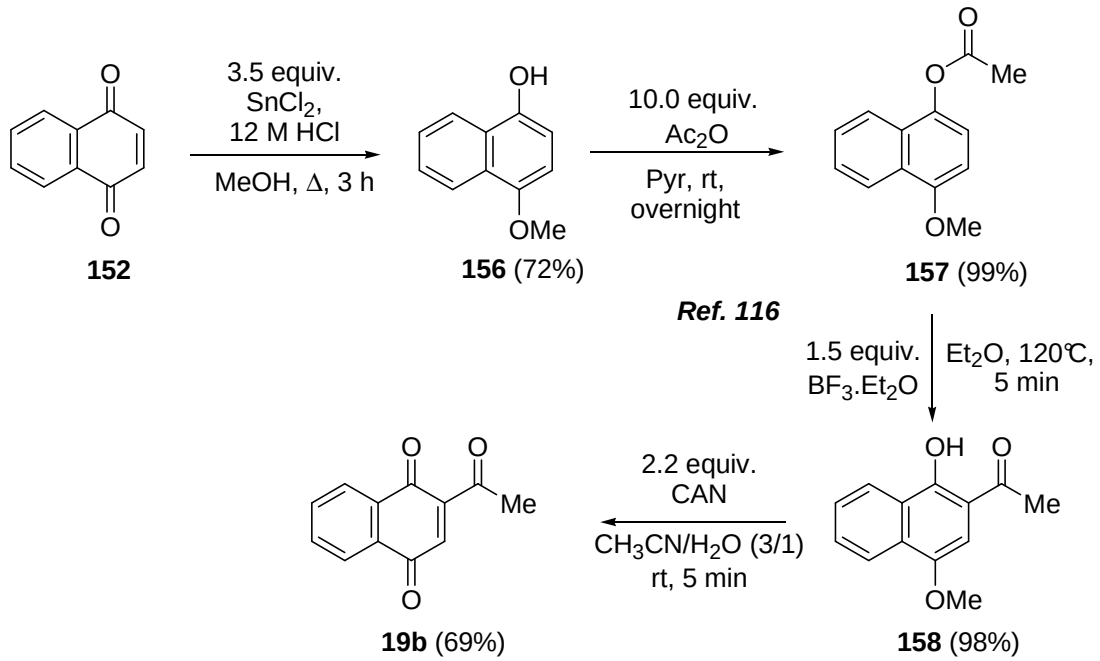
Different literature routes exist to prepare the substrate **19b**, but complicated procedures, harsh conditions and low yields are important drawbacks for these routes. Although the usefullness of phthalide annulation, the preparation of 3-cyanophthalide **149** is not so efficient for a large scale synthesis in addition to the fact that the use of a cyanide salt in acidic solution[101a] causes the process to be environmentally unfriendly and even dangerous. The use of 1,4-naphthoquinone **152** as the starting material towards the synthesis of 2-acetyl-1,4-naphthoquinone **19b** would be the one of choice. Unfortunately the process is recognized to be the longest and the most expensive.[115] In addition, this process was not efficiently reproducible in our hands. The use of cheap 1-naphthol **155** as starting material is severely plagued by poor overall yield (≤18%).[115]



Scheme 3-26. Literature routes for the synthesis of 2-acetyl-1,4-naphthoquinone **19b**

Therefore, the synthesis of 2-acetyl-1,4-naphthoquinone **19b** was achieved using the cerium(IV) ammonium nitrate induced-oxidation of 2-acetyl-4-methoxy-1-naphthol **158**, which was prepared by the literature procedure previously worked out in our group (Figure 3-27).[116] 4-Methoxynaphthol **156** was prepared by the reaction of 1,4-naphthoquinone **152** with 3.5 equivalents of tin(II) chloride in a boiling mixture of methanol and concentrated hydrochloride acid. Pure 4-methoxynaphthol **156** was obtained in 72% yield after column chromatography, which was acetylated nearly quantitatively after treatment with

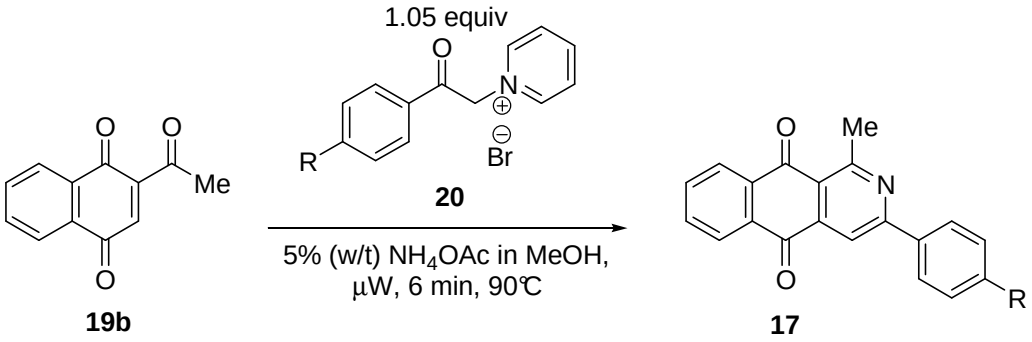
excess of acetic anhydride in pyridine at room temperature to afford the 1-acetoxy-4-methoxynaphthalene **157**. Subsequent Fries rearrangement with 1.5 equivalents of boron(III) fluoride etherate gave 2-acetyl-4-methoxy-1-naphthol **158** in 98% yield. Then, oxidative demethylation of 2-acetyl-4-methoxy-1-naphthol **158** with 2.2 equivalents of cerium(VI) ammonium nitrate in aqueous acetonitrile at room temperature afforded 2-acetyl-1,4-naphthoquinone **19b** in 69% yield after recrystallization from diethyl ether/hexane (9/1).



Scheme 3-27. Synthesis of 2-acetyl-1,4-naphthoquinone **19b**

Microwave reaction of 2-acetyl-1,4-naphthoquinone **19b** and different pyridinium salts **20** was run for 6 minutes in 5% (w/v) solution of ammonium acetate in methanol. Afterwards, the reaction mixtures were cooled down to room temperature and then in a bath of ice-water. The filtration of the cold reaction mixture afforded 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17** in 47-67% yield after washing the crystals with cooled methanol and a second recrystallization from methanol (Table 6).

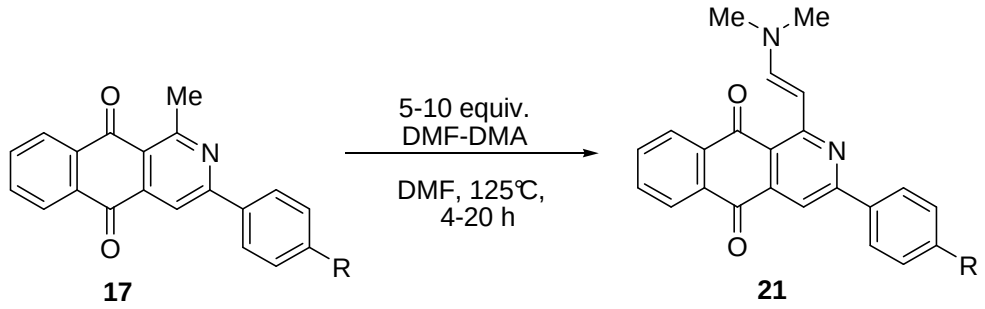
Table 6: Microwave-assisted synthesis of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17**



Entry	Pyridinium salt **20**	R	Compound **17**	Isolated yield (%)
1	**20a**	H	**17a**	52
2	**20b**	Cl	**17b**	67
3	**20i**	F	**17i**	51
4	**20j**	OMe	**17j**	47
5	**20k**	Me	**17k**	48

The presence of the methyl group at C-1 in 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17** allowed its conversion to a 2-(dimethylamino)vinyl moiety. Therefore, the 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17** were reacted with an excess of DMF-DMA in DMF at 125°C for 4-20 hours to give 3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **21** in 23-77% yield (Table 7). The reaction of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17** with DMF-DMA was strongly influenced by the electronic effects of the 3-substituents on substrate **17**, which could be observed by the acidity of hydrogens of the methyl at C-1. Since 3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **21** were found to be instable on silica gel and since the deprotonation of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17** is a reversible reaction, the addition reaction required an excess of DMF-DMA and longer reaction time for derivatives bearing-electron donating substituents at C-3 in order to run the reaction to completion (Table 7).

Table 7: Synthesis of (*E*)-3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **21**



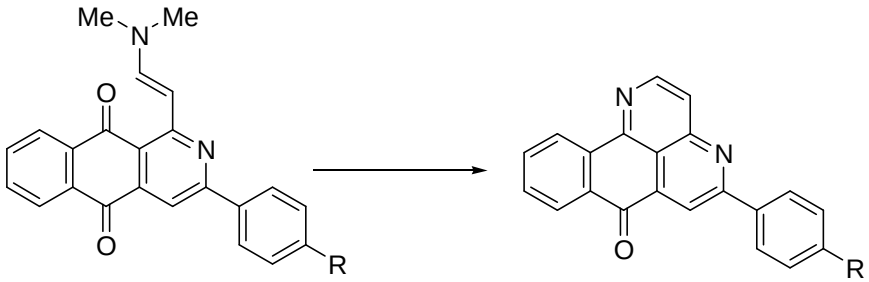
17 **21**

Entry	Compounds **17**	R	DMF-DMA (equiv.)	Reaction time (h)	Compound **21**	Isolated yield (%)
1	**17a**	H	10	16	**21a**	52
2	**17b**	Cl	5	4	**21b**	77
3	**17i**	F	10	19	**21i**	-*
4	**17j**	OMe	10	19	**21j**	23
5	**17k**	Me	10	20	**21k**	39

*Complex mixture was retrieved

Attempts to convert 3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **21a,b** to the corresponding naphthonaphthyridines (sampangine analogues) **22a**,**b** using a boiling solution of 33% (w/v) NH_4Cl in AcOH or stirring in a solution of 25% (w/v) NH_4Cl in AcOH/DMF (5/1) at 125°C[15a,117] gave complex reaction mixtures. However, boiling 3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **21a** in 5% (w/v) solution of NH_4OAc in methanol for 4 hours afforded 5-phenyl-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one **18a** in 89% yield (Table 8, entry 5).

Table 8: Synthesis of 7*H*-naphtho[3,2,1-*de*]naphthyridine-7-ones **22**



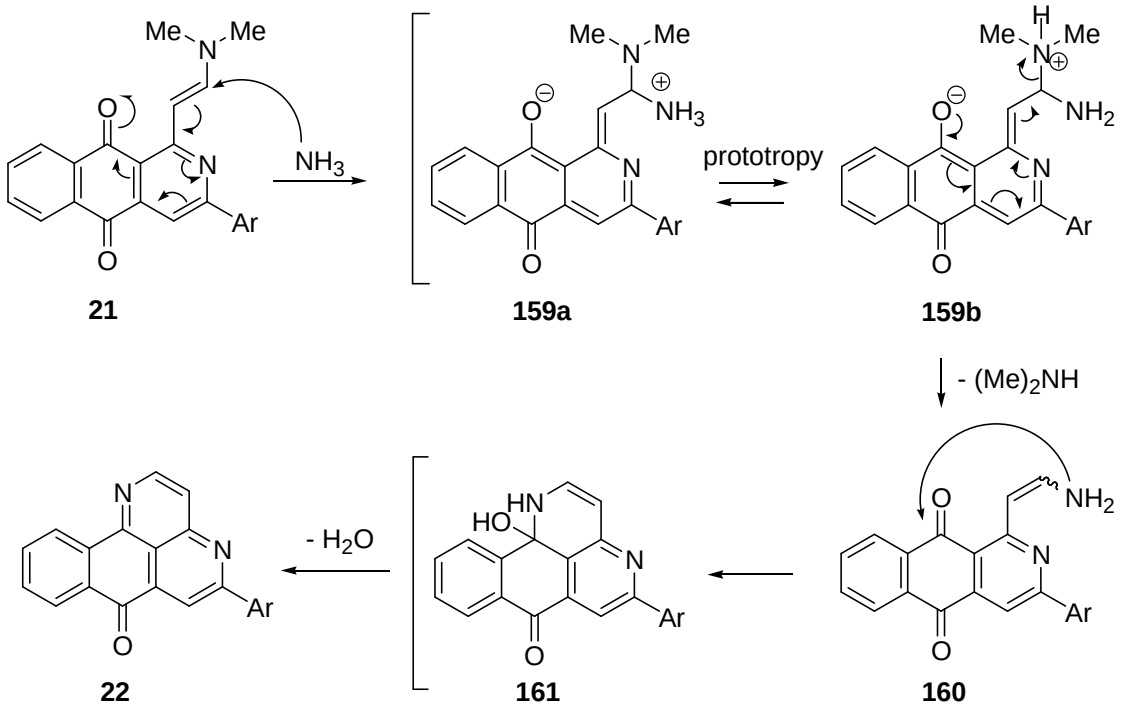
21 **22**

Entry	Compound **21**	R	Reaction conditions	Result	Compound **22** (%)
1	**21a**	H	33% (w/v) NH_4Cl, Δ, AcOH, 1 h[b]	Complex mixture	-
2	**21b**	Cl		Complex mixture	-
3	**21a**	H	25% (w/v) NH_4Cl, AcOH/DMF (5/1), 125°C, 1 h[a]	Complex mixture	-
4	**21b**	Cl		Complex mixture	-
5	**21a**	**H**	**5% (w/v) NH_4OAc, Δ, MeOH, 4 h**	**Naphthyridin-7-one 22**	**89**

[a]***Ref 117*** and [b]***Ref 15a***

From the mechanistic viewpoint, the reaction mechanism for the synthesis of 3-aryl-2-aza-1-methyl anthraquinones **17** is analogous to the mechanism for the synthesis of 3-aryl-2-aza-1-hydroxyanthraquinones **16** (page 49), except for the last step, in which a dehydration reaction instead of a tautomerization affords the target compounds **17**. The reaction mechanism for the synthesis of 3-aryl-2-aza-1-[2-(dimethylamino)vinyl]anthraquinones **21** is completely analogous to the mechanism for the synthesis of 1-[2-(dimethylamino)vinyl]cleistopholine **11a** (page 36). The mechanism for the formation of 5-(phenyl)-7*H*-naphtho[3,2,1-*de*]naphthyridin-7-ones **22** implies a transamination reaction through the Michael acceptor present in the 3-aryl-2-aza-1-[2-(dimethylamino)vinyl]anthraquinones **21**. The conjugate addition of ammonia generated *in situ* accros this Michael acceptor system causes the formation of the intermediate **159a**, which forms the intermediate **159b** after prototropy. Next, elimination of dimethylamine affords enamine **160**, which can undergo ring closure to form intermediates

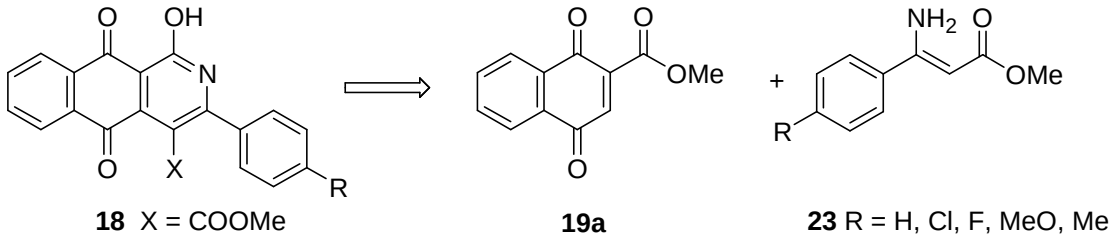
161. Subsequent dehydration affords the targeted sampangine analogues, i.e. 5-phenyl-7*H*-naphtho[3,2,1-*de*]naphthyridin-7-one **22**.



Scheme 3-28. Reaction mechanism for the formation of (7*H*)-naphtho[3,2,1-*de*]naphthyridin-7-one **22**

3.2.3. Efforts towards the synthesis of methyl 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-dione-4-carboxylates 18

Retrosynthetic analysis of 4-methoxycarbonyl-2-azaanthraquinones **18** gives enaminoesters **23** and 2-methoxycarbonyl-1,4-naphthoquinone **19a** as potential starting material. This synthesis calls upon the utilization of the Nenitzescu reaction which is one of the key straigthforward strategies for the preparation of a 5-hydroxyindole library.



Scheme 3-29. Retrosynthetic analysis of 1-hydroxy-2-azaanthraquinones **18**

However, the condensation reaction of an equimolecular quantity of 2-methoxycarbonyl-1,4-benzoquinone **162** and ethyl 3-aminocrotonate **23a** in boiling methanol gave the Michael adduct **163** in 59% yield after 2 hours (Figure 3-30).[118] It appeared that subsequent treatment of the adduct **163** in the presence of an appropriate oxidizing agent would complete the Nenitzescu synthesis with the formation

of ethyl 5-hydroxy-4-methoxycarbonyl-2-methylindole-3-carboxylate **164** while the absence of an oxidizing agent would favour the formation of 4-ethoxy-5,8-dihydroxy-3-methylisoquinolin-1(2*H*)-one **165**. Indeed further treatement of the adduct **163** in boiling acetic acid in the presence 0.18 equivalent of 2-methoxycarbonyl-1,4-benzoquinone **162** as the oxidizing agent for 15 hours, gave the indole **164** (30% yield) and the isoquinolone **165** (23% yield) while isoquinolone **165** (25% yield) was retrieved as the only product in the absence of the oxidizing agent, proving that the formation of the isoquinolone **165** occurs when the adduct **163** is still in the hydroquinone form.

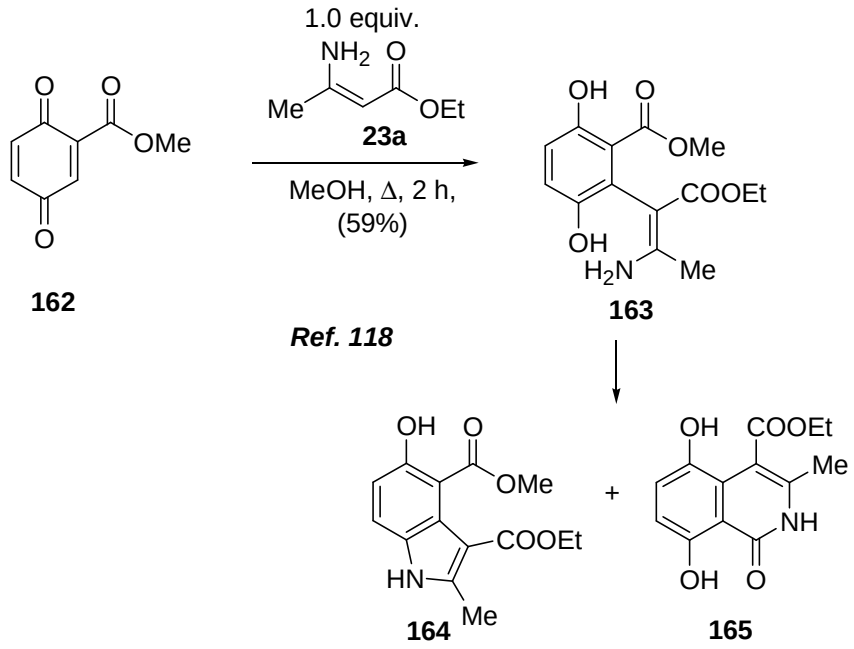
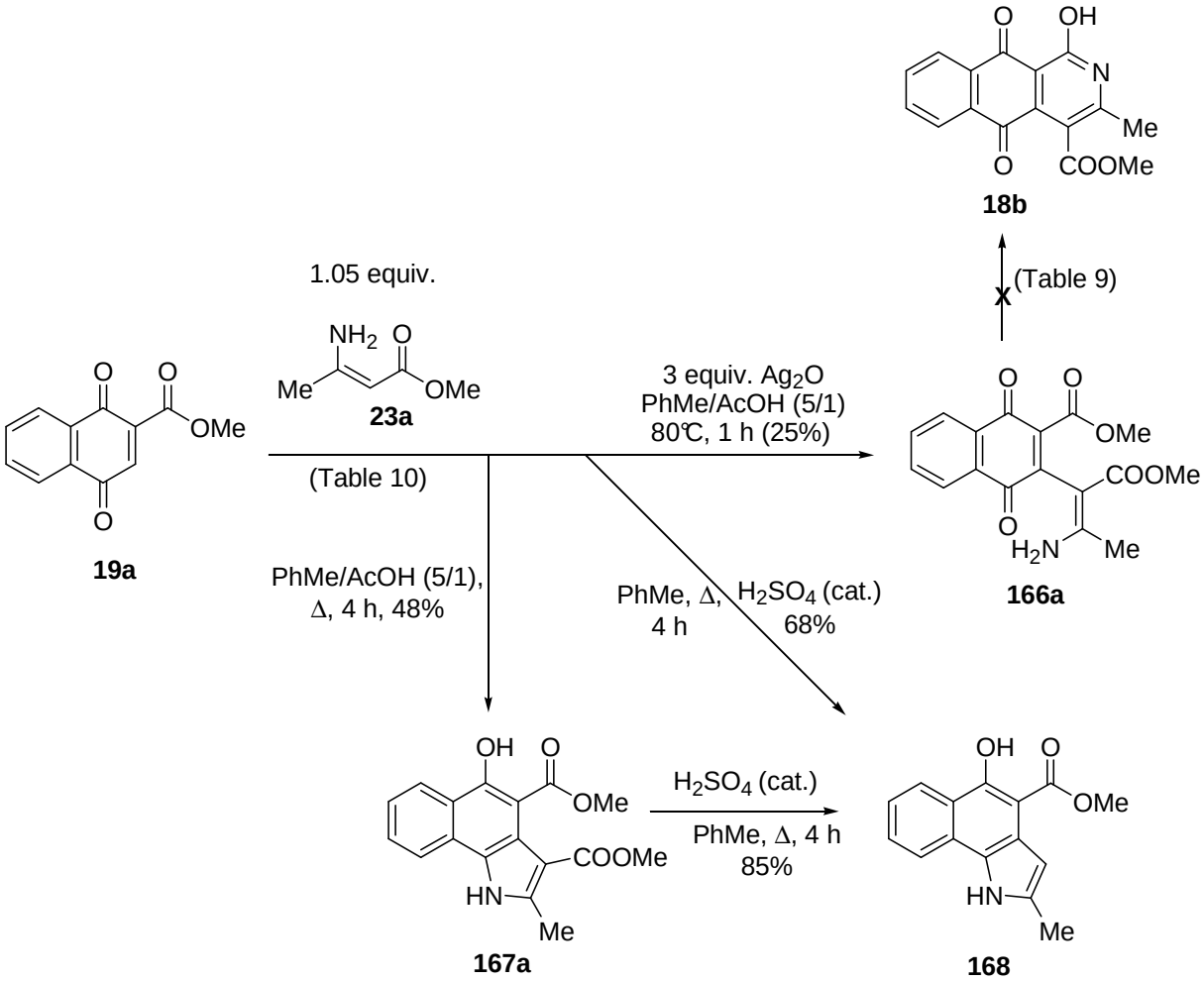


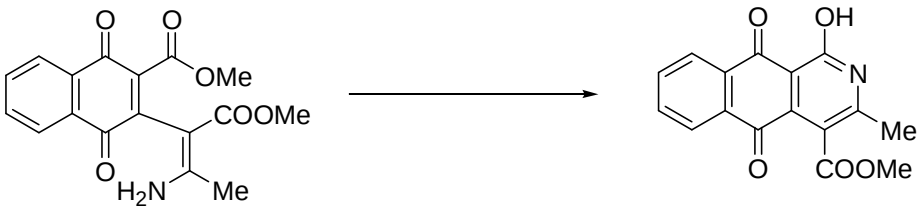
Figure 3-30. Reaction of 2-methoxy-1,4-benzoquinone **162** and enaminoester **23a**

Based on these results, the reaction of 2-methoxycarbonyl-1,4-napthoquinone **19a** with methyl 3-aminocrotonate **23a** was screened to set up optimized reaction conditions for the synthesis of methyl 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-dione-4-carboxylates **18**. Different reactions conditions were tested and produced three different compounds (Scheme 3-31). The reaction of 2-methoxycarbonyl-1,4-napthoquinone **19a** with methyl 3-aminocrotonate **23a** in a boiling mixture of toluene and acetic acid (5/1) gave the 5-hydroxyindole **167a** and the indole **168** in the presence a catalytic amount of sulfuric acid. The product **168** could also be obtained by treatment of compound **167** with a catalytic amount of sulfuric acid. When the reaction is conducted at 80°C, only adduct **166a** could be isolated in a 25% yield. Attemps to cyclize this Michael adduct **166a** to the corresponding 1-hydroxy-3-methylbenzo[*g*]isoquinoline-5,10-dione-4-carboxylate **18b** using heat or $ZnCl_2$ (Table 9) failed.



Scheme 3-31. Reaction of 2-methoxycarbonyl-1,4-naphthoquinone **19a** and enaminoester **23a**

Table 9: Applied attempts to synthesize 2-aza-1-hydroxy-3-methyl-4-methoxycarbonylanthraquinone **18b**



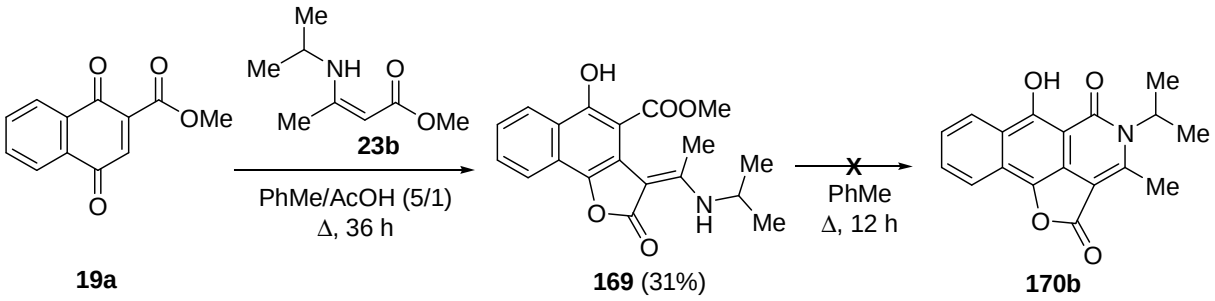
166a **18b**

Entry	Reaction conditions	Results
1	PhMe, Δ, 24 h	Starting material
2	PhMe/AcOH (5/1), Δ, 2 h	Starting material
3	2 equiv. K_2CO_3, PhMe, 80°C, 6 h	Complex mixture
4	1.0 equiv. $ZnCl_2$, Et_2O, rt, 24 h	Starting material
5	1.0 equiv. $ZnCl_2$, Et_2O, Δ, 2 h	Complex mixture

Table 10: Optimization of the reaction of 3-methoxycarbonyl-1,4-napthoquinone **19a** with methyl 3-aminocrotonate **23a** to afford compounds **166a**, **167a** and **168**.

Entry	Reaction conditions	Result	Isolated product (%)
1	Et_2O, Δ, 4 h	No reaction	-
2	4.0 equiv. K_2CO_3, Et_2O	No reaction	-
3	4.0 equiv. K_2CO_3, EtOH, 50°C	Reaction	**166a** (8%)
4	PhMe, Δ, 4 h	Complex mixture	-
5	PhMe/AcOH (5/1), Δ, 4 h	Reaction	**167a** (48%)
6	PhMe/AcOH (5/1), Δ, 24 h	Reaction	**167a** (39%)
7	PhMe, H_2SO_4(2 drops), Δ, 4 h	Reaction	**168** (68%)
8	3.0 equiv. Ag_2O, CH_2Cl_2, Δ, 3 h	No reaction	-
9	3.0 equiv. Ag_2O, PhMe, Δ, 3.5 h	Reaction	**166a** (12%)
10	PhMe/AcOH (5/1), 80°C, 4 h	Reaction	**166a** (25%)
11	3.0 equiv. MnO_2, PhMe, Δ, 1 h	Complex mixture	-
12	3.0 equiv. MnO_2, PhMe/AcOH (5/1), Δ, 1 h	Complex mixture	-

In order to arrange a more suitable action of the amino group of enaminoesters **23**, methyl *N*-isopropyl-3-aminocrotonate **23b** was reacted with the activated quinone **19a** in a boiling mixture of toluene and acetic acid (5/1). After 36 hours, only the enaminolactone **169** was retrieved. Therefore, it was considered that *N*-substituted 3-alkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-1-ones **170** obtained upon prolonged heating of enaminolactone **169** could be key intermediates towards the synthesis of benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **171** (Figure 3-3). Yet, this type of azaanthraquinones is unknown in the literature. Unfortunely, the prolongation of heating to 12 hours of compound **169** did not give the desired product **170b** (Scheme 3-32).



Scheme 3-32. Reaction of 2-methoxycarbonyl-1,4-naphthoquinone **19a** and enaminoester **23b**

Figure 3-3. Benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **171** and **172**

However, *N*-substituted 3-alkylbenzo[*g*]isoquinoline-1,5,10(*2H*)-triones **172**, a partial structural pattern found in Kibdelone A **173** (Figure 3-4), has been synthesized to a very limited extend.[119a] Kibdelone A **173** belongs to a novel family of bioactive heterocyclic polyketides produced by a rare soil actinomycete *Kibdelosporangium* sp. (MST-108465) and exhibits potent selective cytotoxicity against a panel of human tumor cell lines as well as significant antibiotic and nematocidal activity.[119]

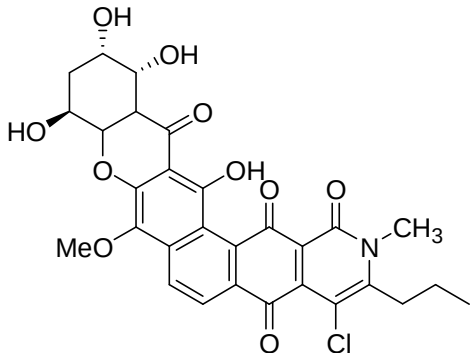
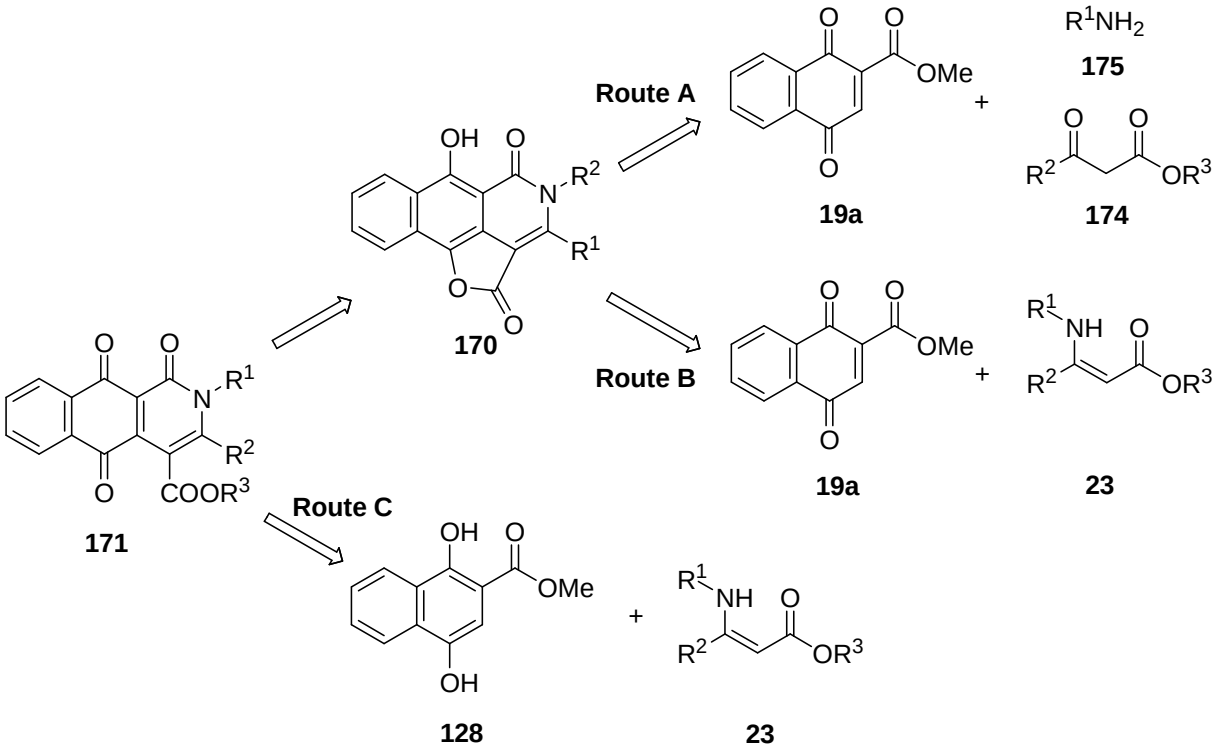


Figure 3-4. Structure of kibdelone A **173**

In this manuscript, the first synthesis of substituted benzo[*g*]isoquinoline-1,5,10(*2H*)-triones **171** is reported. Retrosynthetic analysis suggested that three possible routes could lead to the synthesis of the targeted alkyl 2,3-dialkylbenzo[*g*]isoquinoline-1,5,10(*2H*)-trione-4-carboxylates **171** (Scheme 3-33). Two routes rely on the synthesis of 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **170** as key intermediates, which may most likely be prepared by treating 2-methoxycarbonyl-1,4-naphthoquinone **19a** with either β-ketoesters **174** and primary amines **175** (Route A) or ready-made *N*-

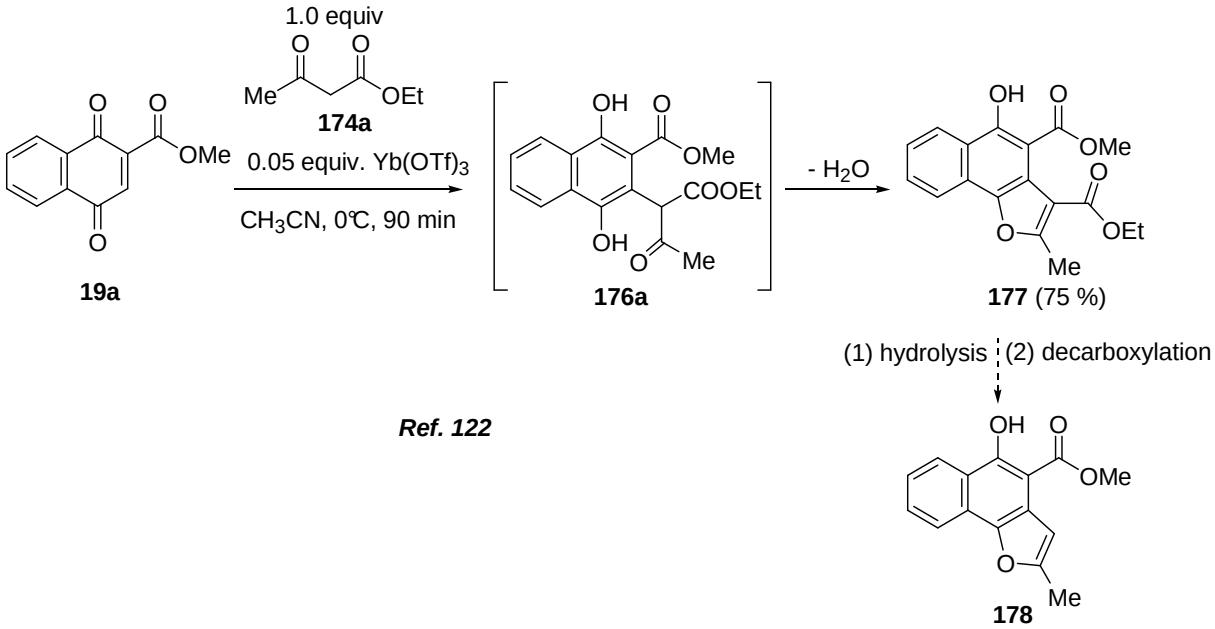
alkyl enaminoesters **23** (Route B). A third route, which will be investigated, concerns the oxidative addition reaction of *N*-alkyl enaminoesters **23** with methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** (Route C) as entries towards the synthesis of alkyl 2,3-dialkylbenzo[*g*]isoquinoline-1,5,10(2*H*)-trione-4-carboxylates **171**.



Scheme 3-33. Retrosynthetic analysis of benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **171**

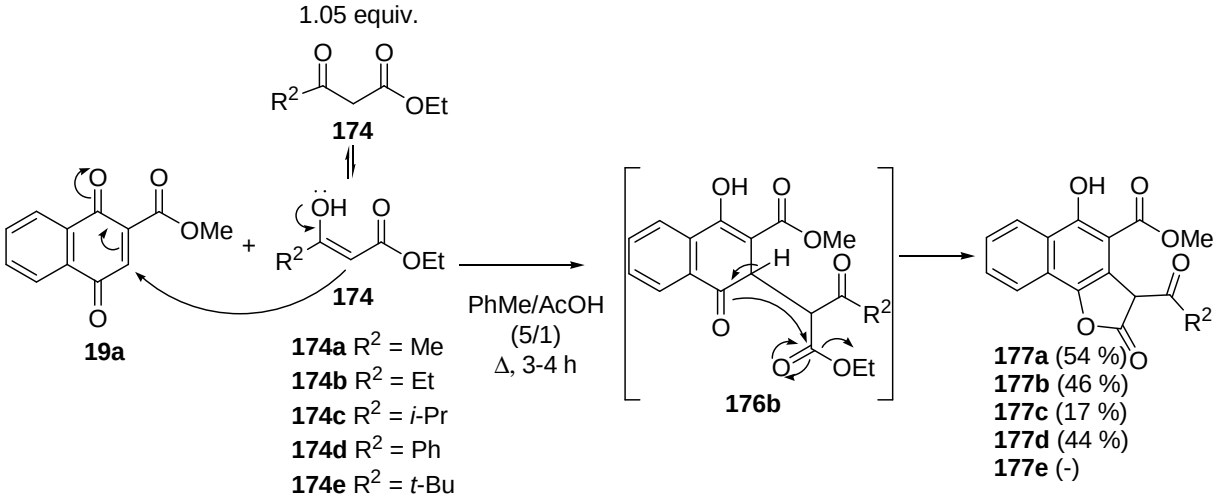
3.2.3.1. Route A

The addition of β-ketoesters to quinones under basic[120] and radical[121] conditions has been well described, but few reports are disclosed on this addition reaction under acidic conditions[122] despite the fact that experiments[121-122] and *ab initio* calculations[123] showed that quinones behave better as electrophiles under acidic conditions. Therefore, the addition of β-ketoesters **174** to 2-methoxycarbonyl-1,4-naphthoquinone **19a** was conducted under acidic conditions in order to avoid the formation of the kinetic product of the reaction, i.e ethyl 5-hydroxy-3-methoxycarbonyl-2-methylnaphtho[1,2-*b*]furan-4-carboxylate **177** and its subsequent decarboxylated derivative **178**, which would divert the course of the synthesis (Scheme 3-36).[122] The naphtho[1,2-*b*]furan **177** arises from the intramolecular nucleophilic attack of the intermediate phenol of the adduct **176a** across the ketone function of the acetonyl moiety.



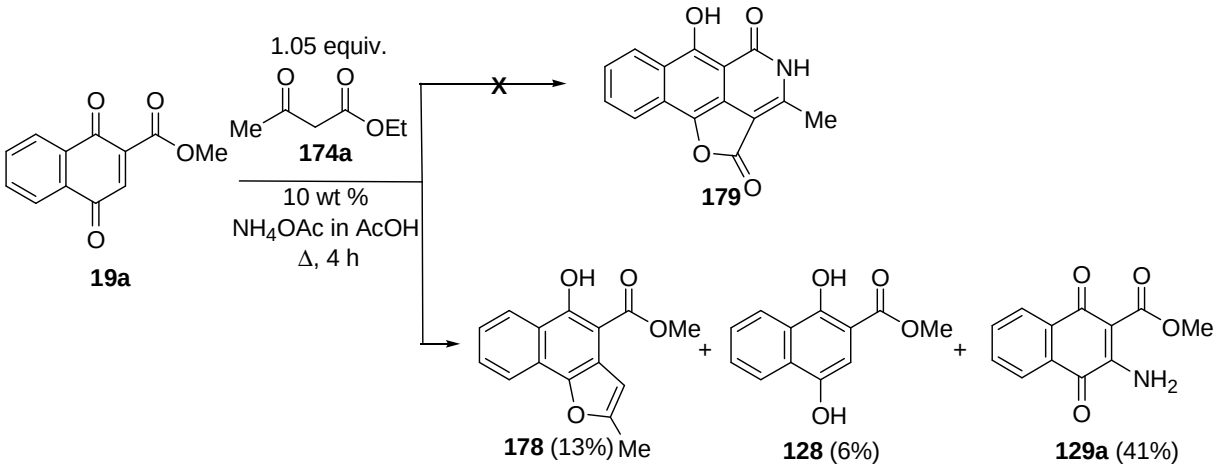
Scheme 3-34. Reaction of 2-methoxycarbonyl-1,4-naphthoquinone **19a** with ethyl acetoacetate **174a**

Therefore, test reactions were conducted under different reaction conditions treating the activated naphthoquinone **19a** with ethyl acetoacetate **174a**. The desired naphtho[1,2-*b*]furan-2(3*H*)-one **177** was obtained in 54% yield when using a mixture of toluene and acetic acid (5/1) under reflux for 4 hours. Extending the optimized reaction conditions for the synthesis of other derivatives **177b-d** from 2-methoxycarbonyl-1,4-naphthoquinone **19a** and higher β-ketoesters **174** was successful in low (17%) to moderate yield (54%) except for compound **177e** due to the steric hindrance of the bulky *t*-butyl group, which afforded a very complex mixture without a trace of the targeted compound **176e** as checked by NMR and LC-MS analysis.



Scheme 3-35. Synthesis of naphtho[1,2-*b*]furan-2(3*H*)-ones **177**

In a following part, a one-pot synthesis of benzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **179** was investigated by reaction of the activated naphthoquinone **19a** with ethyl acetoacetate **174a** and ammonium acetate in boiling acetic acid (Scheme 3-36). However, no trace of compound **179** was observed while the naphtho[1,2-*b*]furan **178** was isolated *albeit* in low yield (13%) in conjunction with methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129** in 6% and 41% yields, respectively after column chromatographic purification.

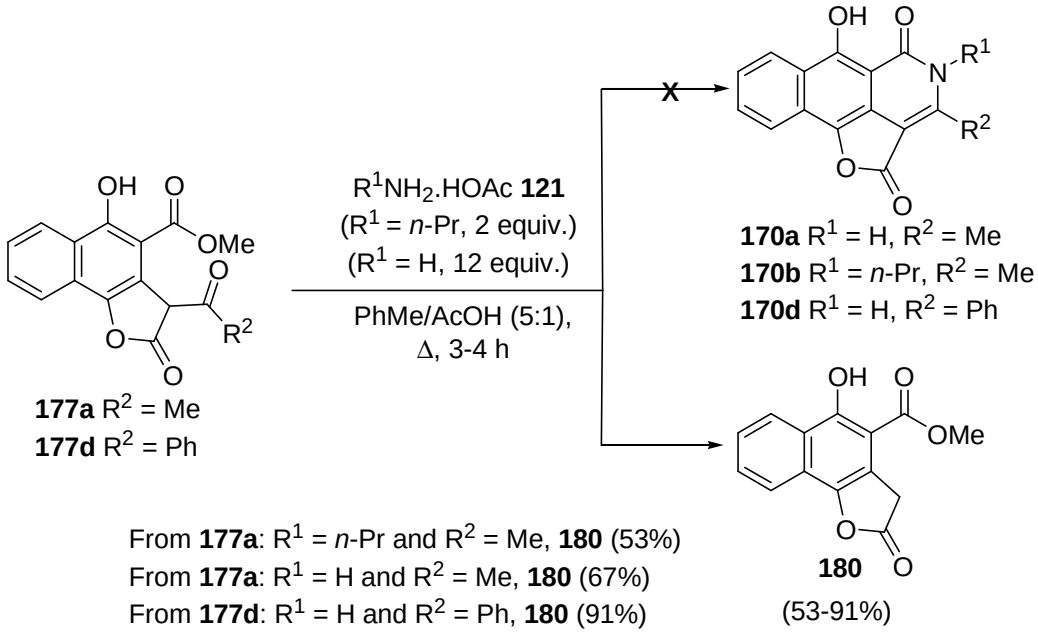


Scheme 3-36. Reaction of 2-methoxycarbonyl-1,2-naphthoquinone **19a** and ethyl acetoacetate **174a** with NH_4OAc in acetic acid

The formation of the tricyclic compound **178** arose from a condensation reaction outlined previously. The formation of methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** was also observed recently by the reaction of the activated naphthoquinone **19a** with an excess of ammonium acetate in boiling acetic acid.[122] Therefore, the outcome of the competitive addition of ammonia and the enolate of ethyl acetoacetate **174a** to 2-methoxycarbonyl-1,4-naphthoquinone **19a** led favorably towards the facile ammonia addition compared to that of ethyl acetoacetate **174a**. Under these conditions, the ammonia adduct **129a** is formed preferentially in comparison with compound **178**. This fact was supported by the respective isolated yields of each addition product, and as a consequence, treatment of the activated naphthoquinone **19a** with β-ketoesters **174** and ammonium acetate in boiling acetic acid did not appear to be the right condition for an efficient one-pot three-components synthesis of 3,4-dialkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **170**. Thus, an alternative synthesis was to be envisaged in order to prepare the target intermediates **170** from methyl 3-acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates **178** and primary amines **175**. Unfortunately, treatment of methyl 3-acetyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **177a** with two equivalents of *n*-propylammonium acetate **121b**,

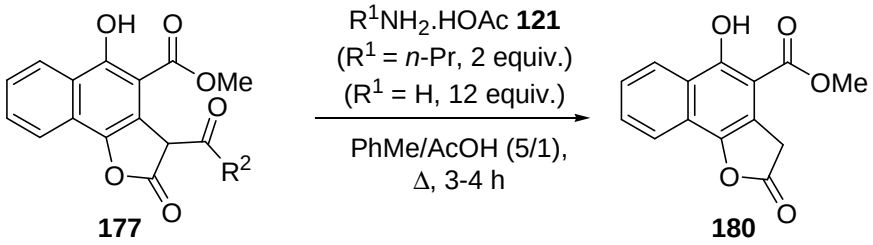
which was generated *in situ* by the reaction of the corresponding equivalents of *n*-propylamine **175b** and acetic acid at 0°C for 30 minutes, in boiling in toluene-acetic acid (5/1) resulted in the formation of methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **180** in 53% yield instead of the targeted 6-hydroxy-3-methyl-4-*n*-propylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **170b**. Facing this drawback, different attempts were made to insert the nitrogen atom using excess of ammonium acetate in different solvents in order to reduce the eventual steric effect that might be exhibited by an alkyl group.

However, all the attempts failed to afford **170a** and provided the same unexpected methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **180** in 46-67% yield (Table 11, entries 2-4), a novel compound so far undescribed in the literature. An attempt to increase the substrate electrophilicity of the carbonyl group by substitution of the methyl group in methyl 3-acetyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **177a** with a phenyl group in methyl 3-benzoyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **177d** improved the yield of the same product **180** to 91 % (Table 11, entry 5), probably by limiting side reactions.



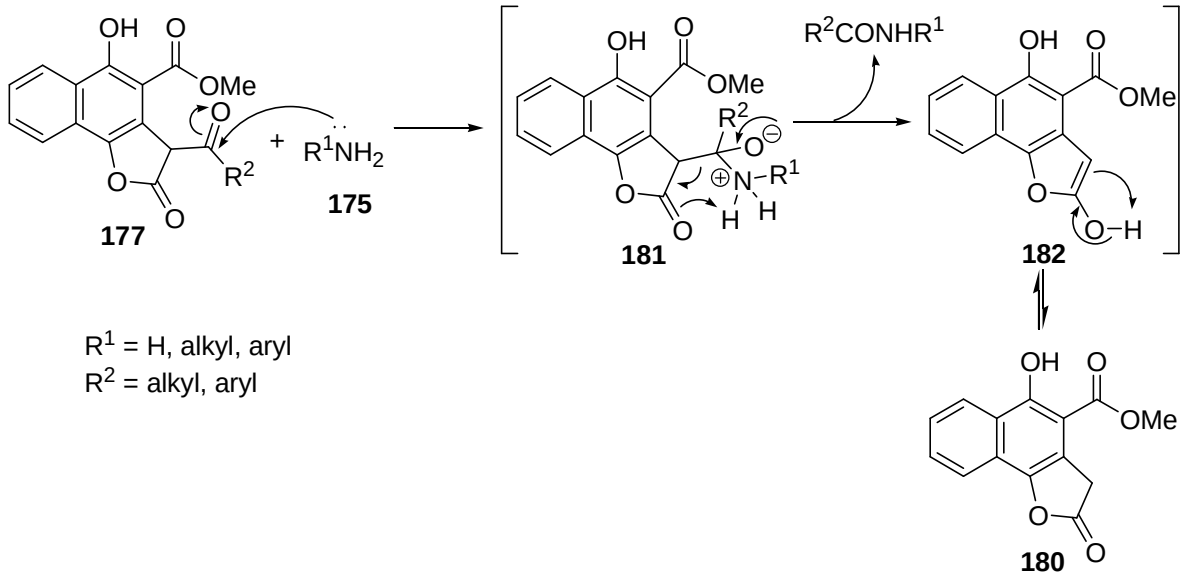
Scheme 3-37. Synthesis of methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **180**

Table 11: Reaction conditions for the conversion of methyl 3-acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates **177a,d** to methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **180**



Entry	Substrate	Equiv. of R^1NH_2.HOAc	Solvent and reaction conditions	Isolated yield of **180** (%)
1	**177a**	2 (R^1 = *n*-Pr)	PhMe/AcOH (5/1), Δ, 3 h	53
2	**177a**	12 (R^1 = H)	PhMe, Δ, 4 h	46
3	**177a**	12 (R^1 = H)	AcOH, Δ, 4 h	54
4	**177a**	12 (R^1 = H)	Toluene/AcOH (5/1), Δ, 4 h	67
5	**177d**	12 (R^1 = Ph)	Toluene/AcOH (5/1), Δ, 4 h	91

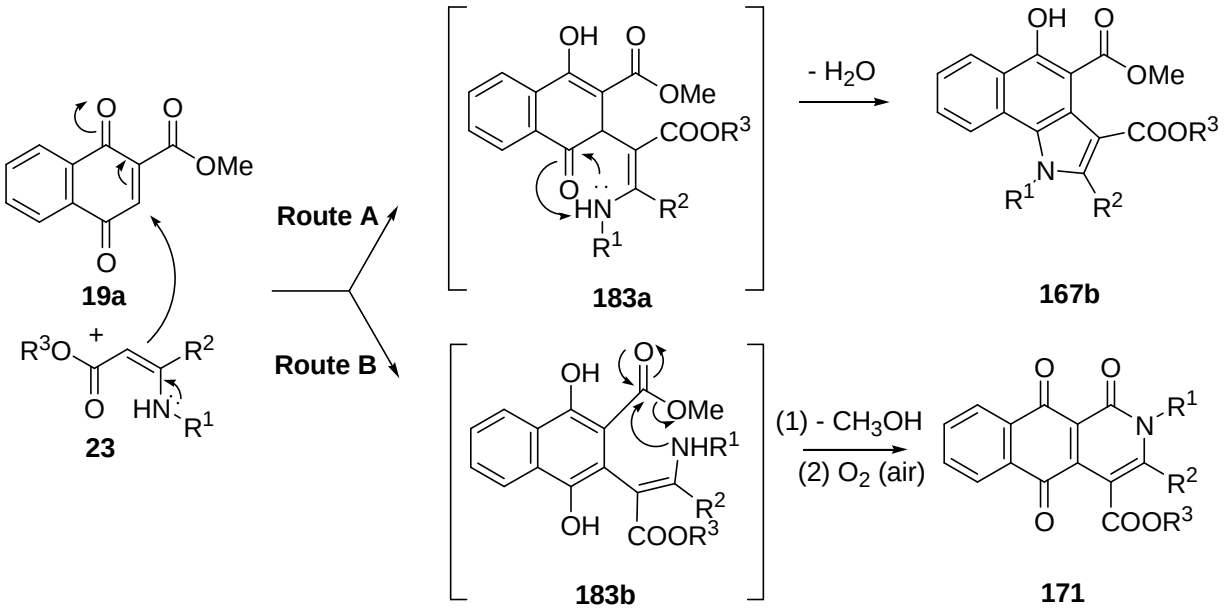
The formation of methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **180** can be explained by a nucleofuge group expulsion of the intermediate **181**, which is formed after the addition of the amine across the acyl or benzoyl group of naphthofuran derivatives **177**, and subsequent keto-enol tautomerism (Scheme 3-38). The difficult access to the key intermediates **170** by reaction of naphthofurans **177** with amines **175** put a serious impediment to this first route A towards the targeted benzo[*g*]isoquinoline-1,5,10(*2H*)-triones **171** and prompted us to work out the second route B, which calls upon *N*-substituted enaminoesters **23**.



Scheme 3-38. Reaction mechanism of formation of compound **180**

3.2.3.2. Route B

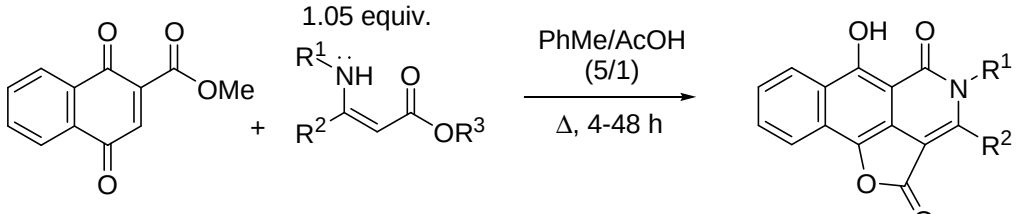
The reaction of enaminoesters with simple quinones is known in the literature as the Nenitzescu reaction.[124] In case of 2-methoxycarbonyl-1,4-naphthoquinone **19a** as the substrate, enaminoesters **23**[125] add to this activated quinone to form tautomeric intermediates **183a** and **183b**, which can cyclize in two modes. The first mode implies a nucleophilic attack of the amino group of **183a** across the ketone moiety leading to an annelated indole **167b**, while the second mode implies a nucleophilic attack of the amino group of **183b** across the ester carbonyl leading to benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **171** (Scheme 3-39).



Scheme 3-39. Reaction of 2-methoxycarbonyl-2,4-naphthoquinone **19a** with enaminoesters **23**

The reaction of the activated naphthoquinone **19a** with *N*-*n*-propyl- and *N*-ethylamino-2-butenoates **23c** and **23d** in boiling toluene:acetic acid (5:1), as previously established in the case of β-ketoesters, furnished the hydroquinone adducts **184**, which hardly cyclized to 6-hydroxy-4-n-propyl-3-methylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **170c** and 4-ethyl-6-hydroxy-3-methyl-benzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **170d** (Table 12, entries 1 and 2). Nevertheless, the use of *N*-ethylamino-2-pentenoate **23e** resulted in a spontaneous cyclization to the targeted benzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **170e** upon boiling in toluene/acetic acid (5/1) for 4 hours (Table 12, entry 3). Other substituent combinations utilizing enaminoesters **23f**-**g** gave intractable mixtures of compounds, from which the targeted compounds could not be isolated by column chromatography and/or recrystallization. This can be ascribed to a difficult cyclization of intermediate naphtho[1,2-*b*]furans **185**, even upon prolongation of the reaction time to 48 hours, which results in a partial degradation of the compounds (Table 12).

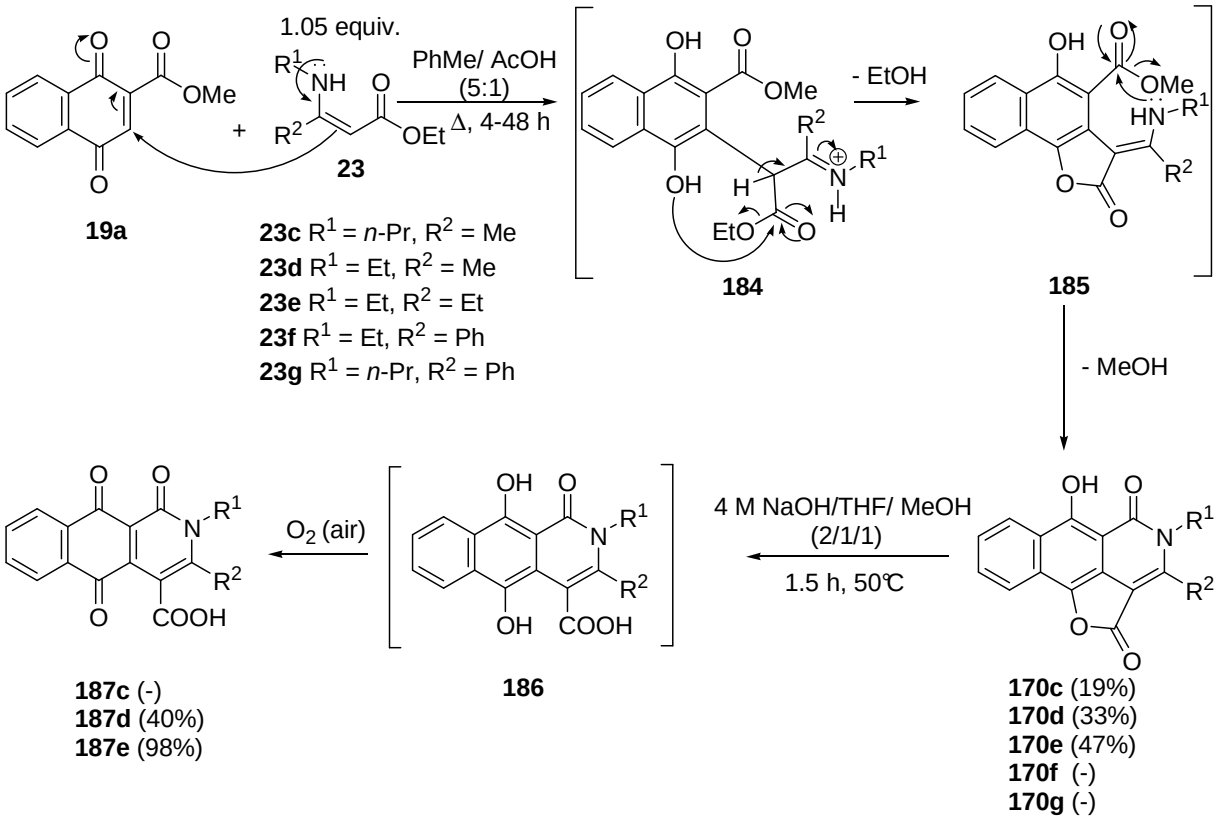
Table 12: Reaction of different *N*-substituted enaminoesters **23** with 2-methoxycarbonyl-1,4-naphthoquinone **19a** in boiling toluene: acetic acid (5/1) to afford 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **170**.



19a **23** **170**

Entry	Enaminoester	R^1	R^2	Reaction time (h)	Isolated product	Yield (%)
1	**23c**	*n*-Pr	Me	36	**169c**	19
2	**23d**	Et	Me	36	**169d**	33
3	**23e**	Et	Et	4	**169e**	47
4	**23f**	Et	Ph	48	-	-
5	**23g**	*n*-Pr	Ph	48	-	-

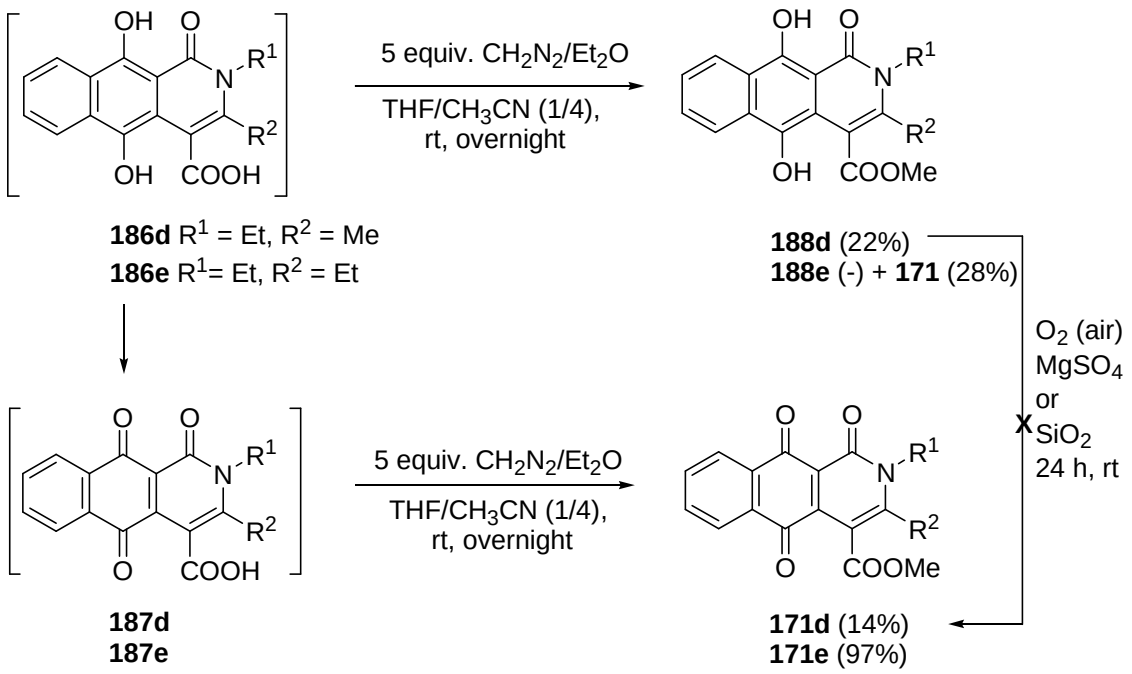
Finally, 4-ethyl-6-hydroxy-3-methylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-one **170d** and 3,4-diethyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **170e** were hydrolyzed to 2-ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **187d** and 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **187e** in 40 and 98% of crude yield, respectively, at 50°C using 4 M NaOH/THF/MeOH (2/1/1) for 1.5 hours and subsequent spontaneous air oxygen oxidation (Scheme 3-40). However, hydrolysis of 6-hydroxy-3-methyl-4-*n*-propylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-dione **170c** under the same conditions gave a complex mixture of reaction products. All attempts to purify compounds **187d** and **187e** by chromatography and recrystallization techniques failed.



Scheme 3-40. Syntesis of 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **187**

Therefore, the crude extracts of the hydrolysis reactions containing 2-ethyl-3-methyl-1,2,5,10-tetrahydro--1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **187d** and 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **187e**, respectively, have been converted to the corresponding methyl esters by treatment with a solution of diazomethane in anhydrous diethyl ether at room temperature. In the first case, methyl 2-ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **171d** was isolated together with methyl 2-ethyl-1,2-dihydro-5,10-dihydroxy-3-methyl-1-oxobenzo[*g*]isoquinoline-4-carboxylate **188d** in 14% and 22% yield, respectively. Different attempts to purify compound **188d** by preparative TLC and recrystallization failed.

In order to get full conversion of the intermediate hydroquinone **188d** to benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **171d**, the workup extract of the diazomethane reaction was stirred with magnesium(II) sulfate or silica gel for 24 hours in the presence of air oxygen. Unfortunately, this operation failed to fully convert the reaction substrate to the targeted benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **171d**. Secondly, methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **171e** was isolated as the sole product in an excellent yield of 97% directly after the treatment of compound **185e** with diazomethane in the presence of air. An attempt to obtain methyl 2,3-diethyl-1,2-dihydro-5,10-dihydroxy-1-oxobenzo[*g*]isoquinoline-4-carboxylate **188e** by running the reaction with diazomethane under nitrogen atmosphere and quickly performing the workup of the reaction gave methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **171e** in 28% yield and a complex fraction, which revealed the presence of very minute quantity of methyl 2,3-diethyl-1,2-dihydro-5,10-dihydroxy-1-oxobenzo[*g*]isoquinoline-4-carboxylate **188e** upon LC-MS analysis.



Scheme 3-41. Synthesis of methyl 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinolines **171**

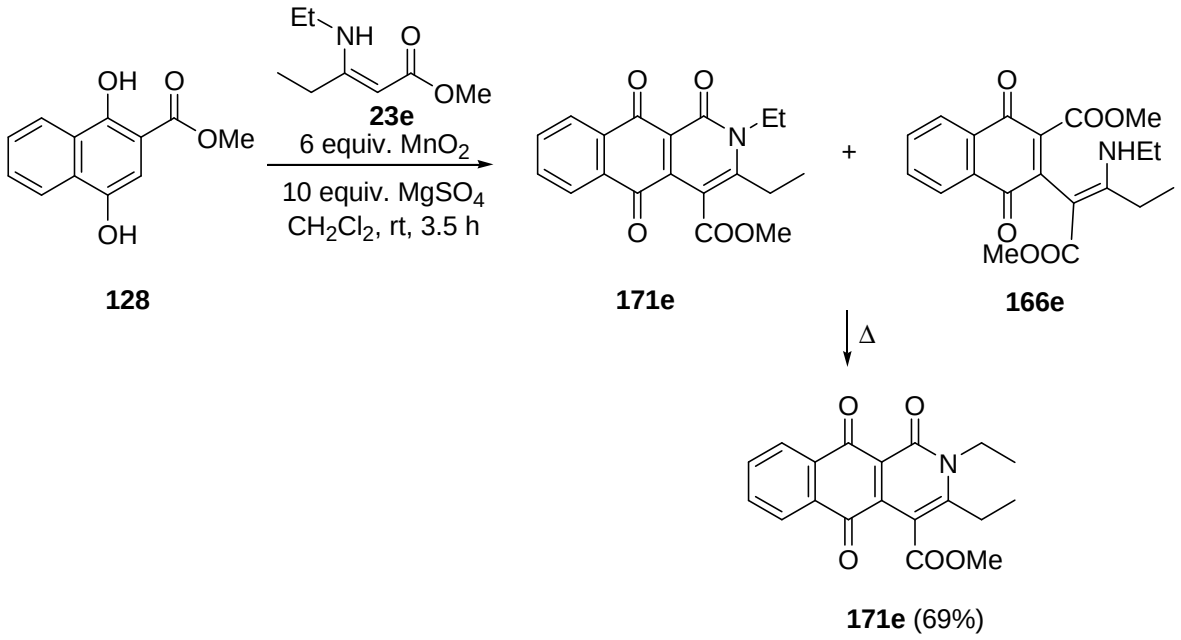
The remarkable differences observed in chemical behavior of compound **188d** compared to compound **188e** on the one hand and of benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **187d** compared to **187e** on the other hand, were clues for the development of a short alternative procedure such as the direct reaction of methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** with enaminoesters **23** under oxidative conditions.

3.2.3.3. Route C

First, the reaction of methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** with enaminoester **23e** was screened in order to optimize the oxidative addition reaction of these reaction substrates. An excess of oxidant was needed to assure the oxidation of hydroquinone **128** before and of the adduct after the addition of enaminoester **23e**. Therefore, methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** and enaminoester **23e** were reacted using manganese(IV) oxide as the oxidant of choice. At the end, methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **171e** was obtained in 69% yield over two steps using 6 equivalents of manganese(IV) dioxide and 10 equivalents of magnesium(II) sulfate in anhydrous dichloromethane for 3.5 hours at room temperature to afford a mixture of the targeted benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **171e** and its precursor **166e**, which was converted subsequently in the target compound **171e** by boiling in a mixture of toluene and acetic acid (5/1) (Table 13, entry 1). In the absence of acetic acid in the second step, the yield of the reaction was lowered (Table 14, entry 2).

The attempts to prepare methyl 2,3-diethyl-1,2,5,6-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate **171e** in a single step resulted in lower yields (Table 13, entries 3 and 4). It was noticed that the presence of acetic acid was detrimental to this direct one step procedure.

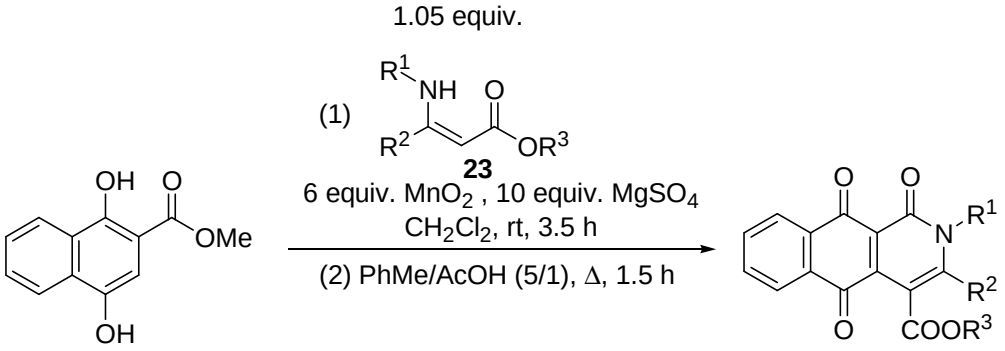
Table 13: Test reactions towards the synthesis of 2,3-diethylbenzo[*g*]isoquinoline-1,5,10(2*H*)-trione **171e**



Entry	Scale (mmol)	Reaction conditions	Yield **171e** (%)
1	1.15	(1) CH_2Cl_2, rt, 3.5 h, (2) Δ, PhMe/AcOH (5/1), 1 h	69
2	2.30	(1) CH_2Cl_2, rt, 3.5 h (2) Δ, PhMe, 1 h	59
3	2.30	Δ, PhMe for 1.5 h	44
4	2.30	Δ, PhMe/AcOH (5/1), 1.5 h	12

Referring to the overall yield of each route, the two-steps procedure (Route C) appeared to be the best entry towards benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **171** compared to the direct one-step oxidative addition (Table 13, entries 3 and 4) and the multistep procedures previously elaborated and described in this manuscript (3.2.3.1 and 3.2.3.2). Having in hand this two-steps procedure, other derivatives (**171c**,**e**-**j**) were prepared accordingly in 29-71% yields (Table 14).

Table 14: Synthesis of alkyl *2*,3-disubstituted 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylates **171** by a two steps procedure involving oxidative addition of enaminoesters **23** to methyl 1,4-dihydroxynaphthalene-2-carboxylate **128**



128 **171**

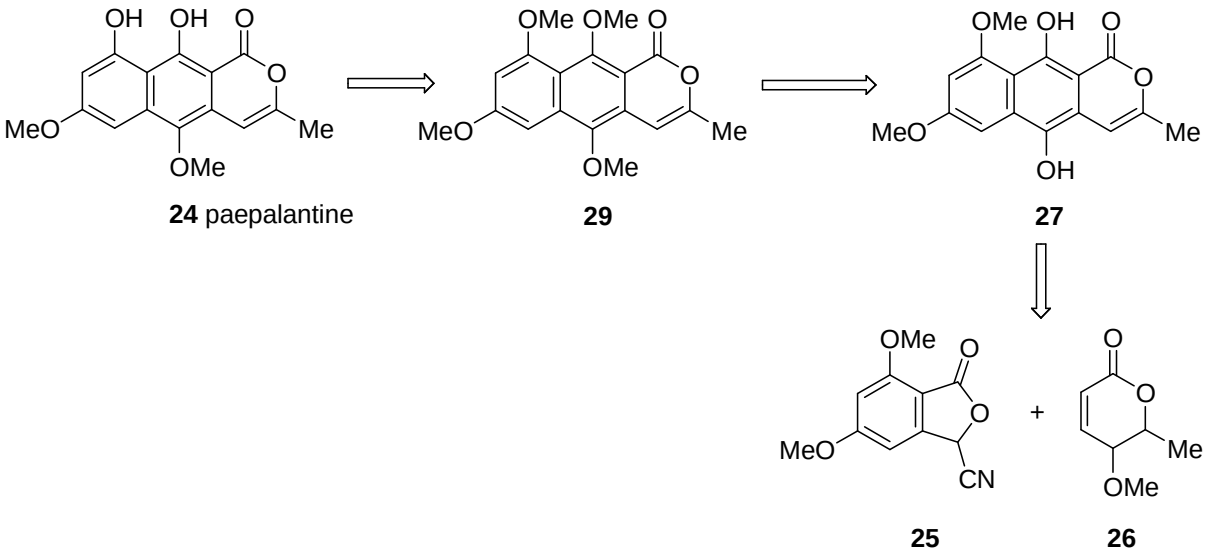
Entry	Enaminoester	R^1	R^2	R^3	Isolated product	Yield (%)
1	**23c**	*n*-Pr	Me	Me	**171c**	46
2	**23d**	Et	Me	Et	**171d**	-*
3	**23e**	Et	Et	Me	**171e**	69
4	**23g**	Et	Ph	Et	**171g**	32
5	**23h**	*n*-Pr	Ph	Et	**171h**	56
6	**23i**	*n*-Pr	Me	Et	**171i**	29
7	**14j**	*n*-Pr	Et	Me	**171j**	71

*Complex mixture

3.3. Efforts towards the first total synthesis of paepalantine 24

Paepalantine **24** is the first isocoumarin isolated from *Paepalanthus bromelioides* (Eriocaulaceae).[19] This natural isocoumarin has a broad spectrum of biological activities including the respiratory burst,[20] antimicrobial,[21] mutagenic and cytotoxic activities.[22] Despite of its biological activity, paepalantine **24** has not been synthesized to date. In continuation of our efforts towards the synthesis of natural products and their derivatives for biological screening, the first synthesis of paepalantine **24** was planned. The phthalide annulation reaction (Michael addition-Dieckmann type reaction) starting from 3-cyanophthalide

25 and pyran-2-one **26** was thought to construct the heterocyclic skeleton of 5,10-dihydroxy-7,9-dimethoxy-(1*H*)-benzo[*g*]isochromen-1-one **27**, the key intermediate towards paepalantine **24** (Scheme 3-42).

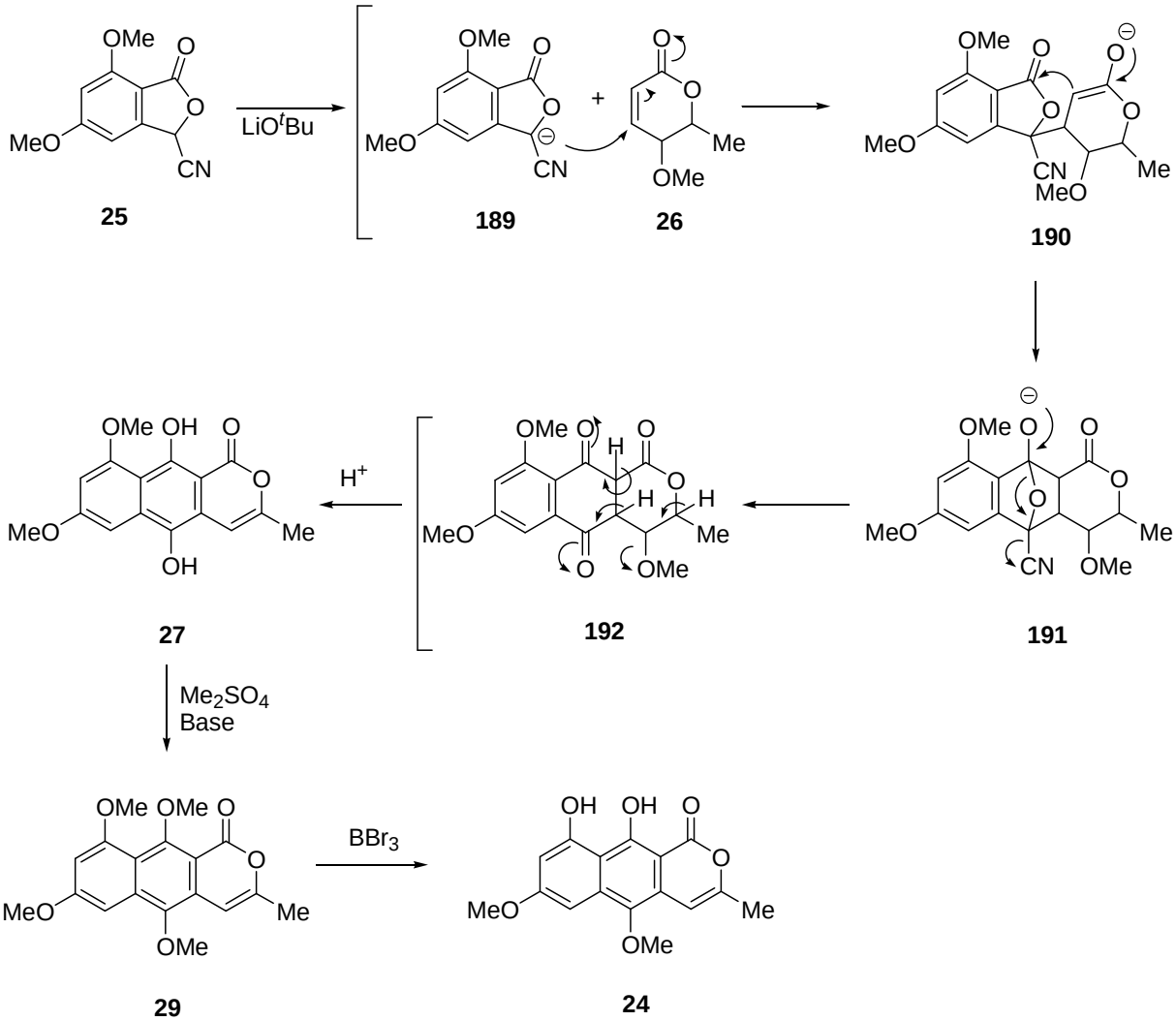


24 paepalantine **29** **27**

25 **26**

Scheme 3-42. Retrosynthetic analysis of paepalantine **24**

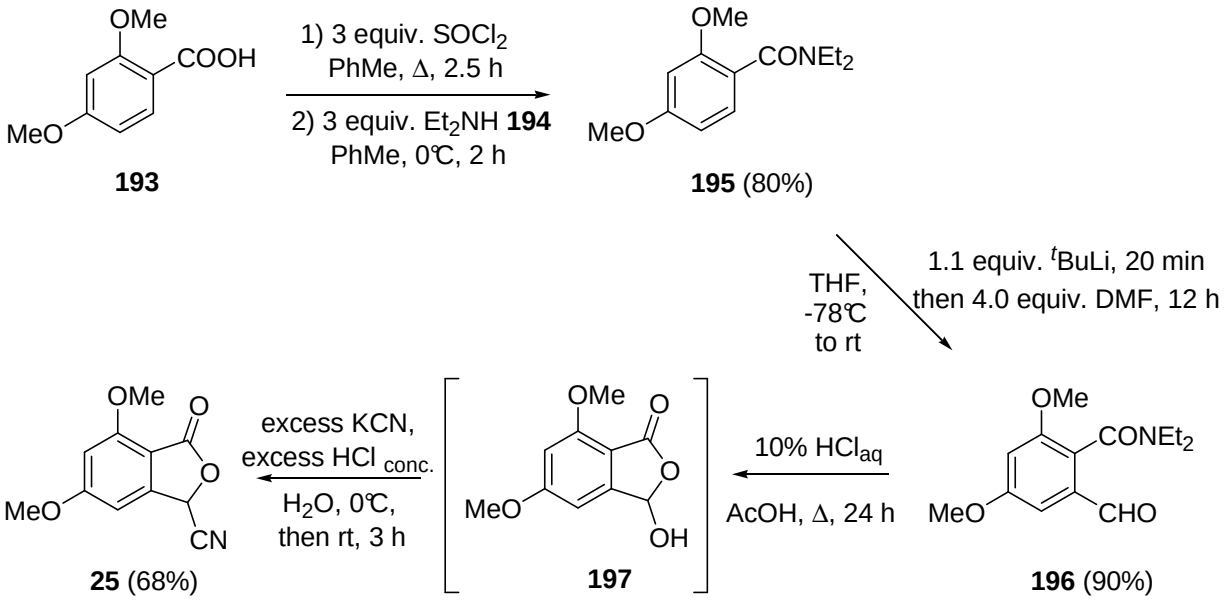
From the mechanistic point of view (Scheme 3-43), the convergent synthesis of paepalantine **24**, involves deprotonation of 3-cyanophthalide **25** with lithium *tert*-butoxide to generate the anion **189**, which will undergo Michael addition to the pyranone **25** to form the adduct **190**. The latter will undergo intramolecular Dieckmann cyclization onto the lactone carbonyl group of the 3-cyanophthalide moiety, after which cyanide is eliminated. Consecutive base promoted tautomerization of **191** will finally give the key intermediate hydroquinone **27**. Total methylation of the latter compound using dimethyl sulfate and selective demethylation using boron(III) bromide should give the paepalantine **24**.



25 189 26 190 191 192 27 29 24

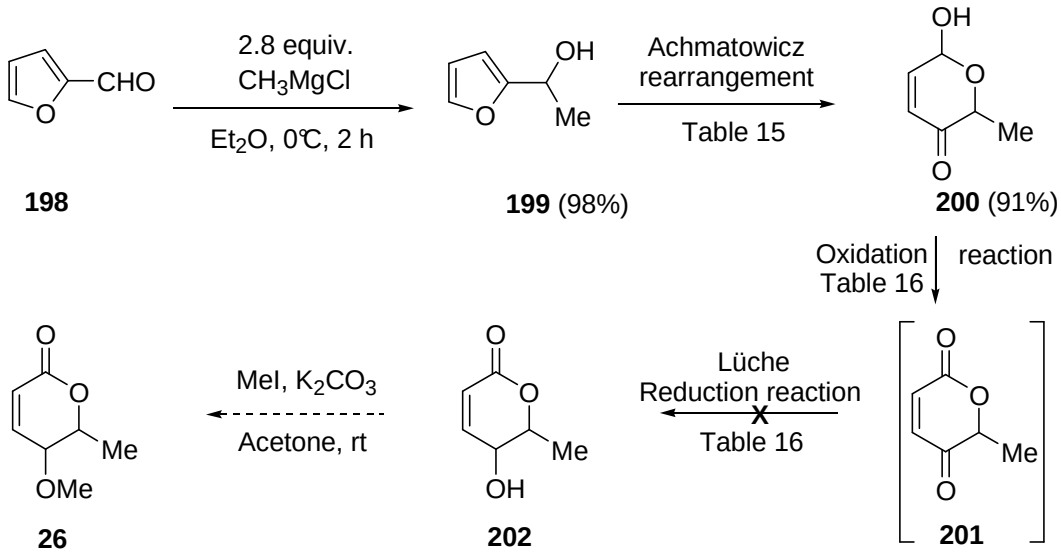
Scheme 3-43. Reaction mechanism for the formation of paepalantine **24**

Thus, the synthesis of paepalantine **24** implies coupling of the 3-cyanophthalide **25** and the pyran-2-one **26**. The synthesis of 3-cyanophthalide **25** (Scheme 3-44) started by conversion of the commercially available 2,4-dimethoxybenzoic acid **193** to the corresponding *N,N*-diethyl-2,4-dimethoxybenzamide **195** in 80% yield using 3 equivalents of thionyl chloride in boiling toluene for 2 hours and treating the resulting intermediate acid chloride with 3 equivalents of diethylamine **194** at 0°C for 2 hours.[126] Treating *N,N*-diethyl-2,4-dimethoxybenzamide **195** with 1.1 equivalents of *tert*-butyllithium for 20 minutes at – 78°C, after which the reaction was quenched with 4.0 equivalents of DMF in THF afforded *N,N*-diethyl-2-formyl-4,6-dimethylbenzamide **196** in 90% yield. Subsequent hydrolysis of *N,N*-diethyl 2-formyl-4,6-dimethylbenzamide **196** with acetic acid and 10% HCl under reflux for 24 hours caused intramolecular cyclization to give 3-hydroxy-5,7-dimethoxyphthalide **197**. Finally, the desired to 3-cyano-5,7-dimethoxyphthalide **25** was obtained in 78% yield by reaction with hydrogen cyanide, wich was generated *in situ* using potassium cyanide and concentrated hydrochloric acid.



Scheme 3-44. Synthesis of 3-cyanophthalide **25**[126]

The synthesis of the second substrate (Scheme 3-45) for the envisaged annulation reaction commenced with a Grignard reaction reaction of methylmagnesium chloride across furfural **198** (Scheme 3-45). In this way, 1-(2-furyl)ethanol **199** was obtained in 98% yield and subsequently an Achmatowicz rearrangement was envisaged to afford pyran-3-one **200**. A set of reaction conditions was screened in order to optimize the Achmatowicz rearrangement (Table 15). During this screening process, it was found that the rearrangement reaction was a highly sensitive reaction, which required careful monitoring of the reaction temperature. Although the use of both *m*-CPBA and Br_2 has been reported in the literature,[127] NBS was found to give the best results in our hands. In the end, pyran-3-one **200** was obtained in 91% yield by the reaction of 1-(2-furyl)ethanol **199** with NBS in the presence of sodium acetate as base in a mixture of THF and water (4/1).



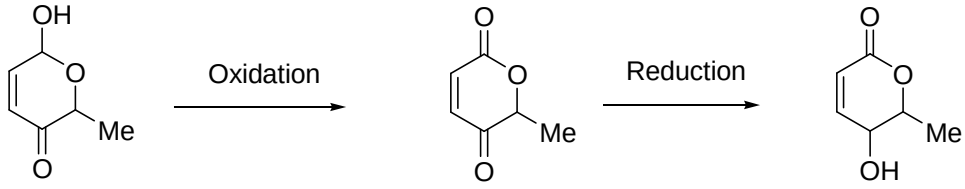
Scheme 3-45. Attempt for the synthesis of pyran-2-one **26**

Table 15: Applied reaction conditions for the Achmatowicz rearrangement reaction of 1-(2-furyl)ethanol **199**

Entry	Oxidant (equiv.)	Solvent	Temperature (°C)	Reaction time (h)	Result
1	*m*-CPBA (1.5)	CH_2Cl_2	-4 to 0	1	Complex mixture
2	*m*-CPBA (1.5)	CH_2Cl_2	-4 to 0	3	Complex mixture
3	*m*-CPBA (1.5)/ NaOAc (1.5)	CH_2Cl_2	-4 to 0	1	Complex mixture
4	*m*-CPBA (1.1)/ NaOAc (1.1)	CH_2Cl_2	-4 to 0 (addition *m*-CPBA) then rt	3	Complex mixture
5	Br_2	MeOH	- 40	1	**200** (10%)
6	NBS (1.1)/ NaOAc (1.1)	THF/H_2O (4/1)	-4 to 0 (addition NBS) then rt	3	**200** (20%)
7	NBS (1.1)/ NaOAc (1.1)	THF/H_2O (4/1)	-4 to 0 (addition NBS) then rt	1	**200** (57%)
8	NBS (1.1)/ NaOAc(2.2)/ $NaHCO_3$ (1.1)	THF/H_2O (4/1)	-4 to 0 (addition NBS) then rt	1	**200** (91%)

The literature reported that pyran-2-one **202** could be obtained efficiently from the Achmatowicz reaction product **200** through oxidation of this pyran-3-one **200** by a $CrO_3{\cdot}NH_4Cl$ complex to the intermediate **201** and subsequent Luche reduction with $NaBH_4$ in the presence of $CeCl_3$.[127a]

Table 16: Applied reaction conditions in the oxidation-reduction protocol for the synthesis of pyran-2-one **200**



200 **201** **202**

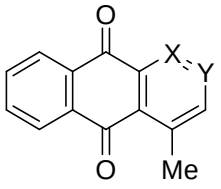
Entry	Oxidation	Reduction	Result
1	4.0 equiv.CrO_3·NH_4Cl CH_2Cl_2, rt, 1.5 h	1.5 equiv. $NaBH_4$ CH_2Cl_2/MeOH (1/1), 0°C, 1.5 h	Complex reaction mixture
2	3.0 equiv.CrO_3·NH_4Cl CH_2Cl_2, rt, 1.5 h	1.5 equiv. $NaBH_4$ CH_2Cl_2/MeOH (1/1), 0°C, 1.5 h	Complex reaction mixture
3	3.0 equiv.CrO_3·NH_4Cl CH_2Cl_2, rt, 0.5 h	1.5 equiv. $NaBH_4$, 2.0 equiv $CeCl_3$ CH_2Cl_2/MeOH (1/1), 0°C, 1.5 h	Complex reaction mixture
4	3.0 equiv.CrO_3·NH_4Cl CH_2Cl_2, rt, 0.5 h	1.5 equiv. $NaBH_4$,1.0 equiv. $CeCl_3$ CH_2Cl_2/MeOH (1/1), 0°C, 1.5 h	Complex reaction mixture

However, despite numerous attempts this procedure only gave complex mixtures in our hands. Although the oxidation reaction could be performed successfully, the resulting compound **201** was found to be highly sensitive towards overoxidation and was found to decompose rapidly at room temperature. As a result, this compound could not be purified and had to be used as such in the next step. However, standard reaction conditions for the Luche reduction failed to give good results (Table 16), which is probably due to the instability of the intermediate **201**. Despite contacting the corresponding author of the literature report[127a] on several occasions, we have never received any reply to our request for information regarding this reaction. Therefore, alternative reaction pathways to the pyran-2-one **202** will have to be investigated in order to obtain a proper substrate for the phthalide annulation reaction after which a first total synthesis of paepalantine can be attempted.

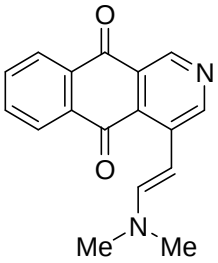
3.4. Conclusion

The present PhD dissertation is an account of a contribution on a series of syntheses of naturally occurring quinones and their analogues, performed at the Laboratory of Sustainable Organic Chemistry and Technology (Faculty of Bioscience Engeneering, Ghent University). It particularly covers the continuing efforts towards the synthesis of 2-azaanthraquinone and naphthyridinone alkaloids. In this respect, the results of three synthetic projects are disclosed.

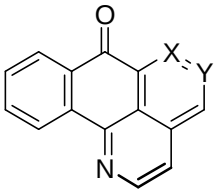
The first project envisaged the synthesis of 2-azasampangine **12b** from 2-azacleistopholine **10b** analogous to the literature based synthesis of sampangine **12a** from cleistopholine **10a** (Scheme 3-1). The preparation of 2-azacleistopholine **10b** was accomplished under ligand-free Heck and Pomeranz-Fritsch reaction conditions in 30% and 50% yield, respectively. These low and moderate yields urge a continuing need of an optimized process. Although the obtained 2-azacleistopholine **10b** was smoothly converted to 4-[2-(dimethyl)aminovinyl]benzo[*g*]isoquinoline **11b** in 86%, the conversion of the latter to 2-azasampangine **12b** failed (Scheme 3-12). Therefore, milder conditions than the one described in literature are needed in order to accomplish this conversion.



10a X = N, Y = CH
10b X = CH, Y = N

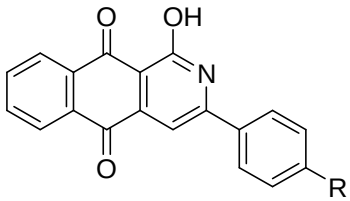


11b

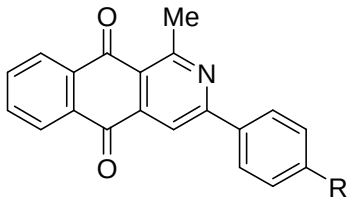


12a X = N, Y = CH
12b X = CH, Y = N

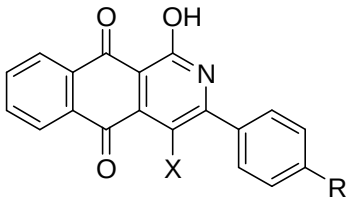
The second project concerned the syntheses of 2-azaanthraquinones **16**, **17** and **18** substituted at the C-1 *peri*-carbonyl position and linked to phenyl groups through a biaryl axis (Figure 1-4). Thanks to the efficiency of pyridium ylid chemisty and reaction conditions previously established in our research group, the syntheses of 2-azaanthraquinones **16** and **17** were smoothly accomplished in 44-75% and 47-67%, respectively (Tables 3 and 6).



16

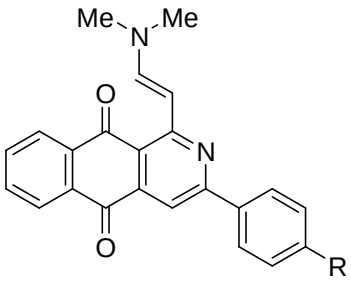


17

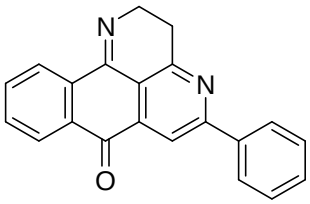


18 X = COOMe

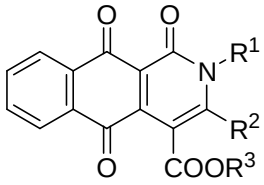
In addition, the presence of a methyl group at C-1 in 2-azaanthraquinones **17** allowed their condensation with DMF-DMA to the corresponding 1-[2-(dimethyl)aminovinyl]benzo[*g*]isoquinolines **21** in 23-77% yield (Scheme 7). Boiling 1-[2-(dimethyl)aminovinyl]-3-phenylbenzo[*g*]isoquinoline **21a** in a 5% solution of ammonium acetate in methanol afforded the corresponding 5-phenyl-7*H*-naphtho[3,2,1]naphthyridin-7-one **22** in 89% yield (Table 8, entry 5). The reaction conditions used in this conversion established new and milder reaction conditions to obtain naphthyridone derivatives from the corresponding methylarenes *via* 2-(dimethyl)aminovinyl intermediates.



21

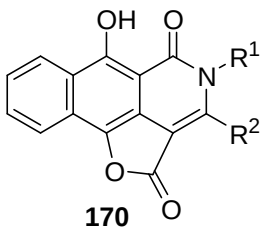


22

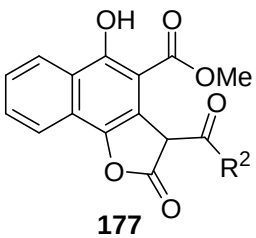


171

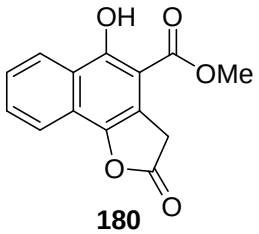
The difficult access to 2-azaanthraquinones **18** through the direct utilization of the Nenitzescu reaction led to an investigation towards the synthesis of benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **171** (Figure 3-2). Therefore, three synthetic routes were explored. The first route consisted of the reaction of β-ketoesters to 2-methoxycarbonyl-1,4-naphthoquinone **19a** in a toluene-acetic acid (5/1) under reflux, which gave methyl 3-acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates **177**. Subsequent reaction of the latter compounds with primary amines afforded methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate **180** instead of 3,4-diakyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **170** which could lead to the targeted benzo[*g*]isoquinoline-1,5,10(2*H*)-triones **171**. The second route implied the reaction of 2-methoxycarbonyl-1,4-naphthoquinone **19a** with *N*-subtituted enaminoesters **23**, which gave 3,4-diakyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-diones **170** in 19-47% yield. Subsequent hydrolysis of the latter compounds followed by methylation using diazomethane afforded the target compounds **171** in 14-97% yield.



170



177

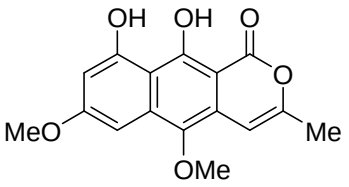


180

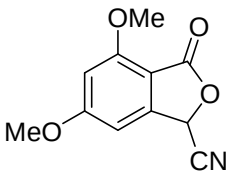
The third route consisted of the oxidative addition of enaminoesters **23** to methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** in the presence of an excess of manganese(IV) oxide in

dichloromethane at room temperature, which was followed by boiling in a mixture of toluene and acetic acid (5/1). This third route gave the targeted 2,3-disubstituted 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylates **171** in 29-71% yield (Table 14).

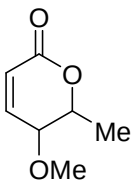
The third project aimed at the first total synthesis of paepalantine **24** (Figure 1-5) by the phthalide annulation reaction of 3-cyanophthalide **25** and pyran-2-one **26** (Scheme 1-5). Since the preparation of pyran-2-one **26** was not accomplished due to the unstability of its precursor, the synthesis of paepalantine **24** remains a challenge.



24 paepalantine



25

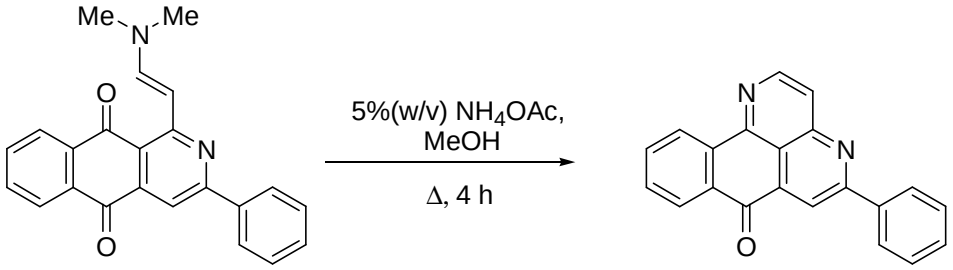


26

3.5. Perspectives

Through the course of this research work, a number of interesting areas of azaanthraquinone chemistry have been explored and some reaction pathways still need to be completed.

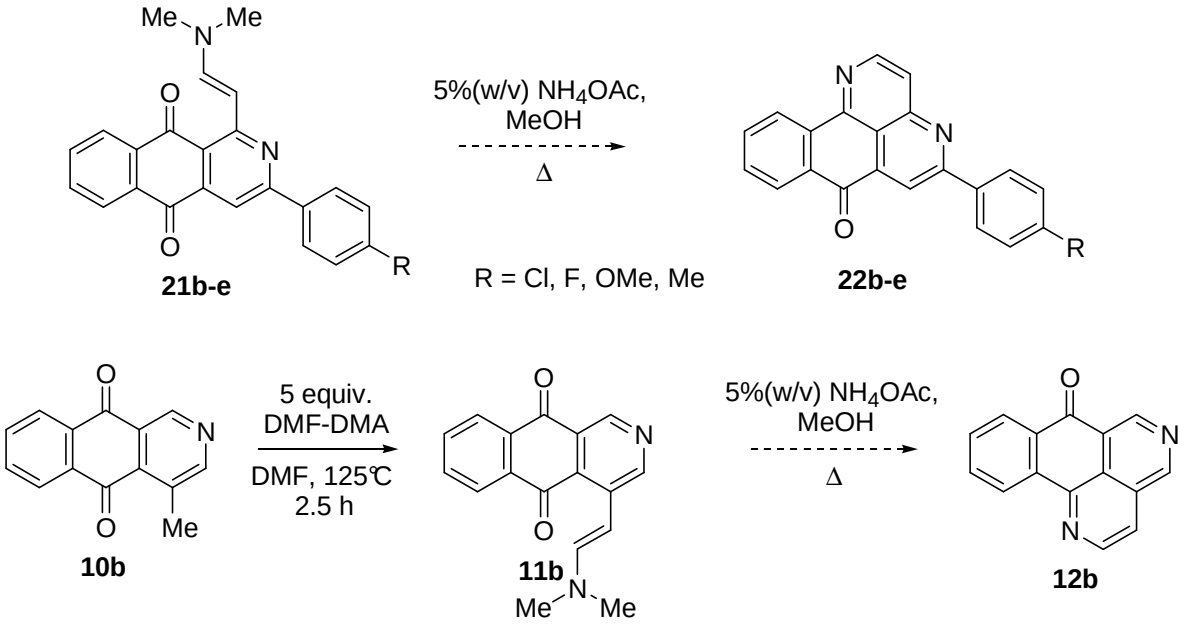
2-Azasampangine **10b** and 5-aryl-7*H*-naphtho[3,2,1-*de*]naphthyridin-7-ones **22** are potentially bioactive compounds. In the present research work, mild and efficient conditions to obtain 5-aryl-7*H*-naphtho[3,2,1-*de*]naphthyridin-7-one **22a** from heating 3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]-isoquinoline-5,10-dione **21a** in a 5% (w/v) solution of ammonium acetate in methanol were established (Scheme 3-36).



21a **22a** (89%)

Scheme 3-46. Synthesis of naphthyridone **22a**

Therefore, the synthesis of other 5-aryl-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one derivatives **22b-e** will be executed in the future using the same procedure. This procedure will also be used to accomplish the synthesis of 2-azasampangine **12b** from 4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **11b** (Scheme 3-47).



Scheme 3-47. Pathways to the synthesis of naphthyridones **22b-e** and 2-azasampangine **12b**

Paepalantine **24** (Figure 3-5) is a naturally occurring isocoumarine with a large spectrum of biological activity. Due to the importance of the phthalide annulation reaction strategy in the synthesis of pyranonaphthoquinone derivatives and the availability of several procedures to construct pyran-2-one **26** (Figure 3-5), the total synthesis of paepalantine **24** with the phthalide annulation reaction in the key step still remains a challenge.

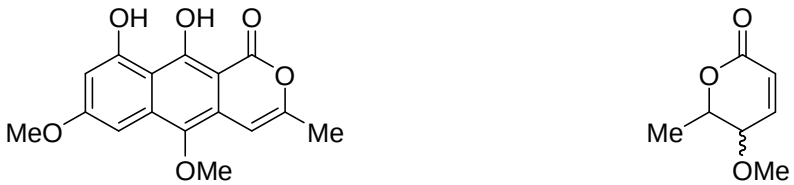
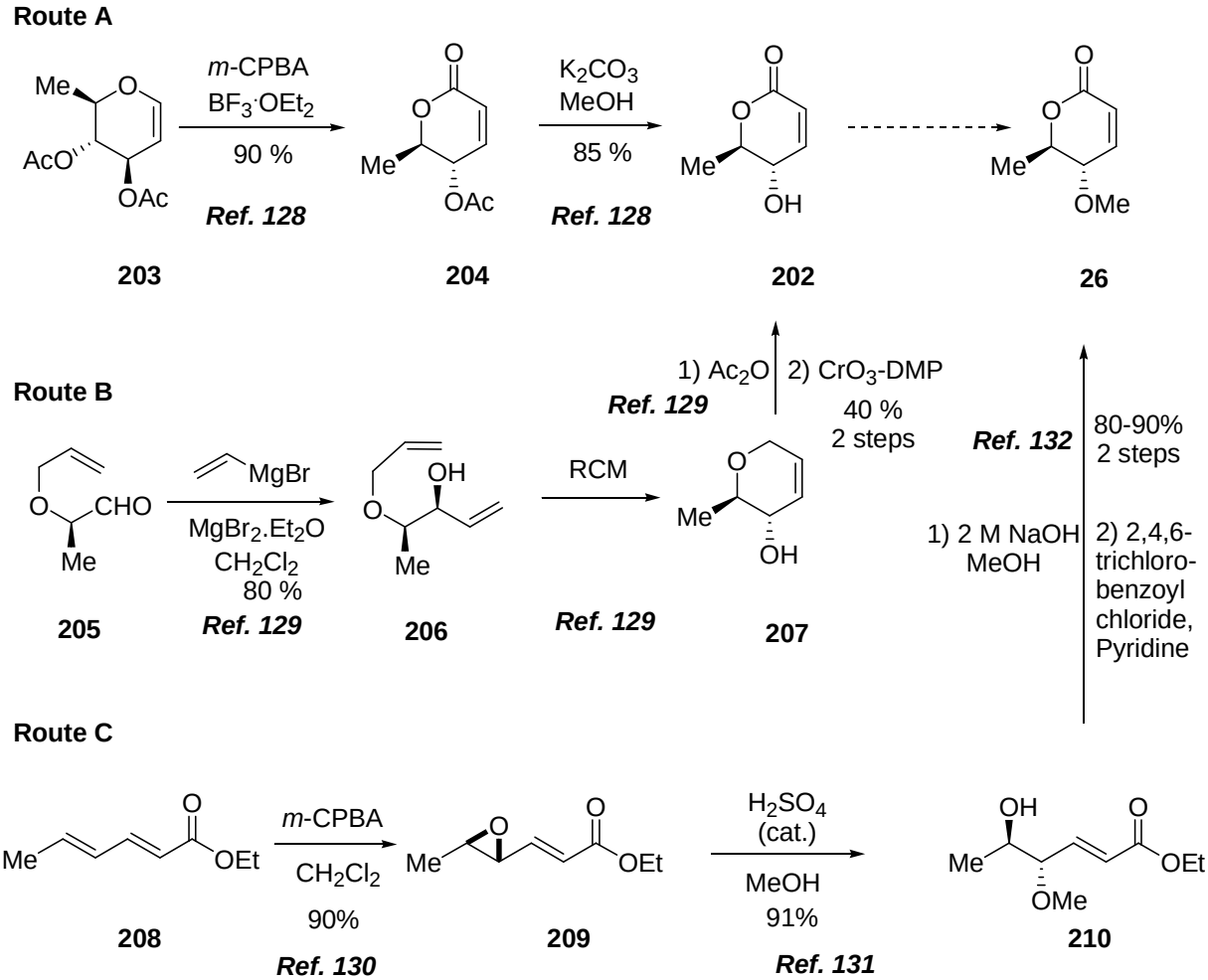


Figure 3-5. Structures of paepalantine **24** and pyran-2-one **26**

Therefore, alternative routes to the synthesis of pyran-3-one **26** as the key step have to be considered (Scheme 3-48). Notably, the use of a rhamnose derivative **203** as a starting material (Route A), ring-closing metathesis in the key step (Route B) or ethyl sorbate **209** as starting material (Route C) are potential routes. Considering the availability of the starting materials, route C appears to be the most straightforward choice.



Scheme 3-48. Alternative routes to the synthesis of pyran-3-one **26**

Tuberculosis is an infectious and deadly disease caused by *Mycobacterium tuberculosis*. A serious illness causing about 2-3 million deaths each year worldwide with an important incidence in Sub-Saharan regions.[133a] Although more than a dozen of antimycobacterial drugs (first and second-line drugs) are currently available for the therapy, there is still need for new, affordable and effective antibiotics that may shorten TB therapy duration and eliminate drug-resistant strains. Quinones, and in particularly, cleistopholine **10a** and sampangine **12a**, the two lead-molecules of the present research work, are recognized to be active against *Mycobacterium* species. Cleistopholine **10a** displays a strong antimycobacterial activity (MIC 12.5 µg/ml).[65] An even stronger MIC-value (MIC 1.56 µg/ml) is found for the synthetic 4-[2-(dimethylaminovinyl)]cleistopholine **11a** and benzo[2,3]cleistopholine **211**. Sampangine **12a** has been reported with a MIC value of 0.78 µg/ml, ressembling rifampicin **213** (MIC 0.78 µg/ml),[101] a current first-line drug for the treatment of tuberculosis. Synthetic derivatives such as benzo[4,5]sampangin **212a** (MIC 0.39 µg/ml) and ascididemin **212b** (MIC 0.25 µg/ml) are even more promising.

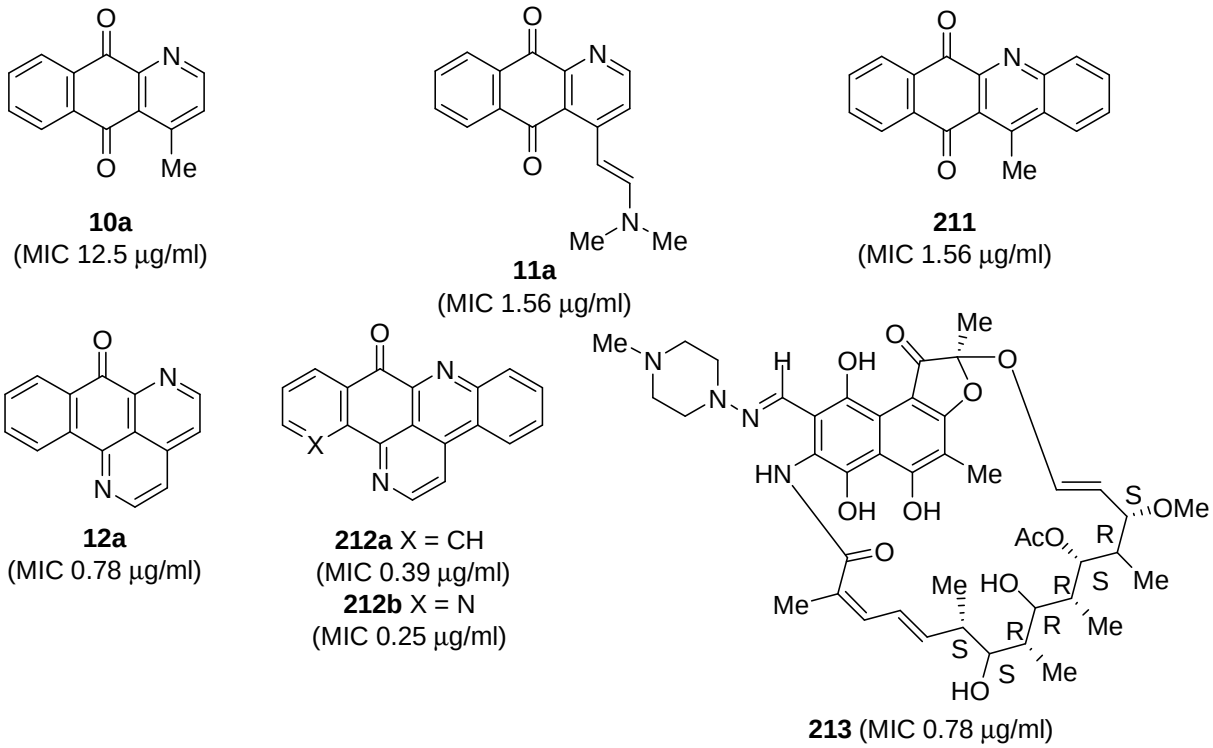
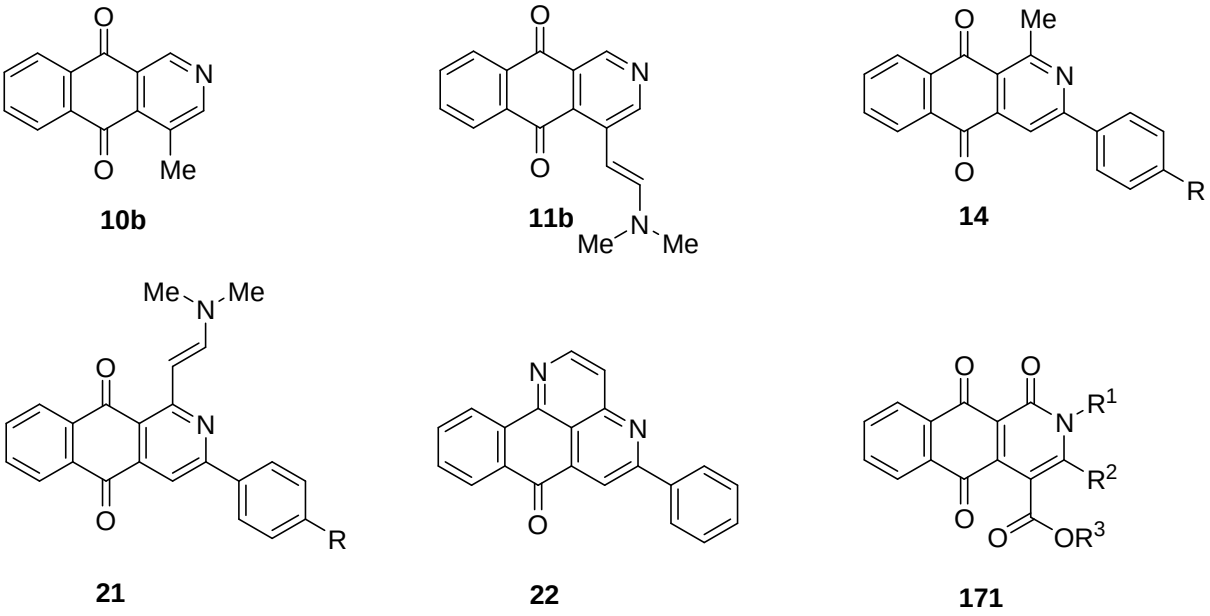


Figure 3-6. Examples of active coumpounds against *Mycobacterium* species

Since 2-azaanthraquinones display improved biological activity in comparison with their 1-azaanthraquinone analogues, 2-azacleistopholine **10b**, 2-aza-4-dimethylvinylcleistopholine **11b**, 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17a-e,** 3-aryl-1-dimethylaminovinylbenzo[*g*]isoquinoline-5,10-diones **21a-e**, 5-phenyl-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one **22** and 2,3-disubstituted alkyl 1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylates **171**, which have been synthesized in the course of this PhD research are expected to be bioactive compounds. Since quinones are increasingly recognized as active agents against *Mycobacterium* species,[15e,101,133] they will be tested in the future against *M. tuberculosis*, which causes the infectious and deadly disease tuberculosis.

Since the classical plating techniques are plagued by the slow growth of *M. tuberculosis* and intensive work in enumeration of colony forming units (CFU), these compounds (Figure 3-7) will be tested by the luciferase screening assay. This method developed in collaboration with the Department of Mycobacterial Immunology (Scientific Institute of Public health, Brussels) uses a lumiscent strain of *M. tuberculosis* H37Rv.[134]



R = H, Cl, F, Me, OMe R^1 = Et, *n*-Pr R^2 = Me, Et, Ph R^3 = Me, Et

Figure 3-7. Compounds to be tested against *Mycobacterium* species

Chapter 4: Experimental section

4.1. Instrumental material

4.1.1. Column chromatography

Column chromatography was carried out using a glass column with silica gel (Aldrich, particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Solvent systems were determined *via* initial TLC analysis on silica gel (Merck, Kieselgel $60F_{254}$, precoated 0.25 mm). Compounds were revealed by UV light (λ = 254 and 366 nm) or $KMnO_4$ oxidation.

4.1.2. NMR spectroscopy

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Jeol JNM-EX 300 NMR spectrometer. Peak assignments were performed with the aid of the DEPT, 2D COSY, HSQC, HMBC techniques. The NMR samples were prepared with commercially available deuterated solvents with tetramethylsilane as an internal standard.

4.1.3. Mass spectroscopy

Low resolution mass spectra were recorded using an Agilent 1100 series VS (ESI, 4000 V) mass spectrometer [ESI: **E**lectron **S**pray **I**onisation positive ($M+H^+$) and negative ($M-H^+$) modes] *via* a direct inlet or *via* LC-MS coupling [*Phenomenen huna* column; 250×3 mm length, 5 µm particle size, 100 A pore size with 5 mM NH_4OAc in H_2O (LC-MS grade) and Acetonitrile (LC-MS grade) as eluents]. High resolution mass spectra were recorded on a Finnigan MAT 95 XPAPI-GC-Trap tandem mass spectrometer or a tandem spectrometer Agilent 6220 TOF-LC/MS

4.1.4. Infrared spectroscopy

Infrared (IR) spectra were recorded with a Perkin Elmer BX FT-IR spectrometer using the attenuated total reflection technology (ATR).

4.1.5. Elementary analysis

Elemental analyses were executed with a Perkin Elmer Series II CHNS/O Analyzer 2400.

4.1.6. Melting point

Melting points were recorded on a Buchi Melting point B-540 apparatus and are not corrected.

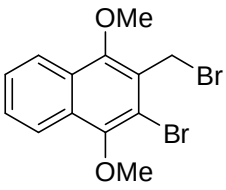
4.1.7. Microwave reactions

Microwave reactions were performed in a CEM Discover® microwave

4.2. Effort towards a short and efficient synthesis of 2-azacleistopholine 10b and 2-azasampangine 12b

4.2.1. Synthesis of 2-bromo-3-bromomethyl-1,4-dimethoxynaphthalene 94[91]

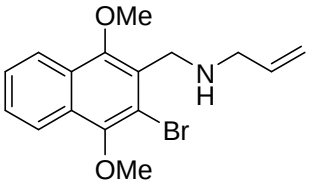
A mixture of 1,4-dimethoxy-2-methylnaphthalene **98**[91] (0.02 mol, 4.04 g) and *N*-bromosuccinimide (0.021 mol, 3.74 g) in tetrachloromethane (100 ml) was stirred at room temperature for 2 hours. A second portion of *N*-bromosuccinimide (0.021 mol, 3.74 g) was added to the stirred suspension together with dibenzoyl peroxide (2 mmol, 0.48 g) and the mixture was heated under reflux for 2 hours, then cooled to 0°C, filtered and washed with ice cold CCl_4 and evaporated *in vacuo* to give **94** (5.62 g, 78 %) after crystallization from diethyl ether/hexane (9/1). All the spectral data were in accordance with data in the literature.[91]



^{1}H NMR ($CDCl_3$): δ 3.99 (3H, s, CH_3O), 4.08 (3H, s, CH_3O), 4.93 (2H, s, $ArCH_2Br$), 7.55-7.59 (2H, m, H-6 and H-7), 8.06-8.12 (2H, m, H-5 and H-8).

4.2.2. Synthesis of 2-[(allylamino)methyl]-3-bromo-1,4-dimethoxynaphthalene 100[9]

To a stirred solution of allylamine (0.175 mol, 10 g) in ethanol (20 ml) was added dropwise a solution of 2-bromo-3-bromomethyl-1,4-dimethoxynaphthalene **94** (0.0175 mol, 6.3 g) in ethanol (100 ml) and the reaction mixture was stirred in a flask fitted with a $CaCl_2$ tube at room temperature for 2 days. Most of the solvent was evaporated *in vacuo* and the residue was dissolved in dichloromethane (100 ml), washed twice with water and dried ($MgSO_4$). Flash chromatography on silica gel using 2% methanol in chloroform as eluent gave 2-[(allylamino)methyl]-3-bromo-1,4-dimethoxynaphthalene **100** (4.12 g, 91% yield) as a brown oil, which was found to decompose rapidly. Therefore, this compound was used as such in the next step.

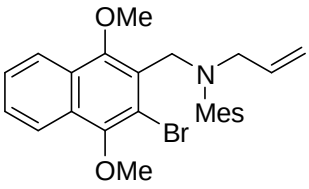


^{1}H NMR ($CDCl_3$): δ 3.30-3.33 (2H, m, $NC\underline{H}_2CH=CH_2$), 3.97 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.12 (2H, s, $ArCH_2$), 5.08-5.30 (2H, m, $CH=C\underline{H}_2$), 5.88-6.01 (1H, m, $C\underline{H}=CH_2$), 7.51-7.58 (2H, m, H-6 and H-7), 8.06-8.11 (2H, m, H-5 and H-8).

4.2.3. Synthesis of *N*-methanesulfonyl-2-[(allylamino)methyl]-3-bromo-1,4-dimethoxynaphthalene 93[9]

A solution of methanesulfonyl chloride (0.012 mol, 1.37 g) in dichloromethane (10 ml) was added dropwise to a stirred solution of 2-[(allylamino)methyl]-3-bromo-1,4-dimethoxynaphthalene **100** (0.012 mol, 4.12 g) and triethylamine (0.012 mol, 1.21 g) in dichloromethane (50 ml) under a nitrogen

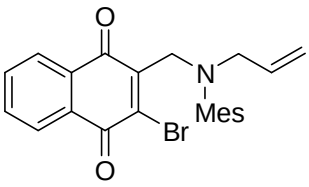
atmosphere. After 2 h, the solution was washed with 2 M aqueous HCl and then with a saturated aqueous solution of sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography on silica gel with ethyl acetate/hexane (1/4) as eluent gave *N*-methanesulfonyl-2-[(allylamino)methyl]-3-bromo-1,4-dimethoxynaphthalene **93** (2.41 g, 60% yield) as white crystals.



^{1}H NMR ($CDCl_3$): δ 3.01 (3H, s, SO_2CH_3), 3.78 (2H, dt, *J* = 1.3, 6.3 Hz, $NCH_2CH{=}C\underline{H}_2$), 3.97 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.85 (2H, s, $ArCH_2$), 4.95-5.13 (2H, m, $CH{=}C\underline{H}_2$), 5.70 (1H, ddt, *J* = 6.3, 10.2, 17.2 Hz, $CH{=}CH_2$), 7.56-7.62 (2H, m, H-6 and H-7), 8.06-8.15 (2H, m, H-5 and H-8).

4.2.4. Synthesis of *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-naphthoquinone 13[9]

A solution of cerium(IV) ammonium nitrate (1.63 g, 3 mmol) in water (10 ml) was added dropwise to a cooled (0°C) solution of *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **93** (0.41 g, 1 mmol) in acetonitrile (20 ml) and the reaction mixture was stirred for an additional 30 min at the same temperature. After the addition of water, the aqueous solution was extracted with small portions of ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallization from ethyl acetate afforded *N*-methanesulfonyl-2-[(allylamino)methyl]-3-bromo-1,4-naphthoquinone **13** (0.17 g, 45% yield).



^{1}H NMR ($CDCl_3$): δ 3.02 (3H, s, SO_2CH_3), 3.96 (2H, br d, *J* = 6.3 Hz, $NCH_2CH{=}CH_2$, 4.58 (2H, s, $ArCH_2$), 5.17-5.31 (2H, m, $CH{=}C\underline{H}_2$), 5.88 (1H, ddt, *J* = 6.3, 10.2, 17.2 Hz, $C\underline{H}{=}CH_2$), 7.74-7.84 (2H, m, H-7 and H-8), 8.11-8.19 (2H, m, H-6 and H-9).

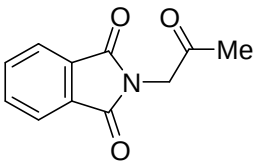
4.2.5. Synthesis of *N*-acetonylphthalimide 107, 2-(phthalimidomethyl)-2-methyl-1,3-dioxolane 109 and 2-aminomethyl-2-methyl-1,3-dioxolane 15a

N-Acetonylphthalimide **107**, 2-(phthalimidomethyl)-2-methyl-1,3-dioxolane **109** and 2-aminomethyl-2-methyl-1,3-dioxolane **15a** were synthesized according to a literature procedure.[95]

4.2.5.1. N-Acetonylphthalimide **107**

Potassium phthalimide **105** (21.6 g, 0.17 mol) and toluene (29 ml) were stirred in a flask fitted with reflux condenser under nitrogen atmosphere. Then, α-chloroacetone (13.3 g, 0.15 mol) was added and the mixture was boiled for 2 hours. After cooling to room temperature, toluene was distilled off *in vacuo*. The solid residue was dissolved by the addition of water (30 ml) and dichloromethane (30 ml). After strong agitation, the mixture was transferred to a separating funnel, after which the organic phase was separated. The remaining aqueous phase was extracted twice with dichloromethane (2×30 ml). The dichloromethane extracts were combined, washed twice with brine and dried over magnesium sulfate.

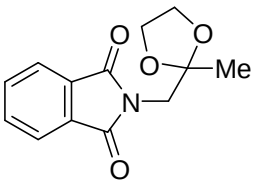
After filtration, the filtrate was concentrated in vacuum to afford 17.6 g (74%) of *N*-acetonylphthalimide **107**, which was used as such in the following step. All the spectral data were in accordance with the literature.[95]



^{1}H NMR ($CDCl_3$): δ 2.30 (3H, s, H-3'), 4.51 (2H, s, H-1'), 7.70-7.83 (2H, m, H-4 and H-5), 7.85-7.90 (2H, m, H-3 and H-6).

4.2.5.2. 2-(Phthalimidomethyl)-2-methyl-1,3-dioxolane **109**

Phthalimidoacetone **107** (17.6 g, 86.7 mmol) was dissolved in toluene (93 ml) and ethylene glycol (10,8 g, 173,4 mmol), followed by the addition of methanesulfonic acid (0.44 g, 4.36 mmol). The mixture was refluxed using a Dean-Stark trap. After 16 hours, the reaction mixture was cooled to room temperature. The reaction was washed with water (2×10 ml) and then with a saturated aqueous $NaHCO_3$ solution (2×10 ml). The organic phase was dried with magnesium sulfate, filtered then concentrated in *vacuo*. The solid residue was recrystallized from methanol to afford 2-(phthalimidomethyl)-2-methyl-1,3-dioxolane **109** (12.01 g, 56% yield). All the spectral data were in accordance with the literature.[95]

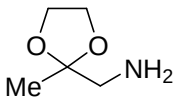


^{1}H NMR ($CDCl_3$): δ 1.46 (3H, s, H-3'), 3.82 (2H, s, H-1'), 3.90-4.04 (2H, m, OCH_2-CH_2O), 4.07-4.14 (2H, m, OCH_2-CH_2O), 7.70-7.83 (2H, m, H-4 and H-5), 7.85-7.90 (2H, m, H-3 and H-6).

4.2.5.3. 2-Aminomethyl-2-methyl-1,3-dioxolane **15a**

Hydroxylamine hydrochloride (8.12 g, 0.12 mol) was dissolved in ethanol (185 ml) in a flask fitted with a reflux condenser, and a $CaCl_2$ tube. Then, the mixture was boiled under reflux to dissolve the hydroxylamine hydrochloride and then cooled to room temperature. Sodium methoxide (5.40 g of Na in 54 ml of methanol, 0.24 mol) was added cautiously, and the contents were stirred while the flask was cooled in an ice bath. 2-(Phthalimidomethyl)-2-methyl-1,3-dioxolane **109** (8.4 g, 0.04 mol) was dissolved in ethanol (75 ml) and the solution was added to the flask. The reaction mixture was stirred at 0°C for 2 hours and kept overnight under nitrogen atmosphere in the freezer at about – 18 °C. The final solution was filtered through Celite, which was washed with diethyl ether (5×50 ml). The combined filtrates were reduced *in vacuo* to about 25 ml on a rotavapor at low temperature (< 40°C). The residual viscous oil was suspended in ether (80 ml) and filtered through Celite a second time. Then, the filtrate was passed through to a short Florisil column which was washed with ether. The filtrate from the Florisil column was concentrated *in vacuo* to remove the diethyl ether. The oily residue was distilled using a short vigreux column (10 cm long) and high vacuum (about 0.25 atm). The fraction boiling at 59-61°C afforded a

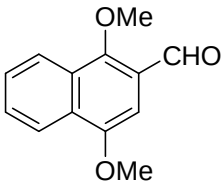
solution of 2-aminomethyl-2-methyl-1,3-dioxolane **15a**. All the spectral data were in accordance with the literature.[95]



^{1}H NMR ($CDCl_3$): δ 1.30 (3H, s, CH_3), 2.77 (2H, s, NCH_2), 3.90-4.15 (4H, br s, OCH_2CH_2O).

4.2.6. Synthesis of 2-formyl-1,4-dimethoxynaphthalene 14[96]

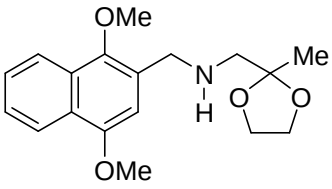
Under a nitrogen atmosphere, phosphorus oxychloride ($POCl_3$) (4.86 ml, 8.1 g, 53.1 mmol, 10 equiv.) was added dropwise to *N*,*N*-dimethylformamide (4.1 ml, 53.1 mmol, 10 equiv.) at 0°C in a flame-dried flask. The Vilsmeier-Haack reagent was allowed to form during 30 minutes at 0°C. In the meantime, a solution of 1,4-dimethoxynaphthalene **110** (1g, 5.31 mmol) in $CHCl_3$ (17 ml) was prepared in a flame-dried flask and under a nitrogen atmosphere, after which it was added to the reaction mixture. After stirring for 10 minutes at room temperature, the reaction mixture was heated under reflux for 80 hours. The reaction mixture was allowed to cool down to room temperature and was placed in an ice bath, after which little pieces of ice were added slowly to the flask. When the reaction mixture was cooled down, it was extracted with chloroform (3×30 ml). The combined organic extracts were washed thoroughly with brine (3×30 ml) and dried over $MgSO_4$. The solvent was evaporated in *vacuo*. Flash chromatography (petroleum ether/ethyl acetate = 85/15) gave 2-formyl-1,4-dimethoxynaphthalene **14** (0.86 g, 75% yield) as yellow needles. Spectral data were in accordance with the literature.[96]



^{1}H NMR ($CDCl_3$): δ 3.96 (3H, s, CH_3O), 4.09 (3H, s, CH_3O), 7.13 (1H, s, H-3), 7.64-7.65 (2H, m, H-6 and H-7), 8.02 (1H, *J* = 2.2 Hz, H-5 or H-8), 8.30 (1H, *J* = 2.2 Hz, H-5 or H-8), 10.58 (1H, s, CHO).

4.2.7. Synthesis of 2-[*N*-(1,4-dimethoxy-2-naphthyl)-aminomethyl]-2-methyl-1,3-dioxolane 111

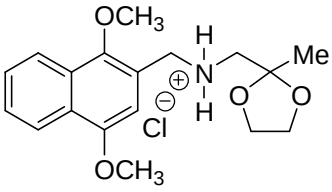
1,4-Dimethoxy-2-formylnaphthalene **14** (1.0 g, 4.62 mmol), 2-aminomethyl-2-methyl-1,3-dioxolane **15a** (0.57 g, 4.62 mmol), and magnesium(II) sulfate (1.12 g, 9.24 mmol) were dissolved in dichloromethane in a flask fitted with a calcium chloride tube and the mixture was stirred for 2 hours at room temperature. After filtration and evaporation of the solvent *in vacuo*, the crude imine was used as such in the next step. In this way, the imine intermediate was dissolved in methanol (10 ml), after which sodium borohydride (0.35 g, 9.24 mmol) was added portion-wise at 0°C. Then, the reaction mixture was stirred for 16 h at room temperature in a flask fitted with a calcium chloride tube. The reaction was quenched by the careful addition of water (5 ml) and the aqueous solution was extracted with dichloromethane (3×10 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford 2-[*N*-(1,4-dimethoxy-2-naphthyl)aminomethyl]-2-methyl-1,3-dioxalane **111** (1.45 g, 100% crude yield) as a viscous oil.



Viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, s, H-3'), 2.76 (2H, s, $ArCH_2N$), 3.89 (3H, s, CH_3O), 3.96 (4H, m, OCH_2CH_2O), 3.99 (3H, s, CH_3O), 4.04 (2H, s, H-2'), 6.86 (1H, s, H-3), 7.46 (1H, dd, *J* = 10.0, 9.0 Hz, H-5 or H-6), 7.55 (1H, dd, *J* = 10.0, 9.0 Hz, H-5 or H-6), 8.04 (1H, d, *J* = 10.0 Hz, H-5 or H-6), 8.23 (1H, d, *J* = 10.0 Hz, H-5 or H-6). ^{13}C NMR ($CDCl_3$): δ 23.00 (CH_3), 48.44 ($ArCH_2N$), 55.54 (OCH_3), 55.7, (OCH_3), 62.36 (NCH_2), 65.07 (2×CH_2O), 103.88 (O-C-O), 104.79 (CH), 109.54 (C_{quat}), 121.88 (CH), 122.38 (CH), 125.21 (CH), 126.57 (CH), 128.23 (C_{quat}), 128.61 (C_{quat}), 146.45 (C_{quat}), 151.26 (C_{quat}). IR (ATR): ν_{max} 3332, 3069, 2936, 1595, 1459, 1368, 1266, 1213, 1162, 1121, 1091, 1055, 768 cm^{-1}. MS m/z (%): 318 ($[M+H]^+$,100).

4.2.8. Synthesis of *N*-[(1,4-dimethoxynaphthalen-3-yl)methyl](2-methyl-1,3-dioxolan-2-yl)methylammonium chloride 112

To a solution of 2-[*N*-(1,4-dimethoxy-2-naphthyl)aminomethyl]-2-methyl-1,3-dioxalane **111** (100 mg, 0.32 mmol) in diethyl ether (10 ml) in a flask equipped with an air outlet, was bubbled freshly prepared gaseous HCl in a fume hood. After 1 hour, the reaction mixture was filtered. The resulting crystals were recrystallized from a solution of diethyl ether and hexane (19/1) to afford *N*-[(1,4-dimethoxynaphthalen-3-yl)methyl](2-methyl-1,3-dioxolan-2-yl)methylammonium chloride **112** (113 mg, 99% yield) as white crystals.



White crystals, m.p.: 161.2-161.7°C. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, s, H-3'), 2.98-3.02 (2H, m, $ArCH_2N$), 3.91 (3H, s, OCH_3), 3.93-3.96 (2H, m, OCH_2CH_2O), 4.09 (3H, s, OCH_3), 4.29-4.33 (2H, m, OCH_2CH_2O), 4.37 (2H, s, H-2'), 7.51-7.61 (2H, m, H-6 and H-7), 7.66 (1H, s, H-3), 8.05 (1H, d, *J* = 10.0 Hz, H-5 or H-8), 8.23 (1H, d, *J* = 10.0 Hz, H-5 or H-8), 9.80 (2H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 22.68 (CH_3), 45.37 (O-C-O), ($ArCH_2N$), 56.57, (OCH_3), 63.28 (OCH_3), 65.17 (2×CH_2O), 104.95 (CH), 106.08 (CH), 118.78 (CH), 122.23 (CH), 122.86 (CH), 126.50 (CH), 127.13 (CH), 127.30 (C_{quat}), 128.14 (C_{quat}), 148.27 (C_{quat}), 151.86 (C_{quat}). IR (ATR): ν_{max} 2889, 2205, 1597, 1458, 1406, 1356, 1266, 1236, 1094, 1036, 923, 885 cm^{-1}. MS m/z (%): 318 ($[M+H-37]^+$,100).

4.2.9. Synthesis of 4-methylbenzo[*g*]isoquinoline-5,10-dione 10b (2-azacleistopholine).

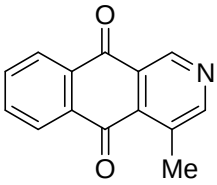
Procedure A:

A mixture of *N*-methanesulfonyl-2-[(allylamino)methyl]-3-bromo-1,4-naphthoquinone **13** (0.65 mmol, 250 mg), potassium carbonate (4.0 mmol, 0.55 g) and palladium(II) acetate (0.33 mmol, 74 mg) in acetonitrile (25 ml) was heated under reflux for 3 hours. Water was added and the aqueous solution was extracted with small portions of ethyl acetate. The combined organic extracts were washed with brine,

dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1/4) as eluent gave 4-methylbenzo[*g*]isoquinoline-5,10-dione **10b** (44 mg, 30% yield).

Procedure B:

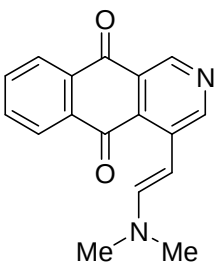
To a solution of 2-[*N*-(1,4-dimethoxy-2-naphthyl)-aminomethyl]-2-methyl-1,3-dioxolane **111** (0.32 mmol, 100 mg) in dichloromethane (2 ml) was added 4 ml of concentrared sulfuric acid. The mixture was stirred for 2 days at room temperature. After completion, the reaction mixture was cooled to 0°C, then quenched with ice, neutralized with an aqueous solution of 2 M NaOH and extracted with dichloromethane (3×10 ml). The combined organic layers were washed with brine, dried with $MgSO_4$ and evaporated *in vacuo* to give a brown solid. Preparative thin layer chromatography with ethyl acetate/petroleum ether (1/4) as eluent gave 4-methylbenzo[*g*]isoquinoline-5,10-dione **10b** (35 mg, 50% yield).



Yellow crystals, m.p.:130.5-131.9 °C. ^{1}H NMR ($CDCl_3$): δ 2.84 (3H, s, CH_3), 7.82-7.86 (2H, m, H-7 and H-8), 8.25-8.30 (2H, m, H-6 and H-9), 8.89 (1H, s, H-3), 9.45 (H-1). ^{13}C NMR ($CDCl_3$): δ 19.4 (CH), 126.6 (C_{quat}), 126.8 (CH), 127.3 (CH), 132.5 (C_{quat}), 133.4 (C_{quat}), 134.1 (C_{quat}), 134.5 (CH), 134.6 (CH), 135.5 (C_{quat}), 147.2 (CH), 157.5 (CH), 183.1 (C=O), 184.8 (C=O). IR (ATR): ν_{max} 1678, 1638, 1617 cm^{-1}. MS *m/z* (%): 224 ([M+H]$^+$, 100).

4.2.10. Synthesis of (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione 11b

To a solution of 2-azacleistopholine **10b** (103 mg, 4.61 mmol) in DMF (3 ml), 5 equivalents of DMF-DMA were added under a nitrogen atmosphere and the reaction mixture was heated for 2.5 hours in an oil bath, which was preheated at 125°C. The reaction was followed up by thin layer chromatography and after completion, the reaction mixture was cooled down to room temperature and poured in 30 ml of water, which was extracted with 5×20 ml of CH_2Cl_2. The organic layers were combined and washed several times with brine, dried over $MgSO_4$, then the solvent was evaporated *in vacuo* to efford (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **11b** (110 mg, 86% yield) in high purity.



Dark blue crystals, m.p: 201.0-201.7°C; ^{1}H NMR ($CDCl_3$): δ 3.05 (6H, s, $N(CH_3)_2$, 6.96 (1H, d, *J* =14.3 Hz, H-1'), 7.26 (1H, d, *J* = 14.3 Hz, H-2), 7.78 (2H, m, H-7 and H-8), 8,25 (2H, m, H-6 and H-9), 9.02 (1H, s, H-3), 9.13 (1H, s, H-1). ^{13}C NMR ($CDCl_3$): δ 29.80 (CH_3), 41.02 (CH_3), 92.54 (CH), 126.52 (CH), 126.83 (C_{quat}), 127.22 (CH), 132.60 (C_{qaut}), 133.68 (CH), 134.41 (CH), 135.12 (C_{quat}), 135.38 (2×C_{quat}), 146.45 (CH), 152.72 (CH), 184.17 (C=O), 185.13 (C=O). IR (ATR): ν_{max} 2920, 1662, 1641, 1690, 1407, 1390, 1373, 1318, 1275, 1246 cm^{-1}. MS m/z (%): 279 ([M+H]$^+$, 100).

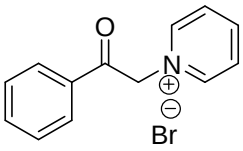
4.3. Synthesis of 3-aryl-1-hydroxybenzo[g]isoquinoline-5,10-diones 16

4.3.1. Synthesis of pyridinium salts 20

The pyridinium salts **20** were prepared according to the literature procedure.[102]

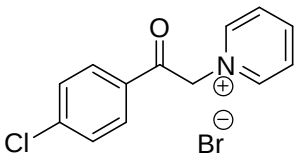
General procedure To a solution of α-bromoacetophenones **124** (5 g, 25.12 mmoles of **124a** and 21.65 mmoles of **124b**) in 50 ml of anhydrous ethyl acetate were added a solution of 1.05 equivalents of pyridine in 10 ml of anhydrous ethyl acetate. The solution was stirred for 24 hours at room temperature and filtered off. The obtained crystals were washed with 10 ml of anhydrous ethyl acetate and dried under high vacuum. After drying over P_2O_5 in a dessicator, the pyridinium salts **20** were stored under a nitrogen atmosphere. All spectral data were in accordance with the literature.[100b]

4.3.1.1. N-Phenacylpyridinium bromide **20a**



^{1}H NMR ($CDCl_3$): δ 7.28 (2H, s, NCH_2COAr), 7.55 (2H, t, *J* = 7.7 Hz, H-2), 7.68 (1H, t, *J* = 7.7 Hz, H-3), 8.07 (2H, t, *J* = 7.1 Hz, H-2'), 8.19 (2H, d, *J* = 7.7 H-1), 8.51 (1H, t, *J* = 7.1 Hz, H-3'), 9.33 (2H, d, *J* = 7.1 Hz, H-1').

4.3.1.2. N-(4-Chlorophenacyl)pyridinium bromide **20b**



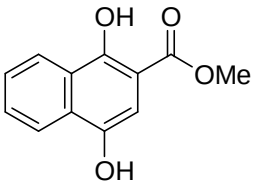
^{1}H NMR ($CDCl_3$): δ 7.31 (2H, s, NCH_2COAr), 7.48 (2H, d, *J* = 8.2 Hz, H-2), 8.06 (2H, t, *J* = 7.1 Hz, H-2'), 8.16 (2H, d, *J* = 7.7 Hz, H-1), 8.51 (1H, t, 7.1 Hz, H-3'), 9.36 (2H, d, J = 7.1 Hz, H-1').

4.3.2. Synthesis of methyl 1,4-dihydroxynaphthalene-2-carboxylate 128 and 2-methoxycarbonyl-1,4-naphthoquinone 19a

Methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** and 2-methoxycarbonyl-1,4-naphthoquinone **19a** were prepared according to the literature procedure.[101,104]

4.3.2.1. Methyl 1,4-dihydroxynaphthalene-2-carboxylate **128**[101,104]

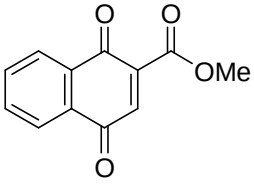
Dimethyl sulfate (0.22 mol, 27.75 g) and *N*,*N*-diisopropylethylamine (0.11 mol, 14.22 g) were added to a solution of 1,4-dihydroxynaphthoic acid **127** (0.10 mol, 20.4 g) in DMF (140 ml). The reaction mixture was heated for 1 h at 85°C and after cooling to room temperature, it was poured in a saturated solution of aqueous sodium bicarbonate. The aqueous phase was extracted with small portions of ethyl acetate (3×85 ml) and the combined organic extracts were washed for an additional time with saturated aqueous sodium bicarbonate and three times with brine. After drying ($MgSO_4$) and solvent evaporation *in vacuo*, methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** was obtained in 84% yield.



^{1}H NMR ($CDCl_3$): δ 3.98 (3H, s, OCH_3), 4.86 (1H, s, OH), 7.11 (1H, s, H-3), 7.57 (1H, t, *J* = 8.5 Hz, H-7 or H-8), 7.62 (1H, t, *J* = 8.5 Hz, H-7 or H-8), 8.13 (1H, d, *J* = 8.5 Hz, H-6 or H-9), 8.40 (1H, d, *J* = 8.5 Hz, H-6 or H-9), 11.56 (1H, s, OH).

4.3.2.2. 2-Methoxycarbonyl-1,4-naphthoquinone **19a**[101,104]

Freshly prepared silver(I) oxide (0.17 mol, 39.39 g)[135] and magnesium(II) sulfate (11 g) were added to a solution of methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** (0.05 mol, 10.91 g) in diethyl ether. The reaction mixture was stirred for 30 min at room temperature, after which it was filtered. Solvent evaporation *in vacuo* of the filtrate furnished the activated naphthoquinone **19a**. Chromatography or recrystalization of 2-methoxycarbonyl-1,4-naphthoquinone **19a** is not advised, since this compound decomposes on silica gel or upon heating. However, minor impurities could be removed by washing the crystals with cold diethyl ether and the activated quinone **19a** could be isolated in a yield of 98%.



^{1}H NMR ($CDCl_3$): δ 3.95 (3H, s, OCH_3), 7.23 (1H, s, H-3), 7.74-7.85 (2H, m, H-7 and H-8), 8.08 (1H, m, H-6 and H-9), 8.15 (1H, m, H-6 and H-9).

4.3.3. Synthesis of 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones 16 and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone 129a

3-Substitited 1-hydroxybenz[*g*]isoquinoline-5,10-diones **16** and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** were prepared according to literature procedures.[101,104]

General procedure A:

To a 10 wt % solution of ammonium acetate (2.0 g) in acetic acid (20 ml) were added 2-methoxycarbonyl-1,4-naphthoquinone **19a** (0.5 g, 2.4 mmol) and a pyridinium salt **20** (2.4 mmol), and the reaction mixture was subsequently boiled under reflux for 1-4 h. After cooling to room temperature, the reaction mixture was poured in water and extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate and dried over magnesium(II) sulfate. After solvent evaporation *in vacuo*, the crude mixture was purified by column chromatography on silica gel to yield the 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones **16**.

General procedure B:

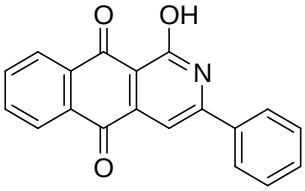
2-Methoxycarbonyl-1,4-naphthoquinone **19a** (0.3 g, 1.38 mmol) and 4-chlorophenacylpyridinium bromide **20b** (1.38 mmol) were added to a previously prepared 5 wt % solution of ammonium acetate in methanol (6 ml). The sealed reaction vessel was introduced in a CEM Discover® microwave apparatus

(ramp time 5 min, p_{max} 275 psi). After 5 min at 115°C, the reaction mixture was cooled to room temperature and then cooled further in air and an ice bath, after which the reaction mixture was filtered. The solid was washed with 20 ml cold methanol and dried *in vacuo* to yield 1-hydroxy-3-(4-chlorophenyl)benz[*g*]isoquinoline-5,10-dione **16b** in 35% yield.

Procedure C:

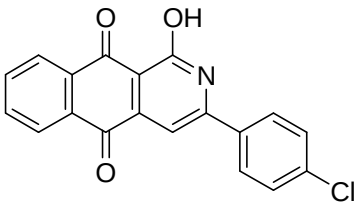
To a 10 wt % solution of ammonium acetate (2.0 g) in acetic acid (20 ml) was added 2-methoxycarbonyl-1,4-naphthoquinone **19a** (2.4 mmol, 0.5 g) and the reaction mixture was subsequently boiled under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured in water and extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over magnesium(II) sulfate. Solvent evaporation *in vacuo* gave 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a**, which was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (4/1) in 72% yield.

4.3.3.1. 1-Hydroxy-3-phenylbenz[g]isoquinoline-5,10-dione **16a**



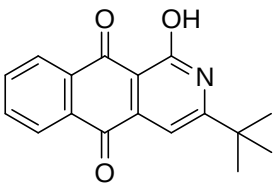
^{1}H NMR ($CDCl_3$): δ 7.52-7.56 (3H, m, H-3', H-4' and H-5'), 7.84–7.94 (2H, m, H-7 and H-8), 8.19 (1H, s, H-4), 8.22–8.27 (2H, m, H-2' and H-6'), 8.32–8.39 (2H, m, H-6 and H-9).

4.3.3.2. 3-(4-Chlorophenyl)-1-hydroxybenz[g]isoquinoline-5,10-dione **16b**



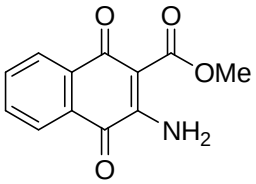
^{1}H NMR ($CDCl_3$): δ 7.48-7.57 (3H, m, H-4, H-3' and H-5'), 7.84-7.94 (2H, m, H-7 and H-8), 8.32-8.39 (2H, m, H-6 and H-9).

4.3.3.3. 3-tert-Butyl-1-hydroxybenz[g]isoquinoline-5,10-dione **16e**



^{1}H NMR ($CDCl_3$): δ 1.44 (9H, s, 3×CH_3), 7.25 (1H, s, H-4), 7.81-7.89 (2H, m, H-7 and H-8), 8.26-8.33 (2H, m, H-6 and H-9).

4.3.3.4. 3-Amino-2-methoxycarbonyl-1,4-naphthoquinone **129a**

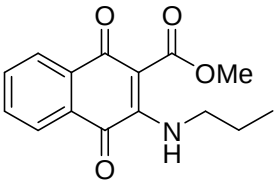


^{1}H NMR ($CDCl_3$): δ 3.92 (3H, s, OCH_3), 7.01 (1H, br s, NH), 7.64-7.70 (1H, m, H-6 or H-7), 7.79-7.85 (1H, m, H-6 or H-7), 8.07-8.10 (1H, m, H-5 or H-8), 8.22-8.24 (1H, m, H-5 or H-8), 9.15 (1H, br s, NH).

4.3.4. Synthesis of 3-alkylamino-2-methoxycarbonyl-1,4-naphthoquinone 129b-d

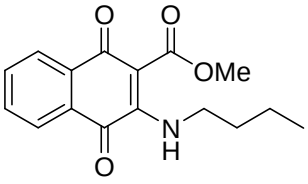
General procedure: To a solution of 4 equivalents of alkylammonium acetate in acetic acid (2 ml) was added a solution of 2-methoxycarbonyl-1,4-naphthoquinone **19a** (1.2 mmol, 0.25 g) in 10 ml of toluene at 0°C and the reaction mixture was subsequently boiled under reflux for 4 hours. After cooling to room temperature, the reaction mixture was poured in water and extracted with dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogencarbonate and dried over magnesium(II) sulfate. Solvent evaporation *in vacuo* gave 3-alkylamino-2-methoxycarbonyl-1,4-naphthoquinones **129b-d**, which were purified by column chromatography on silica gel with petroleum ether/ethyl acetate (4/1).

4.3.4.1. 2-Methoxycarbonyl-3-(n-propylamino)-1,4-naphthoquinone **129b**



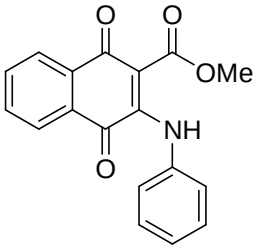
Yield: 87%, reddish brown crystals, m.p : 117.8-118.3°C ^{1}H NMR ($CDCl_3$): δ 1.03 (3H, t, *J* = 7.2 Hz, H-3'), 1.72 (2H, m, H-2'), 3.27 (2H, m, H-1'), 3.98 (3H, s, OCH_3), 6.27 (1H, broad s, NH), 7.64 (1H, m, H-6 or H-7), 7.77 (1H, m, H-6 or H-7), 8.06 (1H, m, H-5 or H-8), 8.14 (1H, m, H-5 or H-8).^{13}C NMR ($CDCl_3$): To date, a decent ^{13}C NMR spectrum of this derivative could not be recorded even upon prolongation of the relaxation delay and increasing the number of recorded scans, δ 11.41 ($NCH_2CH_2\underline{C}H_3$), 22.91 ($NCH_2\underline{C}H_2CH_3$), 45.60 ($N\underline{C}H_2CH_2CH_3$), 52.49 ($OCH_3$), 126.52 (CH), 126.70 (CH), 132.43 (CH), 135.44 (CH). IR (ATR): ν_{max} 3248, 1717, 1683, 1599, 1568 cm^{-1}. MS *m/z* (%): 274 ([M+H]$^+$, 100). Anal. Calcd for $C_{15}H_{15}NO_4$: C 65.92, H 5.53, N 5.13, Found: C 65.25, H 5.24, N 5.05

4.3.4.2. 3-n-Butylamino-2-methoxycarbonyl-1,4-naphthoquinone **129b**



Yield: 75%, reddish brown crystals, m.p : 120.1-121.4°C ^{1}H NMR ($CDCl_3$) : 0.97 (3H, t, *J* = 7.2 Hz, H-4'), 1.46 (2H, q, *J* = 7.2, H-3'), 1.68 (2H, m, H-2'), 3.24 (2H, m, H-1'), 3.94 (3H, s, OCH_3), 6.33 (1H, broad s, NH), 7.64 (1H, m, H-6 or H-7), 7.76 (1H, m, H-6 or H-7), 8.03 (1H, m, H-5 or H-8), 8.13 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): To date, a decent ^{13}C NMR spectrum of this derivative could not be recorded even upon prolongation of the relaxation delay and increasing the number of recorded scans, δ 13.75 ($NCH_2CH_2CH_2\underline{C}H_3$), 20.10 ($NCH_2CH_2\underline{C}H_2CH_3$), 31.49 ($NCH_2\underline{C}H_2CH_2CH_3$), 42.90 ($N\underline{C}H_2CH_2CH_2CH_3$), 52.49 ($OCH_3$), 126.52 (CH), 126.70 (CH), 132.43 (CH), 135.44 (CH). IR (ATR): ν_{max} 3288, 1711, 1688, 1621, 1600, 1514 cm^{-1}. MS *m/z* (%): 288 ([M+H]$^+$, 100). Anal. Calcd for $C_{16}H_{17}NO_4$: C 66.89, H 5.96, N 4.88, Found: C 66.16, H 5.73, N 4.77

4.3.4.3. 2-Methoxycarbonyl-3-arylamino-1,4-naphthoquinone **129d**



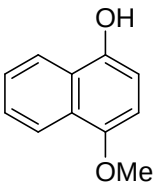
Yield 69%, red crystals, m.p : 166.0-166.9°C ^{1}H NMR ($CDCl_3$): δ 3.24 (3H, s, OCH_3), 7.19 (2H, d, *J* = 7.1 , H-1'), 7.25 (2H, m, H-2'), 7.40, (2H, m, H-3' and H-6 or H-7), 7.70 (1H, m, H-6 or H-7), 7.80 (1H, m, H-5 or H-8), 8.02 (1H, br s, NH), 8.45 (1H, m, H-5 or H-8). ^{13}C NMR ($CDCl_3$): δ 51.8 (OCH_3), 124.6 (2×CH), 126.7 (CH), 126.1 (CH), 127.1 (CH), 129.4 (2×CH), 129.7 (C_{quat}), 132.8 (CH), 132.9 (C_{quat}), 135.7 (CH), 137.2 (C_{quat}), 143.2 (C_{quat}), 165.1 (O=C-O), 180.47 (C=O), 182.04 (C=O). IR (ATR): ν_{max} 3298, 3061, 1722, 1676, 1633, 1607 cm^{-1}. MS *m/z* (%): 308 ([M+H]$^+$, 100). Anal. Calcd for $C_{18}H_{13}NO_4$: C 70.35, H 4.26, N 4.56. Found: C 69.92, H 3.72, N 4.50

4.4. Synthesis of 3-aryl-1-methyl-3-benzo[g]isoquinoline-5,10-diones 17

4.4.1. Syntheses of 4-methoxy-1-naphthol 156, 1-acetoxy-4-methoxynaphthalene 157 and 2-acetyl-4-methoxy-1-naphthol 158.

4.4.1.1. 4-Methoxy-1-naphthol **156**[136]

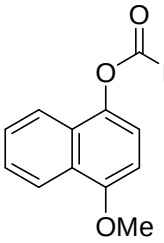
To a solution of 1,4-naphthoquinone **152** (15.8 g, 0.1 mol) in methanol (200 ml) was added dropwise a solution of $SnCl_2$ (0.35 mol) in 12 M HCl (70 ml) at room temperature over a period of 30 minutes. The solution was boiled for 3 hours and cooled to room temperature. Then, methanol was reduced *in vacuo* to about 1/5 of the starting volume. Then, the residue was poured in cold water to give a precipitate which was dissolved in dichloromethane. The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to give pure 4-methoxy-1-naphthol **156** (12,5 g, 72%) after column chromatography using ethyl acetate-hexane (1/9). All spectra data were in accordance with the literature.[136]



^{1}H NMR ($CDCl_3$): δ 3.92 (3H, s, OCH_3), 6.61 (1H, d, *J* = 8.1 Hz, H-3), 6.70 (1H, d, *J* = 8.1 Hz, H-2), 7.47-7.52 (2H, m, H-6 and H-7), 8.08-8.13 (1H, m, H-5), 8.19-8.22 (1H, m, H-8).

4.4.1.2. 1-Acetoxy-4-methoxynaphthalene **157**[136]

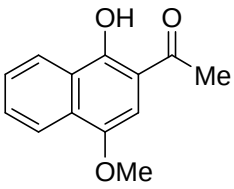
A mixture of 4-methoxy-1-naphthol **156** (4.5 g, 25.8 mmol), pyridine (21.0 ml, 258 mmol) and acetic anhydride (25.0 ml, 258 mmol) was stirred at room temperature overnight. After addition of 150 ml of water, the mixture was extracted with 3×100 ml of ethyl acetate. The combined organic extracts were successively washed with 120 ml of aqueous HCl 2M, 120 ml of water and 149 ml of brine. The organic phase was dried over magnesium sulfate, filtered and evaporated *in vacuo* to furnished 1-acetoxy-4-methoxynaphthalene **157** (5.52 g, 99%). All spectra data were in accordance with the literature.[136]



^{1}H NMR ($CDCl_3$): δ 2.45 (3H, s, $COCH_3$), 3.99 (3H, s, OCH_3), 6.78 (1H, d, *J* = 8.5 Hz, H-3), 7.14 (1H, d, *J* = 8.5 Hz, H-2), 7.52 (2H, m, H-5 and H-6), 7.78 (1H, d, *J* = 7.1 Hz, H-6 or H-7), 8.27 (1H, d, *J* = 7.1 Hz, H-6 or H-7).

4.4.1.3. 2-Acetyl-4-methoxy-1-naphthol **158**[136]

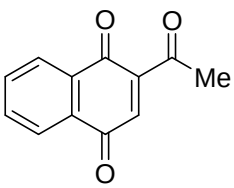
A solution of 1-acetoxy-4-methoxynaphthalene **157** (5.0 g, 23.1 mmol) in 5 ml of diethyl ether was heated at 120 °C, after which 5 ml of $BF_3{\cdot}OEt_2$ was added by a syringe and to afford after 5 minutes greenish-orange solid. The solid was decomposed by cautious addition of 100 ml. The aqueous layer was extracted with 3×100 ml of ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium(II) sulfate and filtered. The solvent was evaporated *in vacuum* to give pure 2-acetyl-4-methoxy-1-naphthol **151** (4.90 g, 98%). All spectra data were in accordance with the literature.[136]



^{1}H NMR ($CDCl_3$): δ 2.83 (3H, s, $COCH_3$), 3.99 (3H, s, OCH_3), 6.52 (1H, s, H-3), 7.67 (1H, d, *J* = 7.1 Hz, H-5 or H-6), 7.84 (1H, t, *J* = 7.1 Hz, H-5 or H-6), 8.11 (1H, d, *J* = 7.1 Hz, H-6 or H-7), 8.19 (1H, d, *J* = 7.1 Hz, H-6 or H-7).

4.4.2. Synthesis of 2-acetyl-1,4-naphthoquinone 19b

A solution of CAN (14.0 g, 26.3 mmol) in water (50 ml) was added to a stirred solution of 2-acetyl-4-methoxy-1-naphthol **158** (2.5 g, 11.6 mmol) in acetonitrile (149 ml). After 5 minutes, the reaction mixture was poured in a solution of 100 ml of ethyl acetate and 50 ml of water prepared beforehand. The aqueous layer was separated from the organic phase and extracted with 2×100 ml of ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give a red solid. Recrystallization using a mixture of diethyl ether-hexane afforded 2-acetyl-1,4-naphthoquinone **19b** (69%) as red crystals.



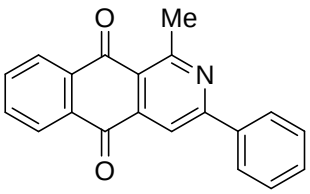
^{1}H NMR ($CDCl_3$): δ 2.67 (3H, s, $COCH_3$), 7.17 (1H, s, H-3), 7.75-7.86 (2H, m, H-6 and H-7), 8.05-8.17 (2H, m, H-5 and H-8).

4.3.3. Synthesis of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones 17

General procedure: 2-Acetyl-1,4-naphthoquinone **19a** (0.35 g, 1.75 mmol) and phenacylpyridinium bromide **20** (1.83 mmol) were added to a previously prepared 5 wt% solution of ammonium acetate in

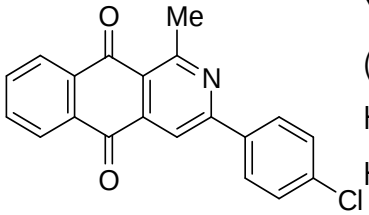
methanol (6 ml). The sealed reaction vessel was introduced in a CEM Discover® microwave apparatus (ramp time 6 min, p_{max} 10.0 psi). After 6 min at 90°C, the reaction mixture was cooled to room temperature and then in ice water, after which the reaction mixture was filtered. The solid was washed with 20 ml of cold methanol and dried *in vacuo* to yield 3-aryl-1-methoxybenz[*g*]isoquinoline-5,10-diones **17**.

4.4.3.1. 1-Methyl-3-phenylbenzo[g]isoquinoline-5,10-dione **17a**



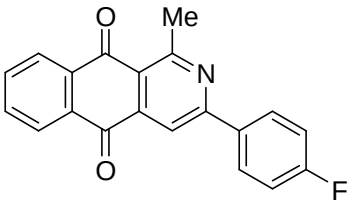
Yield: 52%, brown solid, m.p.: 190.3-191.7°C. ^{1}H NMR ($CDCl_3$): δ 3.17 (3H, s, CH_3), 7.47-7.56 (3H, m, H-3', H-4' and H-5'), 7.80 (1H, t, *J* = 7.4 Hz, H-6 or H-7), 7.86 (1H, t, *J* = 7.4 Hz, H-7 or H-8), 8.33 (2H, dd, *J* = 4.9 and 1.7 Hz, H-2'), 8.29 (2H, dd, *J* = 7.4 and 1.7 Hz, H-6 and H-9), 8.45 (1H, s, H-4). ^{13}C NMR ($CDCl_3$): δ 26.93 (CH_3), 114.34 (CH), 123.15 (C_{quat}), 126.98 (CH), 127.51 (CH), 127.65 (2×CH), 129.09 (2×CH), 130.66 (CH), 132.57 (C_{quat}), 133.90 (CH), 134.55 (C_{quat}), 135.10 (CH), 137.76 (C_{quat}), 141.12 (C_{quat}), 160.74 (C_{quat}), 162.19 (C_{quat}), 183.36 (C_{quat}), 183.78 (C_{quat}). IR (ATR): ν_{max} 3070, 2362, 1677, 1664, 1573, 1375, 1329, 1278, 1243, 1158, 880, 735, 711, 684 cm^{-1}. MS *m/z* (%): 300 ([M+H]$^+$, 100).

4.4.3.2. 3-(4-Chlorophenyl)-1-methylbenzo[g]isoquinoline-5,10-dione **17b**



Yield: 67%, brown solid, m.p.: 223.8-225.4°C. ^{1}H NMR ($CDCl_3$): δ 3.16 (3H, s, CH_3), 7.51 (2H, d, *J* = 8.5 Hz, H-3' and H-5'), 7.80 (1H, t, *J* = 7.4 Hz, H-6 or H-7), 7.86 (1H, t, *J* = 7.42 Hz, H-7 or H-8), 8.19 (2H, d, *J* = 8.5 Hz, H-2'), 8.30 (2H, dd, *J* = 7.4 and 1.7 Hz, H-6 and H-9), 8.42 (1H, s, H-4). ^{13}C NMR ($CDCl_3$): δ 26.88 (CH_3), 114.09 (CH), 123.22 (C_{quat}), 127.02 (CH), 127.57 (CH), 128.92 (2×CH), 129.31 (2×CH), 132.52 (C_{quat}), 133.97 (CH), 134.54 (C_{quat}), 135.19 (CH), 136.15 (C_{quat}), 136.97 (C_{quat}), 141.25 (C_{quat}), 159.39 (C_{quat}), 162.30 (C_{quat}), 183.25 (C_{quat}), 183.68 (C_{quat}). IR (ATR): ν_{max} 3069, 1670, 1661, 1570, 1408, 1370, 1329, 1279, 1092, 845, 706 cm^{-1}. MS *m/z* (%): 334 ([M+H]$^+$, 100).

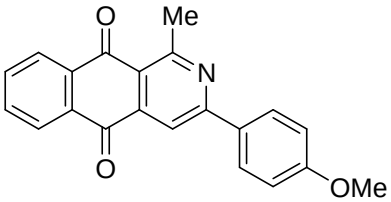
4.4.3.3. 3-(4-Fluorophenyl)-1-methylbenzo[g]isoquinoline-5,10-dione **17i**



Yield: 51%, brown solid, m.p.: 203.0-204.6°C. ^{1}H NMR ($CDCl_3$): δ 3.13 (3H, s, CH_3), 7.20 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.78 (1H, t, *J* = 7.0 Hz, H-6 or H-7), 7.84 (1H, t, *J* = 7.0 Hz, H-7 or H-8), 8.20 (2H, d, *J* = 8.8 Hz, H-2' and H-5'), 8.23-8.30 (2H, m, H-6 and H-9), 8.36 (1H, s, H-4). ^{13}C NMR ($CDCl_3$): δ 26.86 (CH_3), 113.86 (CH), 115.96 (CH), 116.25 (CH), 122.95 (C_{quat}), 126.96 (CH), 127.51 (CH), 129.60 (CH), 129.71 (CH), 132.47 (C_{quat}), 133.90 (CH), 134.49 (C_{quat}), 135.12 (CH), 141.15 (C_{quat}), 159.47 (C_{quat}), 162.22 (C_{quat}), 162.81 (C_{quat}), 166.14 (C_{quat}), 183.23 (C_{quat}), 183.62 (C_{quat}).

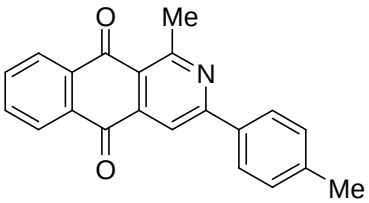
IR (ATR): ν_{max} 3079, 1671, 1662, 1506, 1414, 1370, 1373, 1332, 1275, 1192, 1155, 1017, 843, 748, 710 cm^{-1}. MS *m/z* (%): 318 ($[M+H]^+$, 100).

4.4.3.4. 3-(4-Methoxyphenyl)-1-methylbenzo[g]isoquinoline-5,10-dione **17j**



Yield: 47%, brown solid, m.p.: 192.8-193.5°C. ^{1}H NMR ($CDCl_3$): δ 3.13 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 7.02 (2H, d, *J* = 7.8 Hz, H-3' and H-5'), 7.82 (1H, t, *J* = 7.4 Hz, H-6 or H-7), 7.84 (1H, t, *J* = 7.4 Hz, H-6 or H-7), 8.21 (2H, d, *J* = 7.8 Hz, H-2'and H-5'), 8.27 (2H, dd, *J* = 7.4 and 1.7 Hz, H-6 and H-9), 8.36 (1H, s, H-4). ^{13}C NMR ($CDCl_3$): δ 26.94 (CH_3), 55.54 (OCH_3), 113.39 (CH), 114.46 (2×CH), 126.92 (CH) 127.48 (CH), 129.24 (2×CH), 130.36 (C_{quart}), 131.57(C_{quat}), 132.61 (C_{quat}), 133.74 (CH), 134.66 (C_{quat}), 135.03 (CH), 141.02 (C_{quat}), 160.30 (C_{quat}), 161.91 (C_{quat}), 162.14 (C_{quat}), 183.53 (C_{quat}), 183.65 (C_{quat}). IR (ATR): ν_{max} 2926, 1672, 1663, 1573, 1514, 1375, 1375, 1333, 1278, 1261, 1175, 1030, 842, 713 cm^{-1}. MS *m/z* (%): 330 ($[M+H]^+$, 100).

4.4.3.5. 1-Methyl-3-(4-methylphenyl)benzo[g]isoquinoline-5,10-dione **17k**

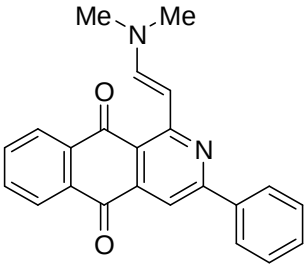


Yield: 48%, brown solid, m.p.: 203.4-204.7°C. ^{1}H NMR ($CDCl_3$): δ 2.44 (3H, s, CH_3), 3.16 (3H, s, CH_3), 7.33 (2H, d, *J* = 8.3 Hz, H-3' and H-5'), 7.82 (1H, t, *J* = 7.4 Hz, H-7 or H-8), 7.86 (1H, t, *J* = 7.4 Hz, H-7 or H-8), 7.99 (1H, s, H-4), 8.15 (2H, d, *J* = 8.3 Hz, H-2'), 8.31 (2H, dd, *J* = 7.4 and 1.7 Hz, H-6 and H-7), 8.45 (1H, s, H-4). ^{13}C NMR ($CDCl_3$): δ 21.55 (CH_3), 26.93 (CH_3), 113.96 (CH), 122.90 (C_{quat}), 126.96 (CH), 127.51 (CH), 127.57 (2×CH), 129.24 (2×CH), 129.24 (C_{quart}), 132.63 (C_{quat}), 133.82 (CH), 134.64 (C_{quat}), 135.06 (CH), 135.06 (C_{quat}), 141.09 (C_{quat}), 160.77 (C_{quat}), 162.16 (C_{quat}), 183.49 (C=O), 183.76 (C=O). IR (ATR): ν_{max} 2925, 2358, 1671, 1662, 1570, 1511, 1374, 1332, 1274, 1261, 1155, 1018, 882, 844, 708 cm.$^{-1}$ MS *m/z* (%): 314 ($[M+H]^+$, 100).

4.4.4. Synthesis of 1-[2-(dimethylamino)vinyl]-3-phenylbenzo[*g*]isoquinoline-5,10-diones 21

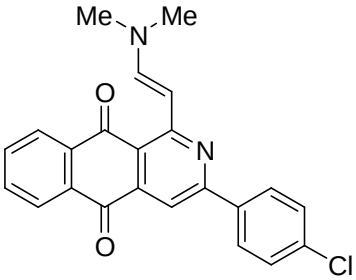
General procedure: To a solution of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **17** (250 mg) in DMF (5 ml), 5-10 equivalents of DMF-DMA were added under a nitrogen atmosphere and the reaction mixture was heated for 4-20 hours in an oil bath at 125°C. The reaction was monitored up by thin layer chromatography and after completion; the reaction mixture was cooled down to room temperature and poured in 30 ml of water, and extraction was performed with 3×40 ml of CH_2Cl_2. The organic layers were combined and washed several times with brine, dried over $MgSO_4$, then concentrated under high vacuum. 3-Aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **21** were obtained in high purity.

4.4.4.1. 1-[2-(Dimethylamino)vinyl]-3-phenylbenzo[g]isoquinoline-5,10-dione **21a**



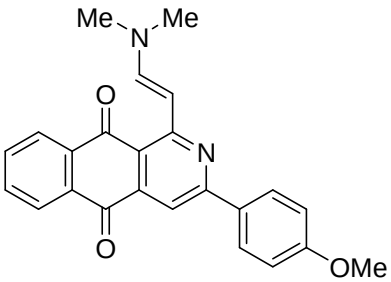
Yield: 52%, black solid, m.p.: 215.3-216.9°C. ^{1}H NMR ($CDCl_3$): δ 3.12 (6H, s, $N(CH_3)_2$), 7.24 (1H, d, *J* = 12.0 Hz, C<u>H</u>=CH-$N(CH_3)_2$), 7.45-7.55 (3H, m, H-3', H-4' and H-5'), 7.71 (1H, t, *J* = 7.5 Hz, H-7 or H-8), 7.81 (1H, t, *J* = 7.5 Hz, H-7 or H-8), 8.03 (1H, s, H-4), 8.17 (2H, d, *J* = 9.0 Hz, H-2' and H-5'), 8.23 (1H, d, *J* = 6.0 Hz, H-6 or H-9), 8.30 (1H, d, *J* = 6.0 Hz, H-6 or H-9), 8.41 (1H, d, *J* = 12.0 Hz, CH=C<u>H</u>-$N(CH_3)_2$).^{13}C NMR ($CDCl_3$): δ 95.43 (CH), 109.97 (CH), 115.31 (C_{quat}), 126.52 (CH), 127.25 (CH), 127.51 (2×CH), 128.78 (2×CH), 130.14 (CH), 132.46 (C_{quat}), 132.83 (CH), 134.72 (CH), 135.48 (C_{quat}), 138.84 (C_{quat}), 141.96 (C_{quat}), 151.12 (CH), 160.20 (C_{quat}), 183.55 (C=O), 184.40 (C=O). IR (ATR): ν_{max} 2907, 1667, 1602, 1557, 1531, 1492, 1425, 1360, 1304, 1240, 1090, 1061, 964, 907, 859 cm^{-1}. MS *m/z* (%): 355 ($[M+H]^+$, 100).

4.4.4.2. 3-(4-Chlorophenyl)-1-[2-(dimethylamino)viny]lbenzo[g]isoquinoline-5,10-dione **21b**



Yield: 77%, black solid, m.p.: 248.9-251.0°C. ^{1}H NMR ($CDCl_3$): δ 3.12 (6H, s, $N(CH_3)_2$), 7.22 (1H, d, *J* = 12.0 Hz, C<u>H</u>=CH-$N(CH_3)_2$), 7.48 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 7.72 (1H, t, *J* = 7.5 Hz, H-7 or H-8), 7.81 (1H, t, *J* = 7.5 Hz, H-7 or H-8), 7.97 (1H, s, H-4), 8.10 (2H, d, *J* = 9.0 Hz, H-2' and H-5'), 8.23 (1H, d, *J* = 6.0 Hz, H-6 or H-9), 8.30 (1H, d, *J* = 6.0 Hz, H-6 or H-9), 8.40 (1H, d, *J* = 12.0 Hz, CH=C<u>H</u>-$N(CH_3)_2$).^{13}C NMR ($CDCl_3$): δ 95.31 (CH), 109.59 (CH), 115.45 (C_{quat}), 126.55 (CH), 127.28 (CH), 128.78 (2×CH), 128.99 (2×CH), 132.38 (C_{quat}), 132.90 (CH), 134.80 (CH), 135.44 (C_{quat}), 136.34 (C_{quat}), 137.25 (C_{quat}), 142.06 (C_{quat}), 151.12 (CH), 158.89 (C_{quat}), 160.19 (C_{quat}), 183.47 (C=O), 184.26 (C=O). IR (ATR): ν_{max} 2907, 1667, 1602, 1557, 1531, 1492, 1425, 1360, 1304, 1240, 1090, 1061, 964, 907, 859 $cm.^{-1}$ MS *m/z* (%): 389 ($[M+H]^+$, 100).

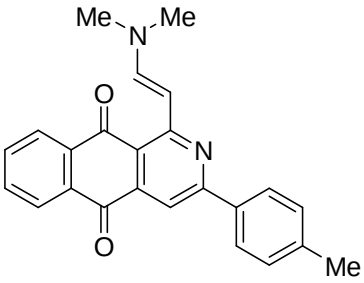
4.4.4.3. 1-[2-(Dimethylamino)vinyl]-3-(4-methoxyphenyl)benzo[g]isoquinoline-5,10-dione **21j**



Yield: 23%, black solid, m.p.: 233.3-235.9°C. ^{1}H NMR ($CDCl_3$): δ 3.12 (6H, s, CH_3), 3.89 (3H, s, OCH_3), 7.01 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 7.22 (1H, d, *J* = 12.3 Hz, C<u>H</u>=CH$N(CH_3)_2$), 7.71 (1H, t, *J* = 7.8 Hz, H-7 or H-8), 7.80 (1H, t, *J* = 7.8 Hz, H-7 or H-8), 8.06 (1H, s, H-4), 8.15 (2H, d, *J* = 8.7 Hz, H-2' and H-5'), 8.22 (1H, d, *J* = 7.8 Hz, H-6 or H-9), 8.30 (1H, d, *J* = 7.80 Hz, H-6 or H-9), 8.43 (1H, d, *J* = 12.3 Hz, C<u>H</u>=CH$N(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 29.80 ($N(CH_3)_2$), 55.51 (OCH_3), 95.50 (CH), 109.36 (CH), 114.14 (2×CH), 114.80 (C_{quat}), 126.48 (CH) 127.22 (CH), 129.05 (2×CH), 131.39 (C_{quart}), 132.45 (C_{quat}), 132.74

(CH), 134.69 (CH), 135.54 (C_{quat}), 141.77 (C_{quat}), 150.95 (CH), 159.65 (C_{quat}), 160.07 (C_{quat}), 161.50 (C_{quat}), 183.35 (C=O), 184.52 (C=O). IR (ATR): ν_{max} 2923, 1669, 1636, 1599, 1527, 1428, 1361, 1302, 1236, 1174, 1103, 1015, 834, 709 cm^{-1}. MS *m/z* (%): 385 ($[M+H]^+$, 100).

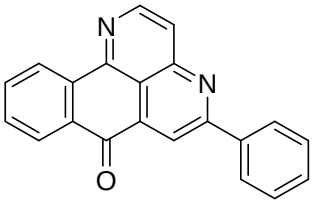
4.4.4.4. 1-[2-(Dimethylamino)vinyl]-3-(4-methylphenyl)benzo[g]isoquinoline-5,10-dione **21k**



Yield: 39%, black solid, m.p.: 228.6-229.5°C. ^{1}H NMR ($CDCl_3$): δ 2.43 (3H, s, CH_3), 3.11 (6H, s, $N(CH_3)_2$), 7.22 (1H, d, *J* = 12.6 Hz, C<u>H</u>=CHN$(CH_3)_2$), 7.33 (2H, d, *J* = 8.2 Hz, H-3' and H-5'), 7.78 (1H, t, *J* = 7.4 Hz, H-7 or H-8), 7.80 (1H, t, *J* = 7.4 Hz, H-7 or H-8), 7.99 (1H, s, H-4), 8.07 (2H, d, *J* = 8.2 Hz, H-2'), 8.21 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.29 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.39 (1H, d, *J* = 12.6 Hz, CH=C<u>H</u>N$(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 21.54 (CH_3), 95.46 (CH), 109.77 (CH), 115.09 (C_{quat}), 126.49 (CH), 127.24 (CH), 127.43 (2×CH), 127.43 (C_{quart}), 129.53 (2×CH), 132.46 (C_{quat}), 132.78 (CH), 134.69 (CH), 135.52 (C_{quat}), 136.05 (C_{quat}), 140.43 (C_{quat}), 141.84 (C_{quat}), 151.06 (CH), 160.10 (C_{quat}), 183.46 (C=O), 183.76 (C=O). IR (ATR): ν_{max} 2924, 1667, 1606, 1560, 1535, 1507, 1361, 1302, 1269, 1242, 1102, 806, 844, 709 cm^{-1}. MS *m/z* (%): 391 ($[M+Na]^+$, 100).

4.4.5. Synthesis of 5-phenyl-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one 22

1-[2-(Dimethylamino)vinyl]-3-phenylbenzo[*g*]isoquinoline-5,10-dione **21a** (45 mg, 0.127 mmol) was mixed with 10 ml of a 5 %(w/v) solution of ammonium acetate in methanol and then refux for 4 hours. After completion of the reaction, the reaction mixture was cooled at room temperature and diluted with dichloromethane (15 ml). Then, the reaction mixture was washed with saturated sodium bicarbonate solution (25 ml) and brine (3×25 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by preparative TLC using dichloromethane as eluent to afford 5-phenyl-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one **22** (35 mg, 89 % yield).



Yellow solid, m.p.: 222.0-223.3°C. ^{1}H NMR ($CDCl_3$): δ 7.54-7.62 (3H, m, H-3', H-4' and H-5'), 7.68 (1H, t, *J* = 7.4 Hz, H-9 or H-10), 7.87 (1H, t, *J* = 7.4 Hz, H-9 or H-10), 8.02 (1H, d, *J* = 5.9 Hz, H-3), 8.32 (2H, dd, *J* = 7.7 and 1.7 Hz, H-2' and H-6'), 8.41 (1H, d, *J* = 7.9 Hz, H-11), 8.81 (1H, s, H-6), 8.87 (1H, d, *J* = 7.9 Hz, H-8), 8.95 (1H, d, 5.9 Hz, H-2). ^{13}C NMR ($CDCl_3$): δ 116.72 (C_{quat}), 118.66 (CH), 122.31 (CH), 125.50 (CH), 128.06 (C_{quat}), 128.06 (2×CH), 129.27 (2×CH), 130.84 (CH), 131.01 (CH), 131.93 (C_{quat}), 135.19 (CH),135.38 (C_{quat}), 136.48 (C_{quat}), 138.19 (C_{quat}), 148.06 (CH), 149.91 (C_{quat}), 151.00 (C_{quat}), 162.80 (C_{quat}), 183.55 (C=O). IR (ATR): ν_{max} 3054, 1670, 1592, 1448, 1380, 1367, 1340, 1243, 1233, 1027, 756, 697 cm^{-1}. MS: *m/z* (%) 309 ($[M+H]^+$, 100).

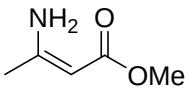
4.5. Efforts towards the synthesis methyl 3-aryl-1-hydroxybenzo[g]isoquinoline-5,10-diones-4-carboxylate 18

4.5.1. Synthesis of enaminoesters 23

The enaminoesters **23** were prepared according to the literature procedure.[125]

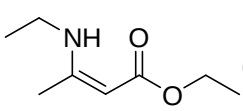
General procedure: To a solution of the corresponding alkyl β-ketoesters (5 g) in toluene (100 ml) and acetic acid (2 ml), ammonium acetate or alkylammonium acetates (76.83 mmoles), prepared *in situ* from equimolecular amounts of alkylamine and acetic acid) was added. The mixture was boiled under reflux using a Dean-Stark apparatus. After cooling the mixture is washed with water (100 ml) and saturated sodium bicarbonate solution (2×100 ml), brine, dried over magnesium sulfate and evaporated *in vacuo* to give pure enaminoesters **23**.

4.5.1.1. Methyl 3-aminobut-2-enoate **23a**[137]



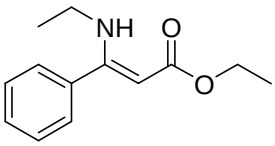
^{1}H NMR ($CDCl_3$): δ 1.95 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 4.53 (1H, s, H-2), 7.9 (1H, br s, N-H).

4.5.1.2. Methyl 3-(N-ethylamino)but-2-enoate **23d**[137]



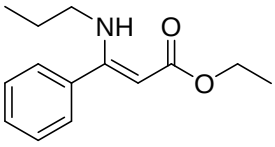
^{1}H NMR ($CDCl_3$): δ 1.16 (3H, t, *J* = 6.6 Hz, $NCH_2C\underline{H}_3$), 1.23 (3H, t, *J* = 6.8 Hz, $OCH_2C\underline{H}_3$), 1.96 (3H, s, H-4), 3.25 (2H, quintet, *J* = 6.6 Hz, $NC\underline{H}_2CH_3$), 4.13 (2H, q, *J* = 6.8 Hz, $OC\underline{H}_2CH_3$), 4.43 (1H, s, H-2), 8.48 (1H, br s, NH).

4.5.1.3. Ethyl 3-(N-ethylamino)-3-phenylprop-2-enoate **23g**[138]



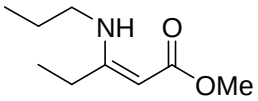
^{1}H NMR ($CDCl_3$): δ 1.12 (3H, t, *J* = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.28 (3H, t, *J* = 6.9 Hz, $OCH_2C\underline{H}_3$), 3.09 (2H, quintet, *J* = 6.9 Hz, $NC\underline{H}_2CH_3$), 4.14 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.57 (1H, s, H-2), 7.34-7.49 (5H, m, C_6H_5), 8.49 (1H, br s, N-H).

4.5.1.4. Ethyl 3-(N-n-propylamino)-3-phenylprop-2-enoate **23h**[139]



^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, *J* = 7.1 Hz, $NCH_2CH_2C\underline{H}_3$), 1.30 (3H, t, *J* = 6.9 Hz, $OCH_2C\underline{H}_3$), 1.53 (2H, sextet, *J* = 7.1 Hz, $NCH_2C\underline{H}_2CH_3$), 3.05 (2H, quintet, *J* = 6.9 Hz, $NC\underline{H}_2CH_2CH_3$), 4.12 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.58 (1H, s, H-2), 7.30-7.46 (5H, m, C_6H_5), 8.57 (1H, br s, N-H).

4.5.1.5. Methyl 3-(N-n-propylamino)pent-2-enoate **23j**

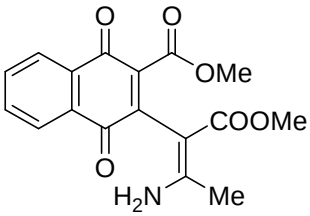


^{1}H NMR ($CDCl_3$): δ 0.94 (3H, t, *J* = 6.6 Hz, $NCH_2CH_2C\underline{H}_3$), 1.16 (3H, t, *J* = 6.8 Hz, $CH_2C\underline{H}_3$), 1.67 (2H, sextet, *J* = 6.6 Hz, $NCH_2C\underline{H}_2CH_3$), 2.24 (2H, q, *J* = 6.8 Hz,

$C\underline{H}_2CH_3$), 3.18 (2H, q, *J* = 6.6 Hz, $NC\underline{H}_2CH_2CH_3$), 3.63 (3H, s, OCH_3), 4.53 (1H, s, H-2), 8.58 (1H, br s, NH).

4.5.2. Synthesis of 2-methoxycarbonyl-3-[1-(methoxycarbonyl)-2-aminoprop-1-enyl]-1,4-naphthoquinone 166a

To a solution of 2-methoxycarbonyl-1,4-naphthoquinone **19a** (2.4 mmol, 0.5 g) in toluene (20 ml) were added acetic acid (4 ml) and 1.05 equivalents of enaminoesters **23a**. The reaction mixture was subsequently heated at 80°C for 1 hour. After cooling to room temperature, the reaction mixture was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and the remaining aqueous phase was extracted with 3×20 ml of dichloromethane. The combined extracts were dried over magnesium(II) sulfate. Solvent evaporation in *vacuo* furnished a crude solid, which was purified by column chromatography. Compound **166a** (0.2 g, 25%) was obtained after crystallization from diethyl ether/hexane (8/2).

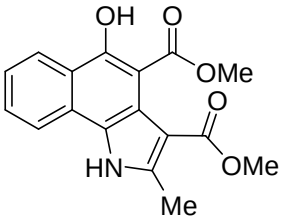


Yield: 25%, orange crystals, m.p.: 1172-118.4°C ^{1}H NMR ($CDCl_3$): δ 1.99 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 7.80 (2H, m, H-6 and H-7), 8.15 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$) : δ 20.18 (CH), 52.23 (CH), 52.97 (CH), 94.81 (C_{quat}), 126.72 (CH), 127.18 (CH), 131.67 (C_{quat}), 131.79 (C_{quat}), 134.43 (CH), 134.51 (CH), 140.67 (C_{quat}), 141.88 (C_{quat}), 164.28 (C_{quat}), 170.91 (C_{quat}), 175.62 (C_{quat}), 181.88 (O-C=O), 183.61 (O-C=O). IR (ATR) : ν_{max} 2970, 1742, 1662, 1594, 1570, 1440, 1374, 1330, 1276, 979, 843, 714 cm^{-1}. MS *m/z* (%): 330 ([M+H]$^+$, 100).

4.5.3. Synthesis of dimethyl 5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3,4-dicarboxylate 167a and methyl 2,3-dihydro-5-hydroxy-3-[1-(*iso*propylamino)ethylidene]-2-oxonaphtho[1,2-*b*]furan-4-carboxylate 169

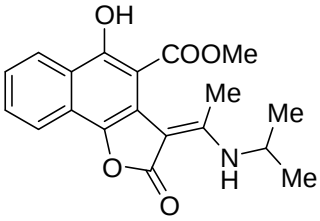
General procedure: To a solution of 2-methoxycarbonyl-1,4-naphthoquinone **19a** (2.4 mmol, 0.5 g) in toluene (16.7 ml) were added acetic acid (3.3 ml) and 1.05 equivalents of enaminoesters **23a,b**, respectively. The reaction mixture was subsequently boiled under reflux for 4-36 hours. After cooling to room temperature, the reaction mixture was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and the remaining aqueous phase was extracted with 3×20 ml of dichloromethane. The combined extracts were dried over magnesium(II) sulfate. Solvent evaporation in *vacuo* furnished a crude solid, which was recrystallized from methanol.

4.5.3.1. Dimethyl 5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3,4-dicarboxylate 167a



Yield: 39-48%, brown solid, m.p : 148.0-148.9°C ^{1}H NMR ($CDCl_3$): δ 2.59 (3H, s, H-1'), 3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.48 (1H, m, H-7 and H-8), 7.64 (1H, m, H-7 and H-8), 7.83 (1H, m, H-6 or H-9), 8.44 (1H, m, H-6 or H-9), 8.89 (1H, s, NH), 11.19 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 13.55 (CH_3), 51.52 (OCH_3), 52.09 (OCH_3), 101.08 (C_{quat}), 109.50 (CH), 117.99 (C_{quat}), 119.04 (CH), 122.22 (C_{quat}), 124.01 (C_{quat}), 124.35 (CH), 125.46 (CH), 129.48(CH), 138.00 (C_{quat}), 156.14 (C_{quat}), 167.47 (O=C-O), 171.56 (O=C-O). IR (ATR): ν_{max} 3248, 1693, 1664, 1633 cm^{-1}. MS *m/z* (%): 282(100), 314 ([M+H]$^+$, 13).

4.5.3.2. Methyl 2,3-dihydro-5-hydroxy-3-[1-(*iso*propylamino)ethylidene]-2-oxonaphtho[1,2-*b*]furan-4-carboxylate 169



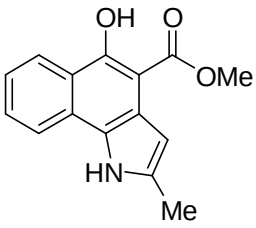
Yield: 31%, green crystals, m.p: 157.5-158.1°C ^{1}H NMR ($CDCl_3$): δ 1.36 (6H, d, *J* = 6.6 Hz, 2×CH_3), 2.17 (3H, s, CH_3), 3.89 (1H, sept, *J* = 6.6 Hz, C<u>H</u>(CH_3)$_2$, 3.91 (3H, s, OCH_3), 7.36 (1H, m, H-7 or H-8), 7.57 (1H, m, H-7 or H-8), 7.94 (1H, m, H-6 or H-9), 8.28 (1H, m, H-6 or H-9), 9.57 (1H, br d, *J* = 8.3 Hz, NH), 11.05 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 17.81 (CH_3), 23.60 (2×CH_3), 45.74 (CH), 52.16 (OCH_3), 92.56 (C_{quat}), 100.82 (C_{quat}), 117.44 (C_{quat}), 120.03 (CH), 121.22 (C_{quat}), 123.48 (C_{quat}), 124.23 (CH), 124.52 (CH), 129.89 (CH), 136.80 (C_{quat}), 156.42 (C_{quat}), 162.02 (C_{quat}), 170.52 (O=C-O), 171.16 (O=C-O). IR (ATR) ν_{max}: 1638, 1685, 1582 cm^{-1}. MS *m/z* (%): 342 ([M+H]$^+$, 100).

4.5.4. Methyl 5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-4-carboxylate 168

<u>*Procedure A*</u>*:* To a solution of 2-methoxycarbonyl-1,4-naphthoquinone **19a** (2.4 mmol, 0.5 g) in toluene (20 ml) were sulfuric acid (3 drops) and enaminoesters **23a** (0.29 g, 2,5 mmol). The reaction mixture was subsequently boiled under reflux for 4 hours. After cooling to room temperature, the reaction mixture was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and the remaining aqueous phase was extracted with 3×20 ml of dichloromethane. The combined extracts were dried over magnesium(II) sulfate. Solvent evaporation in *vacuo* furnished a crude solid, which was recrystallized from methanol to give methyl 5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-4-carboxylate **168** (0.42 g, 68% yield).

<u>*Procedure B*</u>*:* To a solution of dimethyl 5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-3,4-dicarboxylate **167a** (200 mg, 0.64 mmol) in toluene (10 ml) were sulfuric acid (1 drop). The reaction mixture was subsequently boiled under reflux for 4 hours. After cooling to room temperature, the reaction mixture was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated

and the remaining aqueous phase was extracted with 3×10 ml of dichloromethane. The combined extracts were dried over magnesium(II) sulfate. Solvent evaporation in *vacuo* furnished a crude solid, which was recrystallized from methanol to afford methyl 5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-4-carboxylate **168** (137 mg, 85% yield).

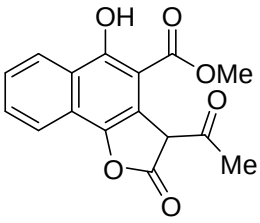


Brown crystals, m.p : 176.8-177.6°C ^{1}H NMR ($CDCl_3$): δ 2.52 (3H, s, H-1'), 4.08 (3H, s, OCH_3), 6.69 (1H, s, H-3), 7.40 (1H, m, H-7 and H-8), 7.61 (1H, m, H-7 and H-8), 7.80 (1H, m, H-6 or H-9), 8.46 (1H, m, H-6 or H-9), 8.50 (1H, s, NH), 12.25 (1H, s, OH).^{13}C NMR ($CDCl_3$): δ 13.87 (CH_3), 52.12 (OCH_3), 99.50 (C_{quat}), 104.02 (CH), 118.75 (C_{quat}), 120.50 (C_{quat}), 121.00 (C_{quat}), 123.31(CH), 124.00 (C_{quat}), 125.01 (C_{quat}), 125.59(CH), 129.41(CH), 133.53 (C_{quat}), 157.94 (C_{quat}), 173.13 (O=C-O). IR (ATR): ν_{max} 3420, 3250, 1694, 1663, 1633 cm^{-1}. MS *m/z* (%): 255 ([M+H]$^+$, 100).

4.5.5. Synthesis of methyl 3-acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates 177.

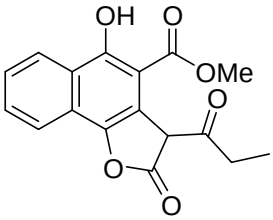
General procedure: To a solution of 2-methoxycarbonyl-1,4-naphthoquinone **19a** (2.4 mmol, 0.5 g) in toluene (16.7 ml) were added acetic acid (3.3 ml) and 1.05 equivalents of β-ketoesters **174a-e**, respectively. The reaction mixture was subsequently boiled under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and the remaining aqueous phase was extracted with 3×20 ml of dichloromethane. The combined extracts were dried over magnesium(II) sulfate. Solvent evaporation in *vacuo* furnished a crude solid, which was recrystallized from ethanol.

4.5.5.1. Methyl 3-acetyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-b]furan-4-carboxylate **177a**



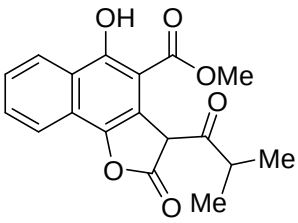
Yield: 54%, green crystals, m.p: 180.9-181.8°C. ^{1}H NMR ($CDCl_3$): δ 2.46 (3H, s, CH_3), 3.93 (3H, s, OCH_3), 5.17 (1H, s, H-3), 7.60-7.67 (1H, m, H-7 or H-8), 7.70-7.77 (1H, m, H-7 or H-8), 7.94 (1H, d, *J* = 8.3 Hz, H-6 or H-9), 8.46 (1H, d, *J* = 8.3 Hz , H-6 or H-9), 11.84 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 29.34 (CH_3), 52.49 (CH), 61.17 (OCH_3), 101.62 (C_{quat}), 114.26 (C_{quat}), 121.10 (CH), 123.51 (C_{quat}), 124.87 (CH), 125.56 (C_{quat}), 127.47 (CH), 130.86 (CH), 143.22 (C_{quat}), 159.07 (=C-O), 169.74 (O=C-O), 170.18 (O=C-O), 197.06 (C=O). IR (ATR) : ν_{max} 3099, 1806, 1721, 1667, 1644, 1600 cm^{-1}. MS *m/z* (%): 301 ([M+H]$^+$, 100). Anal. Calcd for $C_{16}H_{12}O_6$: C 64.00, H 4.03; found: C 63.83, H 3.98. HRMS (ESI) for $C_{16}H_{12}O_6$: 299.0634 [M-H]$^+$, found 299.0563.

4.5.5.2. Methyl 2,3-dihydro-5-hydroxy-3-(1-oxo-n-propyl)naphtho[1,2-b]furan-4-carboxylate **177b**



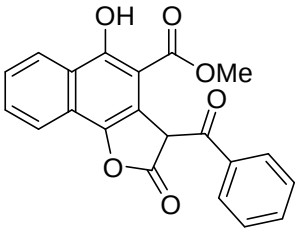
Yield: 46%, green crystals, m.p: 154.7-156.0°C. ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 2.65 (1H, q×d, *J* = 7.2, 8.9 Hz, $C\underline{H}_aH_bCH_3$'), 3.03 (1H, q×d, *J* = 7.2, 8.9 Hz, $CH_a\underline{H}_bCH_3$), 3.91 (3H, s, OCH_3), 5.17 (1H, s, H-3), 7.60-7.68 (1H, m, H-7 or H-8), 7.75-7.78 (1H, m, H-7 or H-8), 7.95 (1H, d, *J* = 8.3 Hz, H-6 or H-9), 8.47 (1H, d, *J* = 8.3 Hz, H-6 or H-9), 11.86 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 7.58 ($CH_2\underline{C}H_3$), 35.74 (CH_2), 52.42 (C-3), 60.53 (OCH_3), 101.60 (C_{quat}), 114.41 (C_{quat}), 121.10 (CH), 123.56 (C_{quat}), 124.89 (CH), 125.53 (C_{quat}), 127.40 (CH), 130.86 (CH), 143.28 (C_{quat}), 169.13 (=C-O), 170.76 (O=C-O), 170.48 (O=C-O), 199.85 (C=O). IR (ATR): ν_{max} 3078, 1804, 1745, 1724, 1660, 1646, 1546, 1598 cm^{-1}. MS *m/z* (%) : 313 ([M-H]$^+$, 100). Anal. Calcd for $C_{17}H_{14}O_6$: C 64.97, H 4.49; found: C 64.54, H 4.00. HRMS (ESI) for $C_{17}H_{14}O_6$: 313.0790 [M-H]$^+$, found 313.0715.

4.5.5.3. Methyl 2,3-dihydro-5-hydroxy-3-(1-oxoisobutyryl)naphtho[1,2-b]furan-4-carboxylate **177c**



Yield: 17%, green crystals, m.p: 178.6-179.4°C. ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, d, *J* = 6.6 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.25 (1H, d, *J* = 6.6 Hz, $CH(CH_3)(C\underline{H}_3)$), 3.20 (1H, sept, *J* = 6.6 Hz, $C\underline{H}(CH_3)_2$, 3.91 (3H, s, OCH_3), 5.30 (1H, s, H-3), 7.64-7.67 (1H, m, H-7 or H-8), 7.72-7.77 (1H, m, H-7 or H-8), 7.96 (1H, d, *J* = 8.3 Hz, H-6 or H-9), 8.48 (1H, d, *J* = 8.3 Hz, H-6 or H-9), 11.96 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 17.58 ($CH(\underline{C}H_3)(CH_3)$, 19.31 ($CH(CH_3)(\underline{C}H_3)$, 39.42 ($\underline{C}H(CH_3)_2$), 52.47 (C-3), 59.65 ($OCH_3$), 101.92 ($C_{quat}$), 114.37 ($C_{quat}$), 121.12 (CH), 123.51 ($C_{quat}$), 124.89 (CH), 125.53 ($C_{quat}$), 127.42 (CH), 130.82 (CH), 143.12 (C_{quat}), 159.13 (=C-O), 170.05 (O=C-O), 170.25 (O=C-O), 202.94 (C=O). IR (ATR): ν_{max} 3790, 2980, 2921 1798, 1716, 1660, 1598 cm^{-1}. MS *m/z* (%): 327 ([M-H]$^+$, 100). Anal. Calcd for $C_{18}H_{16}O_6$: C 65.85, H 4.91; found: C 65.60, H 4.26. HRMS (ESI) for $C_{18}H_{18}O_6$: 327.0947 [M-H]$^+$, found 327.0867.

4.5.5.4. Methyl 3-benzoyl-2,3-dihydro-5-hydroxy-2-oxo-naphtho[1,2-b]furan-4-carboxylate **177d**



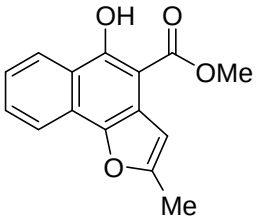
Yield: 44%, green crystals, m.p: 219.1-220.3°C. ^{1}H NMR ($CDCl_3$): δ 3.44 (3H, s, OCH_3), 6.11 (1H, s, H-3), 7.59-7.71 (3H, m, H-3', H-4' and H-5'), 7.72-7.77 (1H, m, H-7 or H-8), 7.77-7.99 (1H, m, H-7 or H-8), 8.00 (1H, d, *J* = 8.3 Hz, H-6 or H-9), 8.17-8.20 (2H, m, H-2' and H-6'), 8.50 (1H, d, *J* = 8.3 Hz, H-6 or H-9), 11.89 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 52.10 (C-3), 55.68 (OCH_3), 101.50 (C_{quat}), 115.56 (C_{quat}), 121.15 (CH), 123.62 (C_{quat}), 124.87 (CH), 125.54 (C_{quat}), 127.34 (CH), 129.18 (2×CH), 129.51 (2×CH), 130.83 (CH), 134.31 (CH), 135.77 (C_{quat}), 143.57 (C_{quat}), 159.23 (=C-O), 169.68 (O=C-O), 170.65 (O=C-O), 190.61 (C=O). IR (ATR): ν_{max} 3056, 1798, 1688, 1660, 1649, 1597

cm^{-1}. MS *m/z* (%): 361 ($[M-H]^+$, 100). Anal. Calcd for $C_{21}H_{14}O_6$: C 69.61, H 3.89; found: C 69.09, H 3.16. HRMS (ESI) for $C_{21}H_{14}O_6$: 361.0790 $[M-H]^+$, found 361.0695.

4.5.6. Synthesis of methyl 5-hydroxy-2-methylnaphtho[1,2-*b*]furan-4-carboxylate 178

To a 10 wt% solution of ammonium acetate (1.0 g) in acetic acid (10 ml) were added 2-methoxycarbonyl-1,4-naphthoquinone **11** (2.4 mmol, 0.50 g) and ethyl acetoacetate **174a** (2.5 mmol, 0.32 g), and the reaction mixture was subsequently boiled under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured in water. The organic phase was separated and the aqueous phase was extracted twice with 5 ml of dichloromethane. The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate and then dried over magnesium(II) sulfate. Solvent evaporation in *vacuo* furnished a mixture of three compounds. Purification by column chromatography on silica gel with hexane/ethyl acetate (9/1) gave methyl 5-hydroxy-2-methylnaphthofuran-4-carboxylate **178** (0.08 g, 13% yield), methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** (0.03 g, 6% yield) and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **129a** (0.23 g, 41% yield).

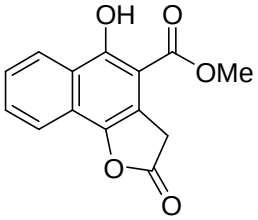
Methyl 5-hydroxy-2-methylnaphthofuran-4-carboxylate **178**



Yield: 13%, white crystals, m.p.:136.0-136.9°C. ^{1}H NMR ($CDCl_3$): δ 2.55 (3H, s, CH_3), 4.07 (3H, s, OCH_3), 6.82 (1H, s, H-3), 7.47 (1H, m, H-7 or H-8), 7.68 (1H, m, H-7 or H-8), 8.14 (1H, m, H-6 or H-9), 8.44 (1H, m, H-6 or H-9), 12.21 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 14.26 (CH_3), 52.28 (CH), 99.50 (C_{quat}), 119.52 (C_{quat}), 120.50 (C_{quat}), 122.20 (C_{quat}), 124.51 (CH), 124.51 (C_{quat}), 124.75 (C_{quat}), 125.59 (CH), 130.01 (CH), 155.09 (C_{quat}), 158.96 (C_{quat}), 175.05 (O=C-O). IR (ATR): ν_{max} 3027, 1638, 1600 cm^{-1}. MS *m/z* (%): 257 ($[M+H]^+$, 100). Anal. Calcd for $C_{15}H_{12}O_4$: C 70.31, H 4.72, found: C 71.00, H 5.15.

4.5.7. Synthesis of methyl 2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylate 180

To a solution of **177a** or **177d** (0.25 g) in toluene (10 ml) and acetic acid (2 ml) was added 12 equivalents of ammonium acetate, and the reaction mixture was heated under reflux for 4 hours. After cooling to room temperature, the reaction mixture was poured in water. The organic phase was separated and the aqueous phase was extracted with 3×8 ml of dichloromethane. The combined organic extracts were washed with a saturated solution of sodium bicarbonate, brine and dried over magnesium(II) sulfate. Solvent evaporation *in vacuo* furnished a solid, which was recrystallized from ethanol to furnish **180**.

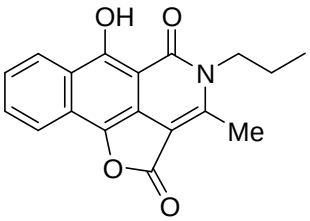


Yield: 53-91%, brown crystals, m.p.:172.5-173.3°C. ^{1}H NMR ($CDCl_3$): δ 4.03 (3H, s, OCH_3), 4.07 (2H, s, H-3), 7.60 (1H, dd, *J* = 7.9, 8.2 Hz, H-7), 7.73 (1H, dd, *J* = 7.9, 7.9 Hz, H-8), 7.96 (1H, *J* = 7.9 Hz, H-9), 8.45 (1H, d, *J* = 8.2 Hz, H-6), 11.93 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 36.80 (CH_2), 52.74 (CH), 101.97 (C_{quat}), 114.79 (C_{quat}), 120.91 (CH), 123.74 (C_{quat}), 124.75 (CH), 126.78(CH), 130.63 (CH), 142.80 (C_{quat}), 158.65 (C_{quat}), 170.80 (O=C-O), 174.87 (O=C-O). IR (ATR): ν_{max} 3566, 3118, 3028, 2958, 1788, 1670, 1644, 1599 cm^{-1}. MS *m/z* (%): 257 ([M-H]$^+$, 100). Anal. Calcd for $C_{15}H_{12}O_4$: C 65.12, H 3.90; found: C 64.70, H 2.62. HRMS (ESI) for $C_{15}H_{12}O_4$: 257.0528 [M-H]$^+$, found 257.0450.

4.5.8. Synthesis of 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-ones 170

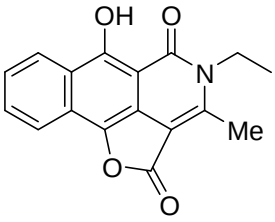
General procedure: To a solution 2-methoxycarbonyl-1,4-naphthoquinone **19a** (2.40 mmol, 0.50 g) in toluene (16.7 ml) were added acetic acid (3.3 ml) and 1.05 equivalents of the appropriate enaminoester **23a-h**, respectively. The reaction mixture was subsequently boiled under reflux for 4-48 hours. The reaction was followed to completion by TLC and LC-MS. After cooling to room temperature, *N*-ethyl-3-methylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-1-ones **170a**, **170d** and **170e** precipitated as yellow-orange solids from the reaction mixture. After filtration of the crystals, the filtrate was poured in a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and the aqueous phase was extracted with 3×20 ml of dichloromethane. The combined organic extracts were dried over magnesium(II) sulfate. Solvent evaporation *in vacuo* furnished crude solids, which were mixed with the isolated yellow-orange precipitate and were then recrystallized from ethanol.

4.5.8.1. 6-Hydroxy-3-methyl-4-n-propylbenzo[g]furo[4,3,2-de]isoquinoline-2,5(4H)-dione **170c**



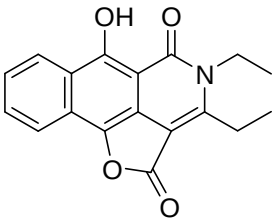
Yield: 19%, orange crystals, m.p.: 241.7-242.9°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.08 (3H, t, *J* = 7.1 Hz, $NCH_2CH_2\underline{C}H_3$), 1.85-1.75 (2H, m, $NCH_2\underline{C}H_2CH_3$), 2.86 (3H, s, CH_3), 4.10 (2H, t, *J* = 7.2 Hz, $NCH_2CH_2CH_3$), 7.49 (1H, ddd, *J* = 1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.68 (1H, ddd, *J* = 1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.98-8.01 (1H, dm, *J* = 8.8 Hz, H-6 or H-9), 8.42-8.45 (1H, m, H-6 or H-9), 10.26 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 11.43 (CH_3), 16.13 (CH_3), 22.84 ($NCH_2\underline{C}H_2CH_3$), 45.37 ($NCH_2$), 100.67 ($C_{quat}$), 101.94 ($C_{quat}$), 120.31 (CH), 120.63 ($C_{quat}$), 122.32 ($C_{quat}$), 122.86 ($C_{quat}$), 124.44 (CH), 124.67 (CH), 129.82 (CH), 134.13 (C_{quat}), 150.72 (C_{quat}), 153.16 (=C-O), 165.36 (O=C-N), 166.51 (O=C-O). IR (ATR): ν_{max} 3170, 1793, 1754, 1676, 1636, 1610, 1225 cm^{-1}. MS *m/z* (%): 310 ([M+H]$^+$, 100). Anal. Calcd for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53; found: C 68.89, H 4.30, N 4.36. HRMS (ESI) for $C_{18}H_{15}NO_4$ 308.1001 [M-H]$^+$, found 308.0930.

4.5.8.2. 4-Ethyl-6-hydroxy-3-methylbenzo[g]furo[4,3,2-de]isoquinoline-2,5(4H)-dione **170d**



Yield: 33%, orange crystals, m.p.: 243.1-244.6°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, t, *J* = 7.1 Hz, $NCH_2C\underline{H}_3$), 2.86 (3H, s, CH_3), 4.23 (2H, q, *J* = 7.1 Hz, $NC\underline{H}_2CH_3$), 7.49 (1H, ddd, *J* = 1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.68 (1H, ddd, *J* = 1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.98-8.02 (1H, dm, *J* = 8.8 Hz, H-6 or H-9), 8.27-8.46 (1H, m, H-6 or H-9), 10.23 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 14.27 (CH_3), 16.01 (CH_3), 38.96 (NCH_2), 101.97 (C_{quat}), 101.97 (C_{quat}), 120.32 (CH), 120.32 (C_{quat}), 122.18 (C_{quat}), 122.87 (C_{quat}), 124.46 (CH), 124.69 (CH), 129.84 (CH), 134.48 (C_{quat}), 150.56 (C_{quat}), 153.16 (=C-O), 165.21 (O=C-N), 167.09 (O=C-O). IR (ATR): ν_{max} 3170, 1793, 1754, 1676, 1636, 1610, 1225 cm^{-1}. MS *m/z* (%): 296 ([M+H]$^+$, 100). Anal. Calcd for $C_{17}H_{13}NO_4$: C 69.15, H 4.44, N 4.74; found: C 68.16, H 3.54, N 4.49. HRMS (ESI) for $C_{17}H_{13}NO_4$: 294.0845 [M-H]$^+$, found 294.0768.

4.5.8.3. *3,4-Diethyl-6-hydroxybenzo[g]furo[4,3,2-de]isoquinoline-2,5(4H)-dione* **170e**



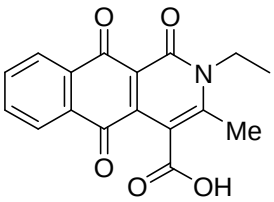
Yield: 47%, yellow crystals, m.p.: 200.7-201.6°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.49 (3H, t, *J* = 7.2 Hz, $NCH_2C\underline{H}_3$), 3.22 (2H, q, *J* = 7.2 Hz, $C\underline{H}_2CH_3$), 4.22 (2H, q, *J* = 7.2 Hz, $NC\underline{H}_2CH_3$), 7.46 (1H, ddd, *J* = 1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.65 (1H, ddd, *J* = 1.4, 7.0, 8.8 Hz, H-7 or H-8), 7.94-7.99 (1H, dm, *J* = 8.8 Hz, H-6 or H-9), 8.38-8.43 (1H, m, H-6 or H-9), 10.20 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 13.91 (CH_3), 14.90 (CH_3), 22.84 ($\underline{C}H_2CH_3$), 38.68 (NCH_2), 100.70 (C_{quat}), 100.90 (C_{quat}), 120.18 (CH), 120.76 (C_{quat}), 122.14 (C_{quat}), 122.72 (C_{quat}), 124.35 (CH), 124.58 (CH), 129.73 (CH), 134.37 (C_{quat}), 153.00 (C_{quat}), 156.38 (=C-O), 165.34 (O=C-N), 166.57 (O=C-O). IR (ATR): ν_{max} 3170, 1793, 1754, 1676, 1636, 1610, 1225 cm^{-1}. MS *m/z* (%): 310 ([M+H]$^+$, 100). Anal. Calcd for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53; found: C 69.39, H 4.47, N 4.40. HRMS (ESI) for $C_{18}H_{15}NO_4$ 308.1001 [M-H]$^+$, found 308.0920.

4.5.9. Synthesis of 2,3-dialkyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acids 187

General procedure 100 mg of 3,4-dialkyl-6-hydroxybenzo[*g*]furo[4,3,2-*de*]isoquinoline-2,5(4*H*)-ones **170d** (0.34 mmol) and **170e** (0.32 mmol) were added to a solution of 2 ml of 4 M NaOH, 1 ml of THF and 1 ml of MeOH. This reaction mixture was stirred for 1.5 hours in an oil bath at 50°C, and which then was allowed to cool down to room temperature. The reaction mixture was poured in 8 ml of 1 M HCl and extracted with 3×5 ml of chloroform. The combined organic extracts were washed with brine and concentrated under reduced pressure to afford compounds **187d** and **187e** (purity 81-83%). All attempts

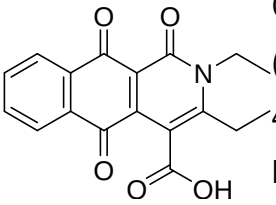
to purify the latter compounds by column chromatography and/or recrystallization techniques failed as it resulted in degradation of the products.

4.5.9.1. 2-Ethyl-3-methyl-1,2,5,10-tetrahydro--1,5,10-trioxobenzo[g]isoquinoline-4-carboxylic acid **187d**



Crude yield: 40%, brown powder, m.p.: 190.6-191.8°C. ^{1}H NMR (DMSO-d_6): δ 1.24-1.28 (3H, t, *J* = 7.1 Hz, $NCH_2\underline{C}H_3$), 2.51 (3H, s, CH_3), 4.12 (2H, q, *J* = 7.1 Hz, NCH_2CH_3), 7.82-7.987 (1H, dd, *J* = 6.3 and 7.1 Hz, H-7 or H-8), 7.90-7.95 (1H, dd, *J* = 6.6 and 7.1 Hz, H-7 or H-8), 8.02 (1H, d, *J* = 7.1 Hz, H-6 or H-9), 8.07 (1H, d, *J* = 7.1 Hz, H-6 or H-9). ^{13}C NMR (DMSO): δ 13.40 (CH_3), 18.65 (CH_3), 79.74 (NCH_2), 111.89 (C_{quat}), 116.66 (C_{quat}), 126.58 (CH), 126.72 (CH), 131.8 (C_{quat}), 134.00 (2×CH), 135.80 (C_{quat}), 141.29 (C_{quat}), 153.56 (C_{quat}), 157.56 (C_{quat}), 168.91 (O=C-N and O=C-O), 180.34 (C=O), 183.76 (C=O). IR (ATR): ν_{max} 3352, 3164, 3071, 2922, 2853, 2626, 2360, 2341, 1716, 1682, 1616, 1521, 1285 cm^{-1}. MS *m/z* (%): 312 ([M+H]$^+$, 100). Purity (LC-MS): 83%.

4.5.9.2. 2,3-Diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylic acid **187e**



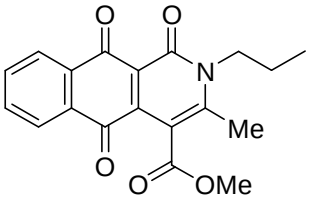
Crude yield: 98%, brown powder, m.p.: 192.1-193.9 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (6H, 2×t, *J* = 7.1 Hz, CH_2CH_3 and NCH_2CH_3), 2.94 (2H, q, *J* = 7.1 Hz, $C\underline{H}_2CH_3$), 4.28 (2H, q, *J* = 7.1 Hz, NCH_2CH_3), 7.71-7.76 (1H, dd, *J* = 7.1 and 7.1 Hz, H-7 or H-8), 7.80-7.85 (1H, dd, *J* = 7.7 and 7.7 Hz, H-7 or H-8), 8.10 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.26 (1H, d, *J* = 7.7 Hz, H-6 or H-9). ^{13}C NMR (DMSO-d_6): δ 14.15 (CH_3), 14.39 (CH_3), 25.28 ($\underline{C}H_2CH_3$), 79.94 (NCH_2), 111.65 (C_{quat}), 117.10 (C_{quat}), 126.60 (CH), 126.72 (CH), 131.79 (C_{quat}), 133.97 (C_{quat}), 134.06 (CH), 135.82 (CH), 141.52 (C_{quat}), 157.67 (C_{quat}), 157.76 (CH), 168.75 (O=C-N and O=C-O), 180.39 (C=O), 183.78 (C=O). IR (ATR): ν_{max} 3342, 3165, 3073, 3025, 2963, 2700, 1750, 1678, 1606, 1528 cm^{-1}. MS *m/z* (%): 326 ([M+H]$^+$, 100). Purity (LC-MS): 81%.

4.5.10. Synthesis of alkyl 2,3-disubstituted-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylate 171

Procedure A: To a solution of *2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzogisoquinoline-4-carboxylic acid* **187e** (200 mg, 0.62 mmol) in 2 ml of THF and 8 ml of acetonitrile was added a freshly-prepared solution of 5 equivalents of diazomethane in dry diethyl ether at room temperature. The reaction was run to completion after 2 hours. Then the reaction mixture was poured in 10 ml of water and extracted with 3x10 ml of ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium sulfate, then filtered. The filtrate was concentrated under *in vacuo* to form a crude solid which was purified by preparative thin layer chromatography using a mixture of hexane/ethyl acetate (1/4) as solvent to afford 203 mg (97%) of compound **171e**.

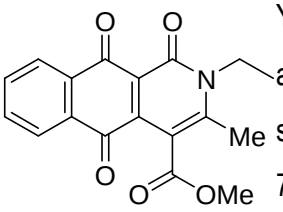
Procedure B, Oxidative addition: To a mixture of methyl 1,4-dihydroxynaphthalene-2-carboxylate **128** (0.5 g, 1.15 mmol), manganese oxide (1.34 g, 6.90 mmol) and magnesium(II) sulfate (2.76 g, 11.50 mmol) was added a solution of enaminoesters **23** (1.05 equivalents in 20 ml of dry dichloromethane). The mixture was stirred at room temperature for 3.5 hours. Then the reaction mixture was filtered and concentrated *in vacuo*. The resulting concentrate was dissolved in 15 ml of toluene and 3 ml of acetic acid, and this mixture was subsequently heated under reflux for 1-1.5 hours. After cooling to room temperature, the reaction mixture was poured in water and extract with ethyl acetate (20 ml×3). The organic phase was washed with saturated sodium bicarbonate, brine, filtered and concentrated *in vacuo*. The obtained compounds were recrystallized from methanol for **171c,e** and from ethanol for **171g-j**.

4.5.10.1. Methyl 2-n-propyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **171c**



Yield: 46%, greenish brown powder, m.p.: not observed-the compound decomposes at 256 °C. ^{1}H NMR ($CDCl_3$): δ 1.01 (3H, t, *J* = 7.4 Hz, $CH_2CH_2C\underline{H}_3$), 1.36 1.77 (2H, sextet, *J* = 7.4 Hz, $NCH_2C\underline{H}_2CH_3$), 3.19 (3H, s,$CH_3$), 4.00 (3H, s, OCH_3), 4.11 (2H, br s, $NC\underline{H}_2CH_2CH_3$), 7.76 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 7.83 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 8.08 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.25 (1H, d, *J* = 7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 11.17 ($NCH_2CH_2\underline{C}H_3$), 22.67 ($NCH_2\underline{C}H_2CH_3$), 30.73 ($CH_3$), 47.07 ($N\underline{C}H_2CH_2CH_3$), 53.91 ($OCH_3$), 110.75 ($C_{quat}$), 118.86 ($C_{quat}$), 126.77 (CH), 127.28 (CH), 131.39 (C_{quat}), 133.59 (C_{quat}), 133.59 (CH), 135.47 (CH), 141.82 (C_{quat}), 151.41 (C_{quat}), 159.00 (O=C-N), 168.40 (O=C-O), 180.20 (C=O), 183.24 (C=O). IR (ATR): ν_{max} 2961, 1717, 1688, 1631, 1592, 1513, 1437, 1415, 1283, 1254, 1164, 969 cm^{-1}. MS *m/z* (%): 340 ([M+H]$^+$, 100). Anal. Calcd for $C_{19}H_{17}NO_5$: C 67.25, H 5.05, N 4.13; found: C 66.39, H 3.78, N 4.93. HRMS (ESI) for $C_{19}H_{17}O_5$: 340.1107 [M+H]$^+$, found 340.1181.

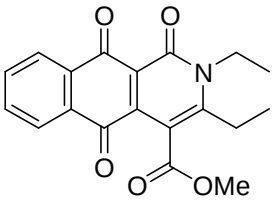
4.5.10.2. Methyl 2-ethyl-3-methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **171d**



Yield: 14%, red orange powder, m.p.: not observed-the compound decomposes at 280 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 3.19 (3H, s,CH_3), 4.09 (3H, s, OCH_3), 4.24 (2H, br s, $NC\underline{H}_2CH_3$), 7.74 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 7.83 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 8.09 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.25 (1H, d, *J* = 7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 14.27 ($NCH_2\underline{C}H_3$), 30.66 (CH_3), 41.32 ($N\underline{C}H_2CH_3$), 53.79 (OCH_3), 110.74 (C_{quat}), 118.83 (C_{quat}), 126.61 (CH), 127.20 (CH), 131.28 (C_{quat}),

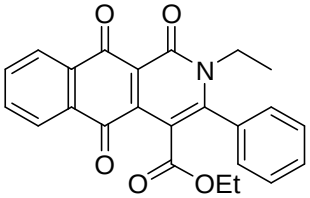
133.23 (C_{quat}), 135.43 (CH), 136.91 (CH), 141.78 (C_{quat}), 151.67 (C_{quat}), 157.94 (O=C-N), 168.33 (O=C-O), 180.36 (C=O), 183.32 (C=O). IR (ATR): ν_{max} 1735, 1687, 1508, 1416, 1281, 1259, 994 cm^{-1}. MS *m/z* (%): 326 ($[M+H]^+$, 100).

4.5.10.3. Methyl 2,3-diethyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **171e**



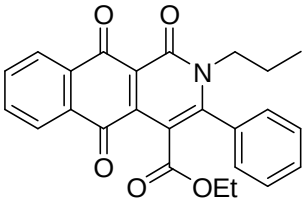
Yield: 69-97%, red orange crystals, m.p.: 183.1-184.2°C. ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, *J* = 7.0 Hz, $CH_2\underline{C}H_3$), 1.41 (3H, t, *J* = 7.0 Hz, $NCH_2\underline{C}H_3$), 2.80 (2H, q, *J* = 7.0 Hz, $\underline{C}H_2CH_3$), 4.00 (3H, s, OCH_3), 4.28 (2H, q, *J* = 7.0 Hz, $N\underline{C}H_2CH_3$), 7.72 (1H, d, *J* = 7.7 Hz, H-7 or H-8), 7.82 (1H, d, *J* = 7.7 Hz, H-7 or H-8), 8.09 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.25 (1H, d, *J* = 7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 13.86 ($CH_2\underline{C}H_3$), 14.13 ($NCH_2\underline{C}H_3$), 25.35 ($\underline{C}H_2CH_3$), 40.88 (NCH_2CH_3), 53.28 (OCH_3), 109.88 (C_{quat}), 117.60 (C_{quat}), 126.67 (CH), 127.22 (CH), 131.47 (C_{quat}), 133.35 (C_{quat}), 133.77 (CH), 135.30 (CH), 141.74 (C_{quat}), 157.33 (C_{quat}), 158.28 (O=C-N), 168.29 (O=C-O), 180.40 (C=O), 183.47 (C=O). IR (ATR): ν_{max} 2946, 1731, 1693, 1632, 1504, 1424, 1283, 1260, 1153, 1087, 994, 749 cm^{-1}. MS *m/z* (%): 340 ($[M+H]^+$, 100). Anal. Calcd for $C_{19}H_{17}NO_5$: C 67.25, H 5.05, N 4.13; found: C 67.04, H 4.47, N 5.53. HRMS (ESI) for $C_{19}H_{17}NO_5$ 340.1107 $[M+H]^+$, found 340.1201. HRMS (ESI) for $C_{19}H_{17}NO_5$: 340.1107 $[M+H]^+$, found 340.1201.

4.5.10.4. Ethyl 2-ethyl-3-phenyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxy-late **171g**



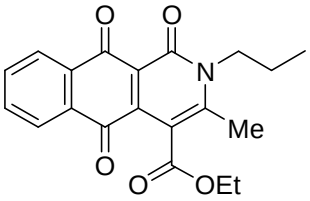
Yield: 32%, yellow orange crystals, m.p.: 193.4-194.2°C. ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, t, *J* = 7.1 Hz,$NCH_2\underline{C}H_3$), 1.21 (3H, t, *J* = 6.9 Hz, $OCH_2\underline{C}H_3$), 3.97 (2H, q, *J* = 7.1 Hz, $N\underline{C}H_2CH_3$), 4.02 (2H, q, *J* = 6.9 Hz, $O\underline{C}H_2CH_3$), 7.37-7.40 (2H, m, H-2' and H-5'), 7.49-7.56 (3H, m, H-3', H-4' and H-5'), 7.73 (1H, t, *J* = 6.0 Hz, H-7 or H-8), 7.83 (1H, t, *J* = 6.0 Hz, H-7 or H-8), 8.10 (1H, d, *J* = 6.0 Hz, H-6 or H-9), 8.28 (1H, d, *J* = 6.0 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 13.66 ($NCH_2\underline{C}H_3$), 13.94 ($OCH_2\underline{C}H_3$), 43.13 ($N\underline{C}H_2CH_3$), 61.77 ($O\underline{C}H_2CH_3$), 111.88 (C_{quat}), 119.24 (C_{quat}), 126.67 (CH), 127.27 (CH), 128.49 (2×CH), 128.75 (2×CH), 130.46 (CH), 131.44 (C_{quat}), 131.57 (C_{quat}), 133.44 (CH), 133.77 (C_{quat}), 135.29 (CH), 141.42 (C_{quat}), 154.69 (C_{quat}), 157.90 (O=C-N), 166.45 (O=C-O), 180.63 (C=O), 183.21 (C=O). IR (ATR): ν_{max} 2991, 1735, 1658, 1628, 1591, 1523, 1488, 1444, 1400, 1327, 1223, 1182, 1149, 1047, 977, 916 cm^{-1}. MS *m/z* (%): 401 ($[M-H]^+$, 100). Anal. Calcd for $C_{24}H_{19}NO_5$: C 71.81, H 4.77, N 3.49; found: C 71.39, H 4.02, N 3.49. HRMS (ESI) for $C_{24}H_{19}O_5$: 402.1263 $[M+H]^+$, found 402.1344.

4.5.10.5. Ethyl 3-phenyl-2-n-propyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **171h**



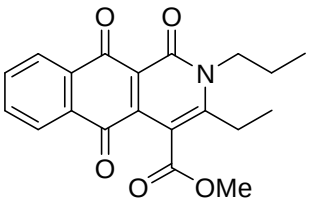
Yield: 56%, orange crystals, m.p.: 169.0-169.4°C. ^{1}H NMR ($CDCl_3$): δ 0.75 (3H, t, *J* = 7.4 Hz, $NCH_2CH_2C\underline{H}_3$), 1.00 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.66 (2H, sext, *J* = 7.4 Hz, $NCH_2C\underline{H}_2CH_3$), 3.82 (2H, q, *J* = 7.4 Hz, $NC\underline{H}_2CH_2CH_3$), 4.02 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.36-7.41 (2H, m, H-2' and H-5'), 7.49-7.56 (3H, m, H-3', H-4' and H-5'), 7.73 (1H, t, *J* = 6.0 Hz, H-7 or H-8), 7.83 (1H, t, *J* = 6.0 Hz, H-7 or H-8), 8.10 (1H, d, *J* = 6.0 Hz, H-6 or H-9), 8.28 (1H, d, *J* = 6.0 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 11.34 ($NCH_2CH_2\underline{C}H_3$), 13.66 ($OCH_2\underline{C}H_3$), 22.09 ($NCH_2\underline{C}H_2CH_3$), 49.30 ($N\underline{C}H_2CH_2CH_3$), 61.77 ($O\underline{C}H_2H_3$), 111.80 ($C_{quat}$), 118.98 ($C_{quat}$), 126.67 (CH), 127.28 (CH), 128.57 (2×CH), 128.67 (2×CH), 130.46 (CH), 131.47 (C_{quat}), 131.57 (C_{quat}), 133.42 (CH), 133.79 (C_{quat}), 135.27 (CH), 141.39 (C_{quat}), 158.00 (C_{quat}), 158.00 (O=C-N), 166.44 (O=C-O), 180.59 (C=O), 183.22 (C=O). IR (ATR): ν_{max} 2980, 1688, 1628, 1593, 1524, 1492, 1446, 1406, 1320, 1285, 1177, 1166, 1024, 977, 928 cm^{-1}. MS *m/z* (%): 416 ([M+H]$^+$, 100). Anal. Calcd for $C_{25}H_{21}NO_5$: C 72.28, H 5.10, N 3.37; found: C 71.39, H 4.55, N 8.21. HRMS (ESI) for $C_{25}H_{21}NO_5$: 416.1419 [M+H]$^+$, found 416.1502.

4.5.10.6. Ethyl 3-methyl-2-n-propyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **171i**



Yield: 29%, brown crystals, m.p.: 128.0-129.9°C. ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, t, *J* = 7.4 Hz, $CH_2CH_2C\underline{H}_3$), 1.40 (3H, *J* = 7.4 Hz,$OCH_2C\underline{H}_3$), 1.77 (2H, sextet, *J* = 7.4 Hz, $NCH_2C\underline{H}_2CH_3$), 3.18 (3H, S, CH_3), 4.26 (2H, br s, $NC\underline{H}_2CH_2CH_3$), 4.48 (2H, q, *J* = 7.4 Hz, $OC\underline{H}_2CH_3$), 7.75 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 7.84 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 8.09 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.26 (1H, d, *J* = 7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): To date, a decent ^{13}C NMR spectrum of this derivative could not be recorded even upon prolongation of the relaxation delay and increasing the number of recorded scans. IR (ATR): ν_{max} 2968, 1725, 1688, 1629, 1592, 1511, 1440, 1417, 1415, 1327, 1282, 1254, 1210, 1174, 1058, 1011, 968 cm^{-1}. MS *m/z* (%): 354 ([M+H]$^+$, 10%), 705 (100%). Anal. Calcd for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N 3.96; found: C 67.66, H 4.71, N 6.61. HRMS (ESI) for $C_{20}H_{19}NO_5$: 354.1263 [M+H]$^+$, found 354.1326.

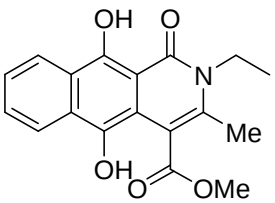
4.5.10.7. Methyl 3-ethyl-2-n-propyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[g]isoquinoline-4-carboxylate **171j**



Yield: 71%, orange crystals, m.p.: 128.6-129.0°C. ^{1}H NMR ($CDCl_3$): δ 1.05 (3H, t, *J* = 7.4 Hz, $CH_2CH_2C\underline{H}_3$), 1.36 (3H, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.79 (2H, sextet, *J* = 7.4 Hz, $NCH_2C\underline{H}_2CH_3$), 2.80 (2H, q, *J* = 7.4 Hz, $C\underline{H}_2CH_3$), 4.00 (3H, s, OCH_3), 4.11 (2H, q, *J* = 7.4 Hz, $NC\underline{H}_2CH_3$), 7.72 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 7.81 (1H, t, *J* = 7.7 Hz, H-7 or H-8), 8.09 (1H, d, *J* = 7.7 Hz, H-6 or H-9), 8.25 (1H, d, *J* = 7.7 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 11.52 (CH_3), 13.80 (CH_3), 22.35 ($\underline{C}H_2CH_3$), 25.35 ($NCH_2\underline{C}H_2CH_3$), 47.16 ($N\underline{C}H_2CH_2CH_3$), 53.26 ($OCH_3$), 109.96 ($C_{quat}$), 117.57 ($C_{quat}$), 126.66 (CH), 127.21 (CH), 131.47 (C_{quat}), 133.35 (C_{quat}), 133.76 (CH), 135.29 (CH), 141.71 (C_{quat}), 157.41 (C_{quat}), 158.42 (O=C-N), 168.29 (O=C-O), 180.43 (C=O), 183.47 (C=O). IR (ATR): ν_{max} 2966, 1728, 1691, 1633, 1593, 1516, 1415, 1330, 1282, 1255, 1147, 1064, 979 cm^{-1}. MS *m/z* (%): 354 ([M+H]$^+$, 100). Anal. Calcd for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N 3.96; found: C 67.73, H 4.92, N 12.35. HRMS (ESI) for $C_{20}H_{19}NO_5$: 354.1262 [M+H]$^+$, found 354.1262.

4.5.11. Synthesis of methyl 1,2-dihydro-5,10-dihydroxy-2-ethyl-3-methyl-1-oxobenzo[*g*]isoquinoline-4-carboxylate 188d

To a solution of 2-ethyl-1,2,5,10-tetrahydro-3-methyl-1,5,10-trioxobenzo[*g*]isoquinoline-4-carboxylic acid **186d** (200 mg, 0.64 mmol) in 2 ml of THF and 8 ml of acetonitrile was added a freshly-prepared solution of 5 equivalents of diazomethane in dry diethyl ether at room temperature. The reaction was run overnigth. Then the reaction mixture was poured in 10 ml of water and extracted with 3x10 ml of ethyl acetate. The combined organic extracts were washed with brine, stirred and dried over magnesium sulfate for 1 hour in open air, then filtered. The filtrate was concentrated under reduced pressure to form a crude solid which was purified by preparative thin layer chromatography using a mixture of hexane/ ethyl acetate (1/4) as solvent to afford 46 mg of compound **188d** (22%) and 29 mg of compound **171d** (14%). For spectral data of compound **171d** *vide supra*



Yield: 22%, green sticky solid, ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, t, *J* = 7.5 Hz, $NCH_2C\underline{H}_3$), 2.90 (3H, s, CH_3), 4.18 (3H, s, OCH_3), 4.25 (2H, q, *J* = 7.5 Hz, $NC\underline{H}_2CH_3$), 7.53 (1H, t, *J* = 9.0 Hz, H-7 or H-8), 7.67 (1H, t, *J* = 9.0 Hz, H-7 or H-8), 8.08 (1H, d, *J* = 9.0 Hz, H-6 or H-9), 8.45 (1H, d, *J* = 9.0 Hz, H-6 or H-9). ^{13}C NMR ($CDCl_3$): δ 14.12 (CH_3), 16.07 (CH_3), 39.63 ($N\underline{C}H_2CH_3$), 63.71 (CH_3O), 99.92 (C_{quat}), 109.13 (C_{quat}), 120.57 (CH), 122.00 (C_{quat}), 122.61 (C_{quat}), 125.04 (CH), 125.68 (CH), 128.05 (C_{quat}), 129.25 (CH), 138.31 (C_{quat}), 151.68 (C_{quat}), 153.48 (C_{quat}), 160.13 (O=C-N), 166.94 (O=C-O). IR (ATR) ν_{max}:

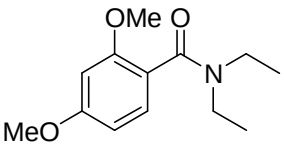
3347, 2944, 2358, 1751, 1672, 1638, 1440, 1396, 1366, 1237, 1044 cm^{-1}. MS *m/z* (%): 328 ($[M+H]^+$, 100).

4.6. Efforts towards the first total synthesis of paepalantine 24

4.6.1. Synthesis of *N,N*-diethyl-2,4-dimethoxybenzamide 195 and *N,N*-diethyl-2-formyl-4,6-dimethoxybenzamide 196[140]

4.6.1.1. N,N-Diethyl-2,4-dimethoxybenzamide **195**

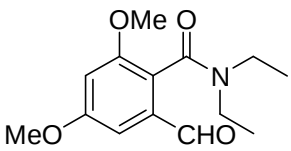
A mixture of 2,4-dimethoxybenzoic acid **193** (6.5 g, 34.96 mmol), thionyl chloride (16 ml) and toluene (200 ml) was boiled for 2.5 hours. The solvent and the excess of thionyl chloride were removed *in vacuo*. The acid chloride residue was dissolved in toluene (80 ml). A solution of diethylamine (11 ml, 106.33 mmol) in toluene (30 ml) was added dropwise to the solution of the crude acid chloride in toluene at 0°C. After stirring for 2 hours, toluene was removed under reduced pressure. The residue was diluted with dichloromethane (100 ml), washed with saturated sodium bicarbonate (3×100 ml) and brine (3×100 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue underwent column chromatography using diethyl ether/hexane (3/1) to give *N,N*-diethyl-2,4-dimethoxybenzamide **195** (7.05 g, 80%) as a viscous yellow oil. Spectra data were in accordance with the literature.[140]



^{1}H NMR ($CDCl_3$): δ 0.98 (3H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 1.16 (3H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 3.08 (2H, q, *J* = 7.1 Hz, $C\underline{H}_2CH_3$), 3.47 (2H, q, *J* = 7.1 Hz, $C\underline{H}_2CH_3$), 3.70 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 6.37 (1H, d, *J* = 2.1 Hz, H-3), 6.40 (1H, dd, *J* = 8. 0, 2.1 Hz, H-5), 7.03 (1H, d, *J* = 8.0 Hz, H-6).

4.6.1.2. N,N-Diethyl-2-formyl-4,6-dimethoxybenzamide **196**

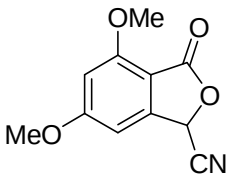
To a stirred solution of *N,N*-diethyl-2,4-dimethoxybenzamide **195** (7.0 g, 29.50 mmol) in tetrahydrofuran (193 ml) at -78°C was added dropwise *tert*-butyllithium (20.3 ml of a 1.5 M solution in hexanes, 30.42 mmol). After stirring for 20 minutes, *N,N*-dimethylformamide (8.5 ml, 117.2 mmol) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 12 hours and the solvent removed *in vacuo*. The residue was dissolved in dichloromethane (60 ml), washed with brine (3×50 ml) and the organic layer was dried over magnesium sulfate. Removal of the solvent *in vacuo* followed by column chromatography using diethyl ether as eluent gave *N,N*-diethyl-2-formyl-4,6-dimethoxybenzamide **196** (7.03 g, 90%) as a viscous yellow oil. Spectra data were in agreement with the literature.[139]



^{1}H NMR ($CDCl_3$): δ 0.94 (3H, t, *J* = 7.1 Hz, $NCH_2C\underline{H}_3$), 1.20 (3H, t, *J* = 7.1 Hz, $NCH_2C\underline{H}_3$), 3.05 (2H, q, *J* = 7.1 Hz, $NC\underline{H}_2CH_3$), 3.40-3.54 (1H, m, $NC\underline{H}_aH_bCH_3$), 3.56-3.68 (1H, m, $NCH_a\underline{H}_bCH_3$), 3.75 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.64 (1H, d, *J* = 2.3 Hz, H-5), 6.96 (1H, d, *J* = 2.3 Hz, H-6), 9.89 (1H, s, CHO).

4.6.2. Synthesis of 3-cyano-5,7-dimethoxy-3*H*-isobenzofuran-1-one 25[141]

A solution of *N,N*-diethyl-2,4-dimethoxy-6-formylbenzamide **196** (860 mg, 3.20 mmol) in acetic acid (40 ml) and 10% hydrochloric acid (40 ml) was boiled for 24 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and ethyl acetate (150 ml) was added to the reaction mixture which was washed with saturated sodium bicarbonate (3×100 ml). The combined aqueous layers were carefully acidified to pH 2 with concentrated hydrochloric acid. The acidified solution was extracted with ethyl acetate (2×250 ml). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* give crude 3-hydroxy-5,7-dimethoxy-3*H*-isobenzofuran-1-one **197** as a colourless solid which added to a solution of potassium cyanide (2.3 g, 35.3 mmol) (480 mg, 2.3 mmol) in water (8 ml) and cooled to 0 °C. Ice (8 g) and concentrated hydrochloric acid (10.7 ml, 0.12 mol) were added to the mixture and stirred for 3 hours to room temperature (Caution: formation of HCN). The reaction mixture was extracted with ethyl acetate (20 ml), the organic layer was washed with saturated sodium bicarbonate (15 ml), water (15 ml) and brine (15 ml), dried over magnesium sulfate and the solvent was removed *in vacuo* to give a brown solid. Purification by flash column chromatography eluting with dichloromethane gave 3-cyano-5,7-dimethoxy-3*H*-isobenzofuran-1-one **25** (479 mg, 68% yield) as a colourless solid. All spectral data were in accordance with the literature.[141]

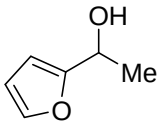


^{1}H NMR ($CDCl_3$): δ 3.94 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 5.91 (1H, s, H-3), 6.54 (1H, d, *J* = 1.7 Hz, H-6), 6.66 (1H, d, *J* = 1.7 Hz, 4-H).

4.6.3. Synthesis of 1-(2-furyl)ethanol 199

Magnesium turnings (6.51 g, 0.28 mol) were placed in a 500 ml 3-neck round-bottom flask and a condenser along with a side arm addition funnel were attached. The apparatus was flame dried and flushed with nitrogen, then anhydrous Et_2O (50 ml) and an iodide crystal were added to the magnesium turnings. A solution of methyl iodide (38 g, 0.27 mol) in anhydrous Et_2O (150 ml) were added dropwise to the magnesium solution. After the addition was completed, the solution was stirred at room temperature for 1 hour after which a solution of freshly distilled furfural **198** (9.6 g, 0.10 mol) in anhydrous Et_2O (150 ml) were added slowly to the Grignard reagent at 0°C, and the solution was stirred

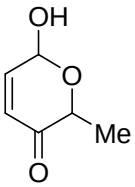
for 3 hours at 0°C and 1 hour at room temperature. The reaction was quenched with a saturated solution of aqueous ammonium chloride and extracted (3×100 ml) with Et_2O. The organic phase was washed with saturated solution of sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1-(2-furyl)ethanol **199** (11.0 g, 98% yield) as a yellow oil. All the spectral data were in accordance with the literature.[142]



^{1}H NMR ($CDCl_3$): δ 1.53 (3H, d, *J* = 6.6 Hz, CHC<u>H</u>$_3$), 2.17 (1H, br s, OH), 4.92 (1H, q, *J* = 6.6 Hz, C<u>H</u>CH$_3$), 6.23 (1H, d, *J* = 3.6 Hz, H-2), 6.33 (1H, dd, *J* = 3.6 and 1.7 Hz, H-3), 7.33 (1H, d, *J* =1.7 Hz, H-5).

4.6.4. Synthesis of 6-hydroxy-2-methyl-6*H*-pyran-3-one 200

To a solution of 1-(2-furyl)ethanol **199** (4.3 g, 38.36 mmol) in water (8 ml) and THF (32 ml) cooled to -4°C were added portionwise under temperature control, a mixture of NBS (7.51 g, 42,91 mmol), $NaHCO_3$ (7.1 g, 84.52 mmol) and NaOAc (3.46 g, 38.36 mmol). The mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated solution of sodium bicarbonate and extracted with Et_2O (3×50 mL), dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography eluting with EtOAc/hexane (1/4) to give 6-hydroxy-2-methyl-6*H*-pyran-3-one **200** (4.48 g, 91% yield) as a greenish yellow oil.

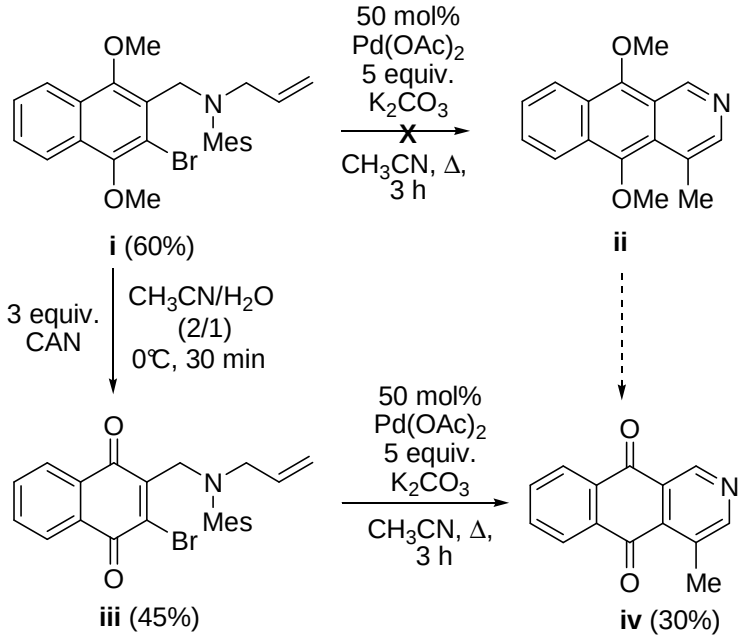


^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (3H, d, *J* = 7.0 Hz, CH_3), 2.20 (1H, br, OH), 4.42 (1H, d, *J* = 7.0 Hz, H-2), 5.05 (1H, d, *J* = 3.1 Hz, H-6), 5.85 (1H, *J* = 10.0 Hz, H-4), 6.60 (1H, dd, *J* = 10.0 Hz, 3.10 Hz, H-5).

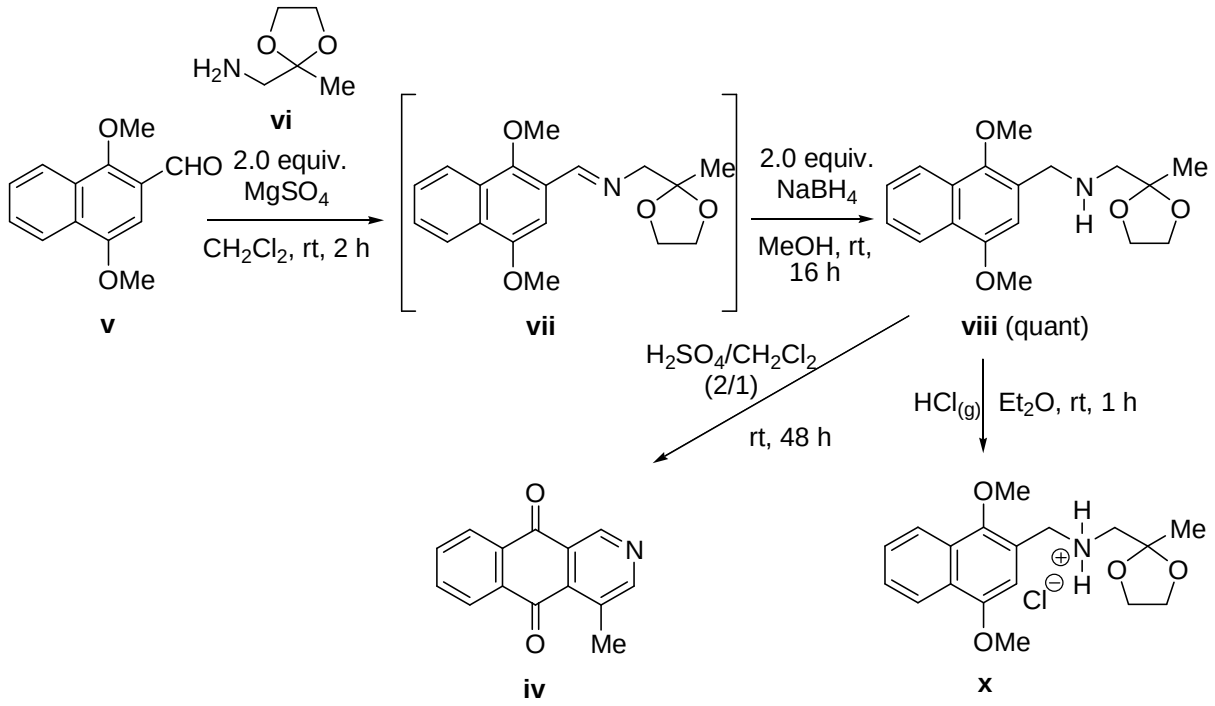
4. Summary

Azaanthraquinones and naphthonaphthyridines represent two important related classes of bioactive compounds. The synthesis of these compounds represents an attractive target for both organic and medicinal chemists. Morever, it is known that 2-azaanthraquinones are more active than the corresponding 1-azaanthraquinones and that the presence of a hydroxyl group at the C-1 *peri*-carbonyl position of 2-azaanthraquinones enhances their biological activity. Another important feature which improves the biological activity of tricyclic azaaromatic compounds is the presence of a covalent bond between the tricyclic aromatic system and another aromatic ring called the biaryl axis. Therefore, the chemistry of 2-azaanthraquinones and their corresponding naphthonaphthyridine analogues was explored during the present research work.

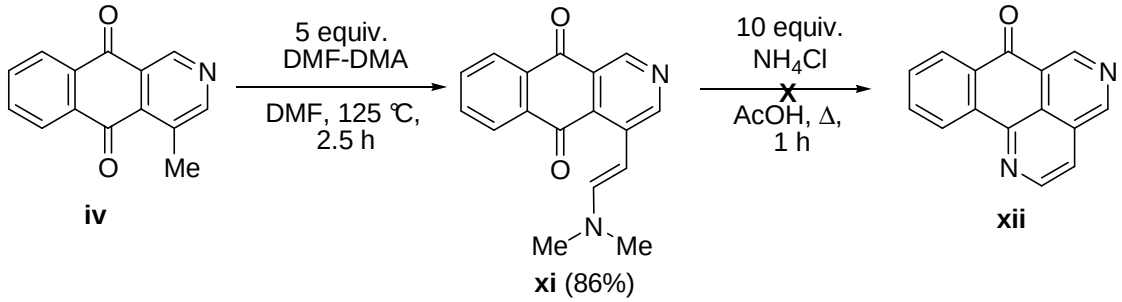
In a first part of the present thesis, the synthesis of 2-azacleistopholine **iv** was achieved by two routes. The first route utilized a ligand-free Heck reaction as the key step. Different attempts to obtain aza ring closure of *N*-methanesulfonyl-2-(allylaminomethyl)-3-bromo-1,4-dimethoxynaphthalene **i** failed to afford 2-azacleistopholine **iv**. This latter compound **iv** was synthesized upon refluxing 2-(allylaminomethyl)-3-bromo-1,4-naphthoquinone **iii**, obtained by oxidation of 1,4-dimethoxynaphthalene **i** with CAN, in the presence of 50 mol% of $Pd(OAc)_2$ in 30% yield.



The second route utilized an acid-promoted intramolecular Pomeranz-Fritsch reaction as the key step. Condensation of 2-formyl-1,4-dimethoxynaphthalene **v** and 2-aminomethyl-2-methyl-1,3-dioxolane **vi** yielded intermediate imine **vii**, which was reduced quantitatively to the corresponding aminomethylnaphthalene **viii**. Different reaction conditions were screened to induce the intramolecular cyclization of the aminomethylnaphthalene **viii** using different Brønsted acids. In the presence of gaseous hydrochloric acid, amine **viii** was protonated to the corresponding ammonium chloride **x**. Reaction of the aminomethylnaphthalene **viii** with sulfuric acid in a biphase system with dichloromethane gave 2-azacleistopholine **iv** in a 50% yield.

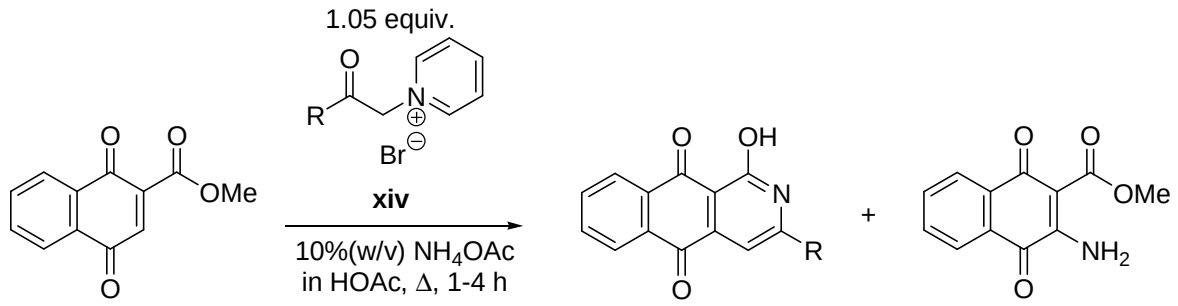


Having 2-azacleistopholine **iv** in hand, (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **xi** was synthesized in a 86% yield upon reaction with DMF-DMA. Subsequent reaction of (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **xi** with an excess of ammonium chloride in acetic acid in order to form 2-azasampangine **xii** only resulted in intractable complex reaction mixtures. Therefore, the synthesis of 2-azasampangine **xii** still remains a challenge.



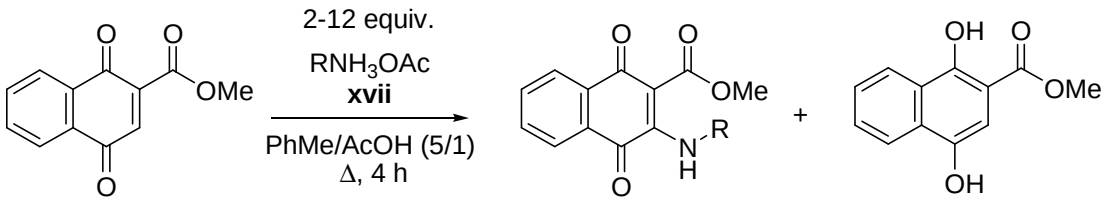
In the second part of this thesis, the synthesis of 2-azaanthraquinones substituted at the C-1 *peri*-carbonyl position and linked to aryl groups at C-3, more specifically 3-aryl-2-aza-1-hydroxyanthraquinones **xv**, 3-aryl-2-aza-1-methylanthraquinones **xxiii** and 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylanthraquinones **xxvii**, was investigated. An additional plan was to synthesize 3-aryl-2-aza-1-(2-dimethylaminovinyl)anthraquinones **xxiv** in order to convert them to the corresponding 2-azasampangine analogues **xxv**.

In continuation of preceding studies in our research group, the reaction of 2-methoxycarbonyl-1,4-naphthoquinone **xiii** with pyridinium salts **xiv** under Krönhke conditions afforded 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-diones **xv** in 40-75% yield and 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **xi** in 15-20% yield as a side product. The formation of the target products **xv** is favoured by the presence of electron-withdrawing groups while their absence favoured the formation of the side product **xvi.**



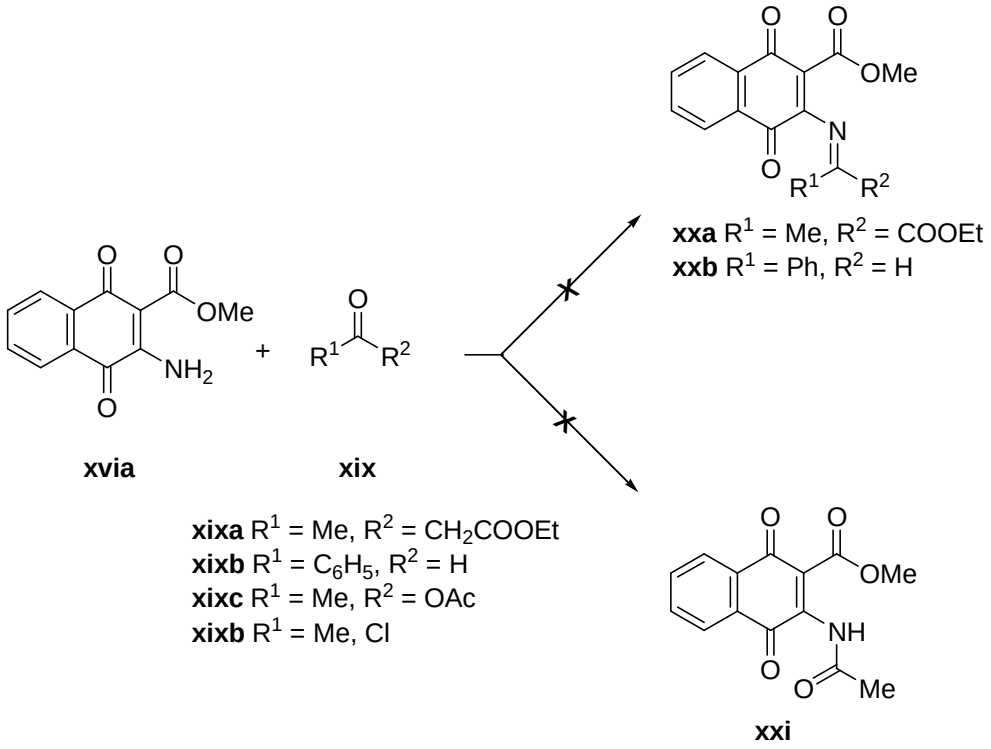
xiii R = C_6H_5, 4-ClC_6H_4, *t*-Bu, OEt, NH_2 **xv** (40-75%) **xvia** (15-20%)

3-Alkylamino- or 3-arylamino-2-methoxycarbonyl-1,4-naphthoquinones **xvi** were prepared by refluxing quinone **xiii** and alkyl- or arylammonium acetates **xvii** in 69-87% with minor presence of methyl 1,4-dihydroxynaphthalene-2-carboxylate **xviii** (0-12%) resulting from the autooxidation-reduction of the starting material **xiii** and the hydroquinone form of alkylaminonaphthoquinones **xvib-c**.

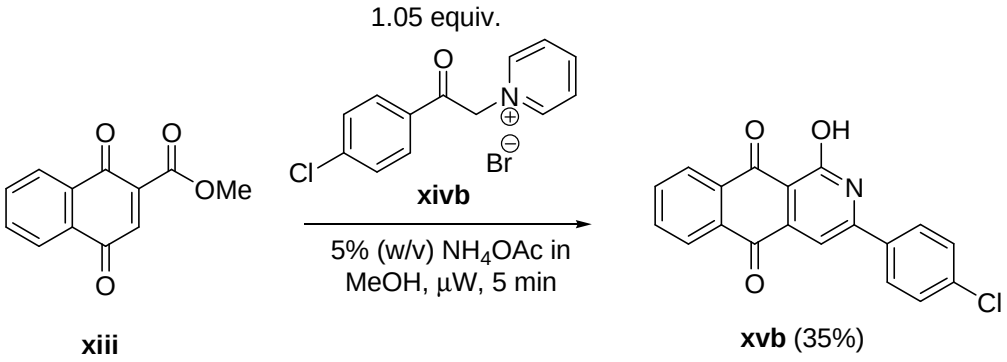


xiii R = *n*-Pr, *n*-Bu, C_6H_5 **xvib-c** (69-87%) **xviii** (0-12%)

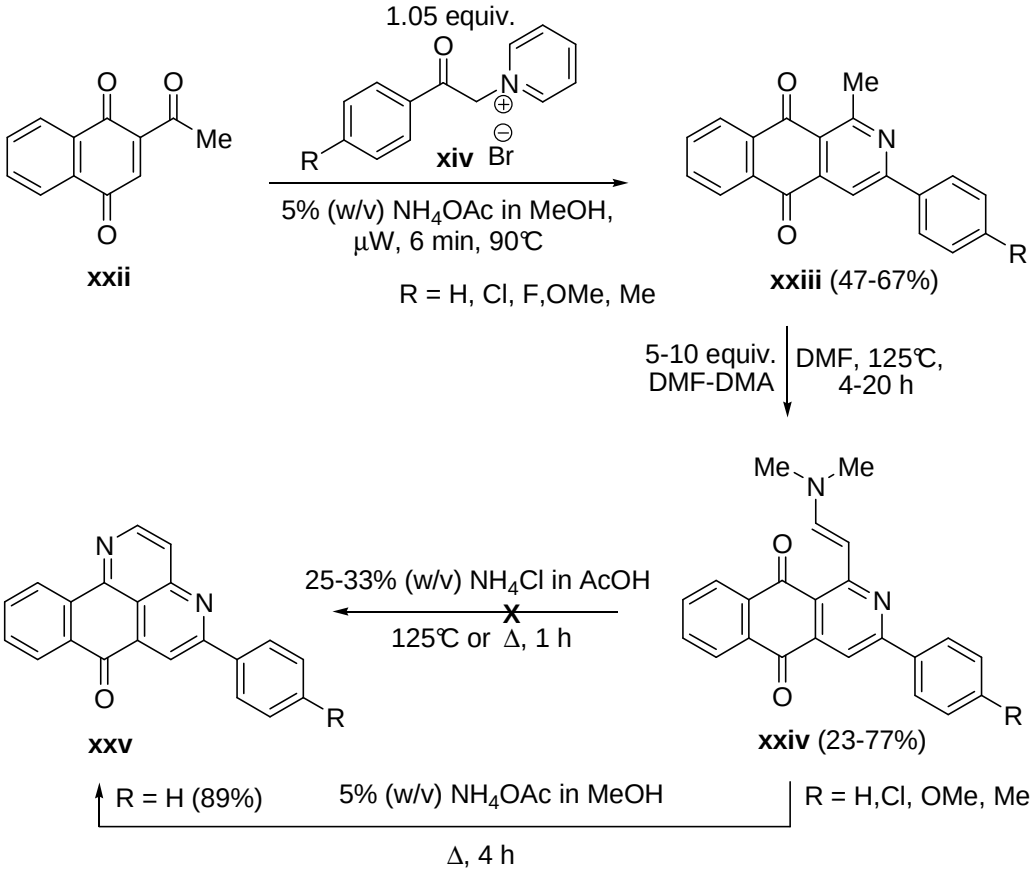
Due to the vinylogous character of the amino group and the intramolecular hydrogen bonds of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone **xvia**, it was found impossible to react it under mild acid, neutral and basic conditions with common electrophiles **xix** such as ethyl acetoacetate **xixa** and benzaldehyde **xixb** to form imines **xx** or to acetylate it using acetic anhydride and acetyl chloride **xixd**.



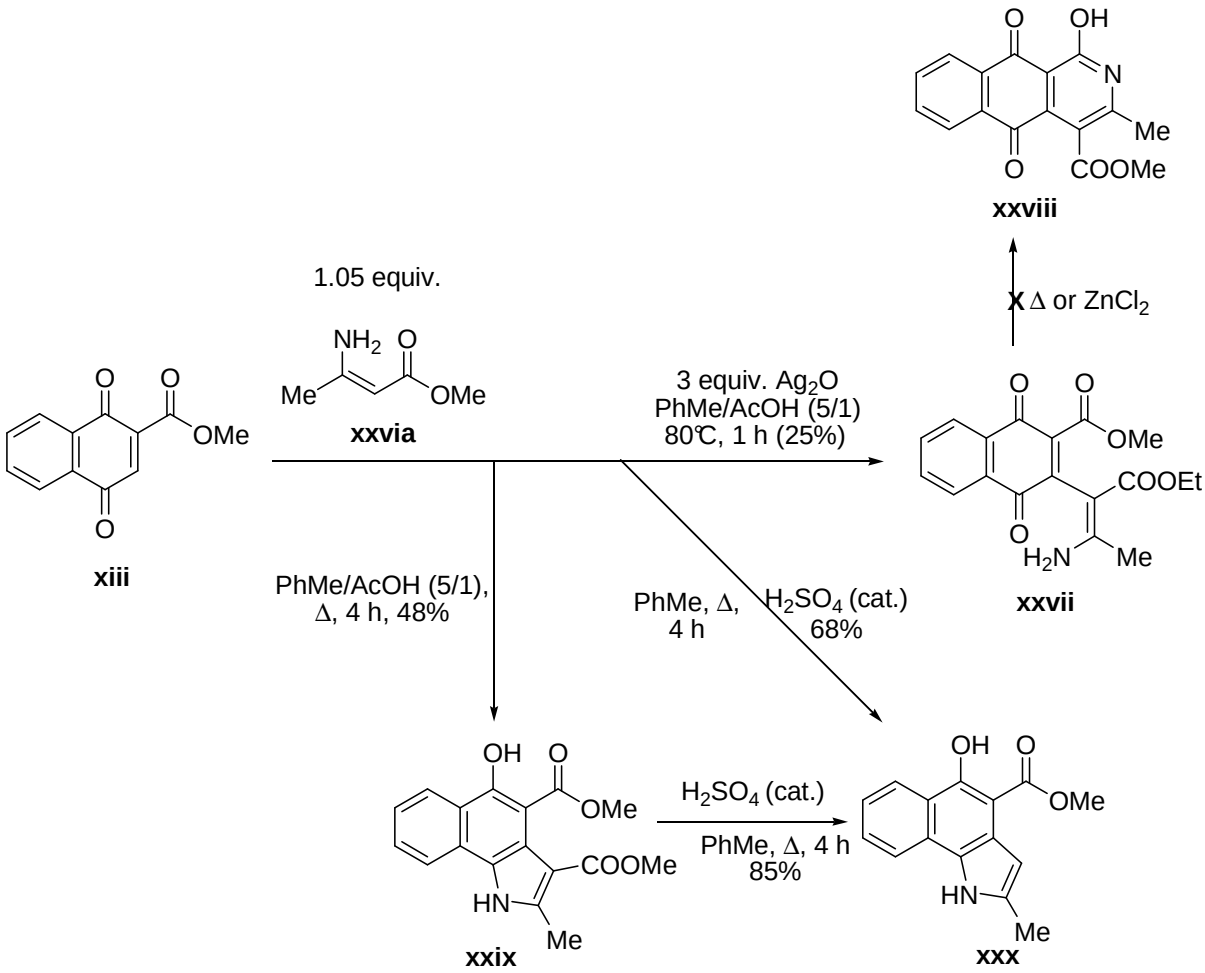
The formation of the side product **xvia** could be avoided when the synthesis of 3-aryl-1-hydroxybenzo[*g*]isoquinoline-5,10-diones **xv** was run under microwave conditions. These conditions were previously optimized in our group.



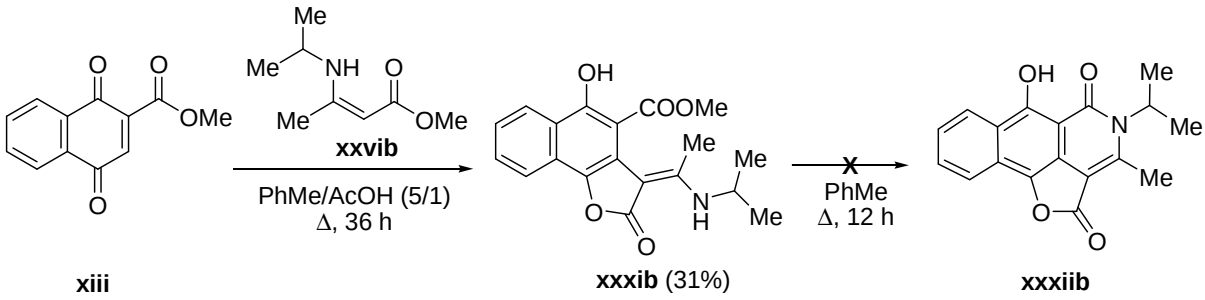
2-Acetyl-1,4-naphthoquinone **xxii** was treated with pyridinium salts **xiv** under the abovementioned microwave assisted Kröhnke conditions to afford 3-aryl-1-methylbenz[*g*]isoquinoline-5,10-diones **xxiii** in 47-67% yield. Subsequently, 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **xxiii** were reacted with an excess of DMF-DMA to give 3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **xxiv** in a 23-77% yield. The reaction of 3-aryl-1-methylbenzo[*g*]isoquinoline-5,10-diones **xxiv** with DMF-DMA was strongly influenced by the electronic effects of the aryl substituent at position C-3 in substrate **xxiv**. Differents attempts to synthetize the corresponding naphthonaphthyridines **xxv** using literature procedures failed. However, boiling 3-aryl-1-(dimethylaminovinyl)benzo[*g*]isoquinoline-5,10-dione **xxiva** in a 5% (w/v) solution of NH_4OAc in methanol afforded 5-phenyl-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one **xxva** in a 89% yield.



The synthesis of 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylanthraquinones **xxxix** was envisaged starting from 3-methoxycarbonyl-1,4-naphthoquinone **xxii** and enaminoesters **xxvi**. In order to find optimized conditions for this synthesis, the reaction of 3-methoxycarbonyl-1,4-napthoquinone **xxiii** with methyl 3-aminocrotonate **xxvia** was screened. This reaction gave the 5-hydroxyindole **xxix** when the starting material was boiled in a mixture of toluene and acetic acid (5/1) and the indole **xxx** was obtained in boiling toluene in the presence of a catalytic amount of sulfuric acid. Compound **xxx** could also be obtained by treatment of indole **xxix** with a catalytic amount of sulfuric acid in toluene under reflux. When the reaction was conducted at 80°C, only the Michael adduct **xxvii** could be isolated in 25% yield. Attemps to cyclize this Michael adduct **xxvii** to the corresponding methyl 1-hydroxy-3-phenylbenzo[*g*]isoquinoline-5,10-dione-4-carboxylate **xxviii** using heat or $ZnCl_2$ failed.

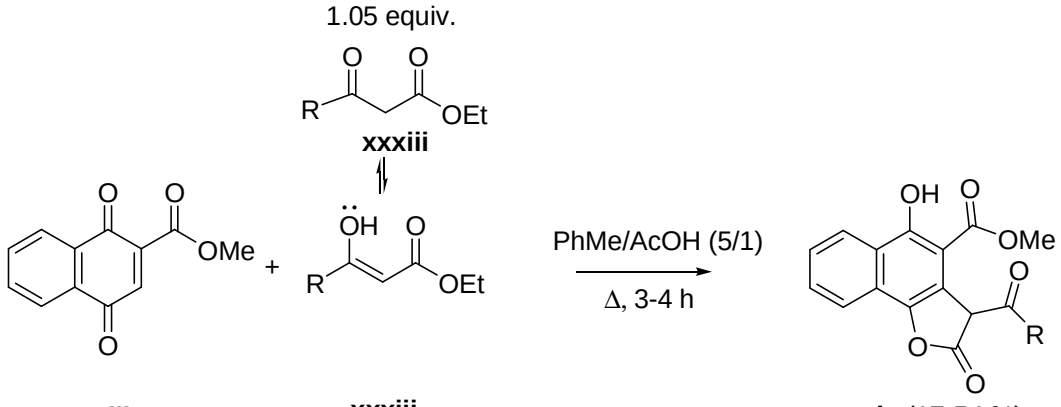


In order to arrange for a more suitable action of the amino group of enaminoesters **xxvi**, methyl *N*-isopropyl-3-aminocrotonate **xxvib** was reacted with the activated quinone **xiii** in a mixture of toluene and acetic acid (5/1) under reflux. After 36 hours, only the enaminolactone **xxxib** was retrieved. Therefore, it was considered that *N*-isopropyl-3-alkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-1-one **xxxiib** could be obtained upon prolonged heating of enaminolactone **xxxib** as a key intermediate towards the synthesis of benzo[*g*]isoquinoline-1,5,10(2*H*)-trione **xxxixb**. Unfortunely, the prolongation of heating to 12 hours did not give the desired benzofuroisoquinoline derivative **xxxiib**.

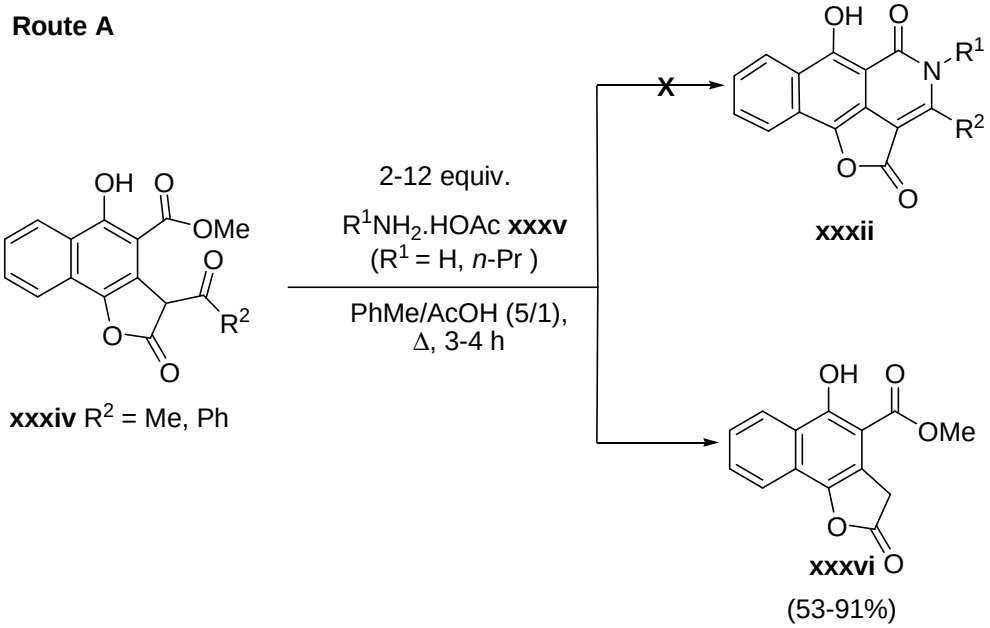


Therefore, three other routes have been explored towards the synthesis of 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylanthraquinones **xxxix**. Two routes rely on the synthesis of *N*-substituted 3-alkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-1-ones **xxxii** as key intermediates, which were prepared by

treating 2-methoxycarbonyl-1,4-naphthoquinone **xiii** with either β-ketoesters **xxxiii** and primary amines **xxxv** (Route A) or *N*-alkyl enaminoesters **xxvi** (Route B). A third route consisted of the oxidative addition of *N*-alkyl enaminoesters **xxvi** onto methyl 1,4-dihydroxynaphthalene-2-carboxylate **xviii** (Route C).

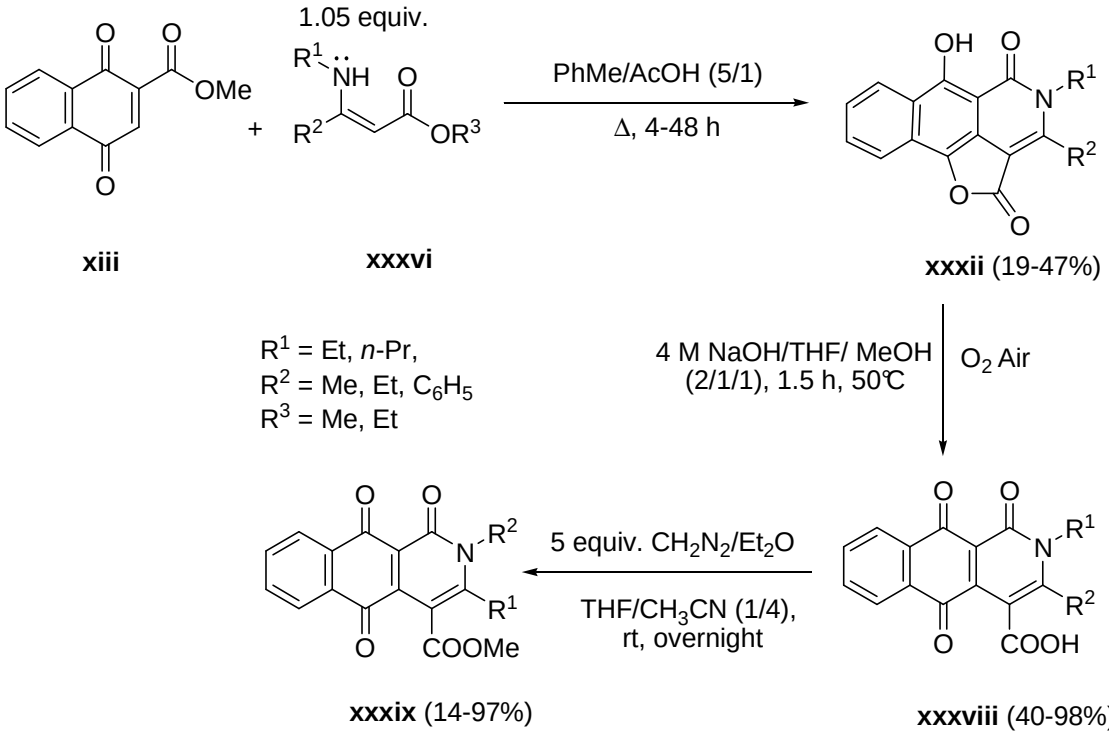


The first route commenced with the reaction of 2-methoxy-1,4-naphthoquinone **xiii** with 3-oxoesters **xxx** under acidic conditions leading to the formation of methyl acyl-2,3-dihydro-5-hydroxy-2-oxonaphtho[1,2-*b*]furan-4-carboxylates **xxxiv**. Subsequent treatment with primary amines **xxxv** in the presence of acetic acid failed to provide *N*-substituted 3-alkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-1-ones **xxxii** but unexpectedly gave lactone **xxxvi**.



The second route utilized a Nenitzescu reaction of 2-acetyl-1,4-naphthoquinone **xiii** with enaminoesters **xxvi** to form *N*-substituted 3-alkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-1-ones **xxxii** which were hydrolized giving the carboxylic acids **xxxviii** which were converted to the corresponding methyl esters **xxxix** in 14-97% yield by treatment with diazomethane.

Route B

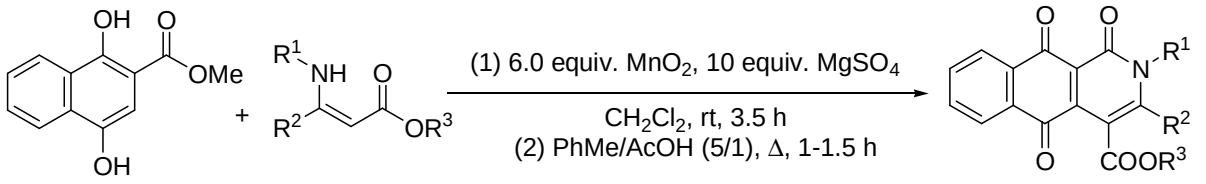


xiii **xxxvi** **xxxii** (19-47%)

xxxix (14-97%) **xxxviii** (40-98%)

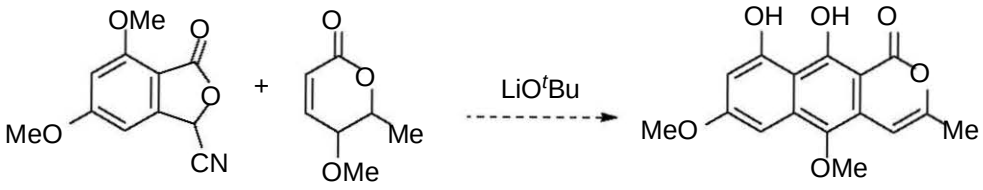
For the third route, the reaction of methyl 1,4-dihydroxynaphthalene-2-carboxylate **xviii** with enaminoester **xxvi** in the presence of manganese(IV) oxide was screened in order to optimize the reaction conditions. A two-step procedure was found to be the best way and *N*-substituted-benzo[*g*]isoquinoline-1,5,10-2*H*-triones **xxxix** were synthesized in 29-71% yield.

Route C



xviii **xxvi** **xxxix** (29-71%)

During this PhD research work, also the first total synthesis of paepalantine **xlii** by a phthalide annulation strategy. Accordingly, 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **xl** would be reacted with 6-hydroxy-2-methyl-6*H*-pyran-3-one **xli**. However, the synthesis of 3-cyano-5,7-dimethoxy-3*H*-isobenzofuran-1-one **xl** was successful while the synthesis of 6-hydroxy-2-methyl-6*H*-pyran-3-one **xli** did not work. Therefore, the first total synthesis of paepalantine **xlii** still remains a challenge.

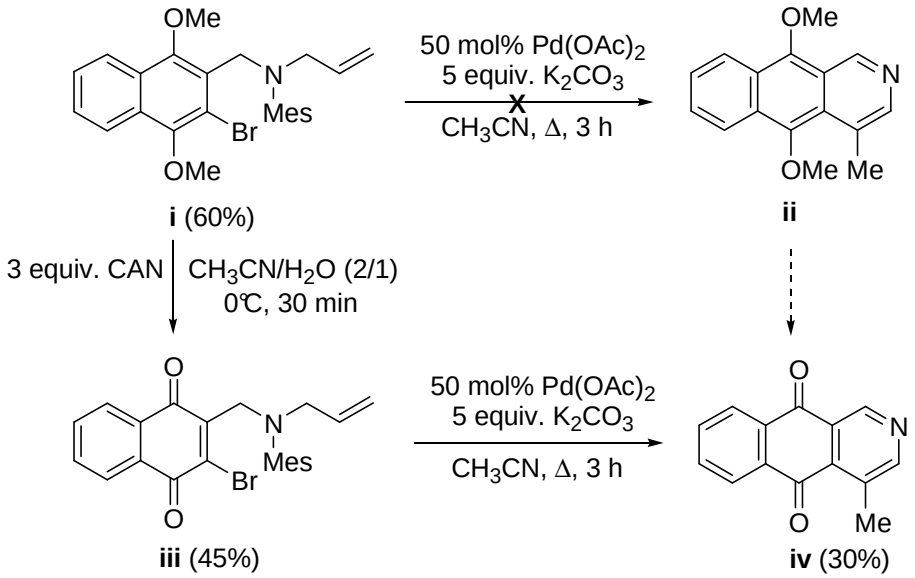


xl **xli** **xlii**

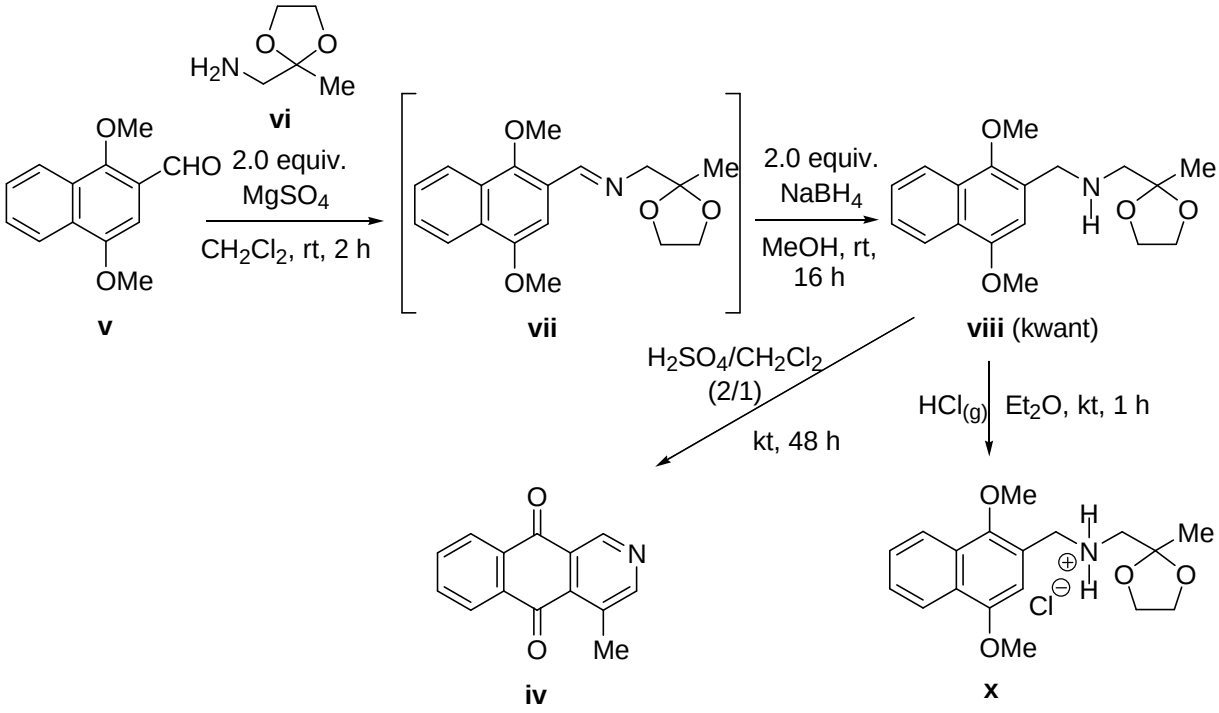
5. Samenvatting

Azaantrachinonen en naftonaftyridines vertegenwoordigen twee belangrijke verwante klassen van bioactieve verbindingen. De synthese van deze verbindingen is een aantrekkelijk doelwit voor zowel organische als medicinale chemici. Bovendien blijkt uit de literatuur dat 2-azaantrachinonen actiever zijn dan de overeenkomstige 1-azaantrachinonen en dat de aanwezigheid van een hydroxylgroep op de C-1 *peri*-carbonylplaats van 2-azaantrachinonen hun biologische activiteit versterkt. Een andere belangrijke eigenschap die de biologische activiteit van tricyclische azaaromatische verbindingen bevordert, is de aanwezigheid van een covalente binding tussen het tricyclische aromatische systeem en een andere aromatische ring die de biarylas wordt genoemd. Bijgevolg is de chemie van 2-azaantrachinonen en hun overeenkomstige naftonaftyridine analogen het onderwerp van deze onderzoeksverhandeling.

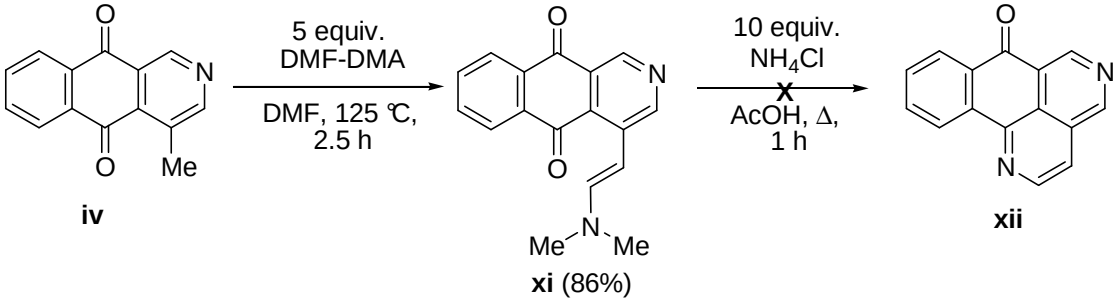
In een eerste deel van het doctoraat werd de synthese van 2-azacleistopholine **iv** voltooid via twee routes. De eerste route gebruikte een ligandvrije Heckreactie in de sleutelstap. Verscheidene pogingen tot aza-ringsluiting van *N*-methaansulfonyl-2-(allylaminomethyl)-3-broom-1,4-dimethoxynaftaleen **i** faalden. Uiteindelijk werd 2-azacleistopholine **iv** gesynthetiseerd door 2-(allylaminomethyl)-3-broom-1,4-naftochinon **iii**, bekomen door oxidatie van 1,4-dimethoxynaftaleen **i** met CAN, te koken onder terugvloei in de aanwezigheid van 50 mol% $Pd(OAc)_2$ in een rendement van 30%.



De tweede route gebruikte een Pomeranz-Fritschreactie in de sleutelstap. Condensatie van 2-formyl-1,4-dimethoxynaftaleen **v** en 2-aminomethyl-2-methyl-1,3-dioxolaan **vi** gaf intermediair imine **vii**, dat kwantitatief gereduceerd werd tot het overeenkomstige aminonaftaleen **viii**. Verscheidene reactieomstandigheden werden getest om de intramoleculaire cyclisatie van dioxolanylmethylamine **viii** uit te voeren gebruik makende van verschillende Brønsted zuren. In de aanwezigheid van gasvormig zoutzuur werd amine **viii** geprotoneerd tot het overeenkomstige ammoniumchloride **x**. 2-Azacleistopholine **iv** werd in een rendement van 50% bekomen door reactie van dioxolanylmethylamine **viii** met zwavelzuur in een tweefasesysteem met dichloormethaan.

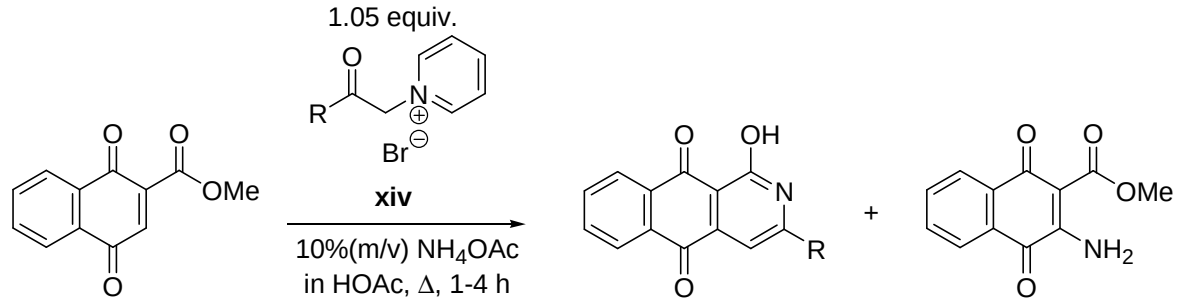


Startende van 2-azacleistopholine **iv** werd (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isochinoline-5,10-dion **xi** gesynthetiseerd in een rendement van 86% door middel van reactie met DMF-DMA. De vervolgreactie van (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isochinoline-5,10-dion **xi** met een overmaat ammoniumchloride in azijnzuur met als doel 2-azasampangine **xii** te vormen resulteerde enkel in niet identificeerbare complexe reactiemengsels. Bijgevolg blijft de synthese van 2-azasampangine **xii** nog steeds een uitdaging.



In het tweede deel van de doctoraatsverhandeling werd de synthese van 2-azaantrachinonen uitgewerkt, die gesubstitueerd zijn op de C-1 *peri*-carbonylplaats en gelinkt zijn aan een arylgroep op C-3. Meer specifiek werd hier de synthese 3-aryl-2-aza-1-hydroxyantrachinonen **xv**, 3-aryl-2-aza-1-methylanthrachinonen **xxiii** en 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylantrachinonen **xxvii** onderzocht. 3-Aryl-2-aza-1-(2-dimethylaminovinyl)antrachinonen **xxiv** werden gesynthetiseerd met als doel deze verder om te zetten in de overeenkomstige 2-azasampangine analogen **xxv**.

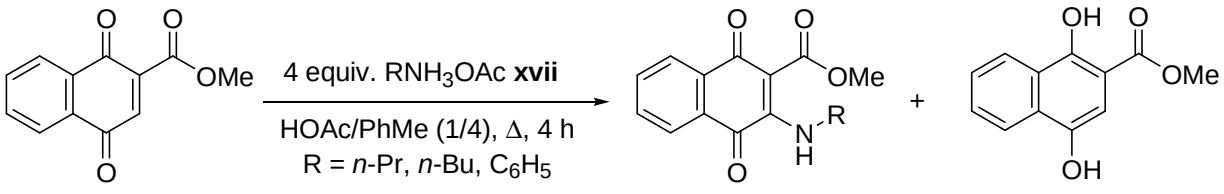
In voortzetting van eerder onderzoek aan de Vakgroep Duurzame Organische Chemie en Technologie, leverde de reactie van 2-methoxycarbonyl-1,4-naftochinon **xiii** met pyridiniumzouten **xiv** onder Krönhke omstandigheden 3-aryl-1-hydroxybenzo[*g*]isochinoline-5,10-dionen **xv** op in een rendement van 40-75% en 3-amino-2-methoxycarbonyl-1,4-naftochinon **xi** als nevenproduct in een rendement van 15-20%. Hierbij werd de vorming van de doelverbindingen **xv** door de aanwezigheid van elektronenzuigende groepen, terwijl de afwezigheid van elektronenzuigende groepen de vorming van nevenproduct **xvi** bevorderde.



xiii **xv** (40-75%) **xvia** (15-20%)

R = C_6H_5, 4-ClC_6H_4, *t*-Bu, OEt, NH_2

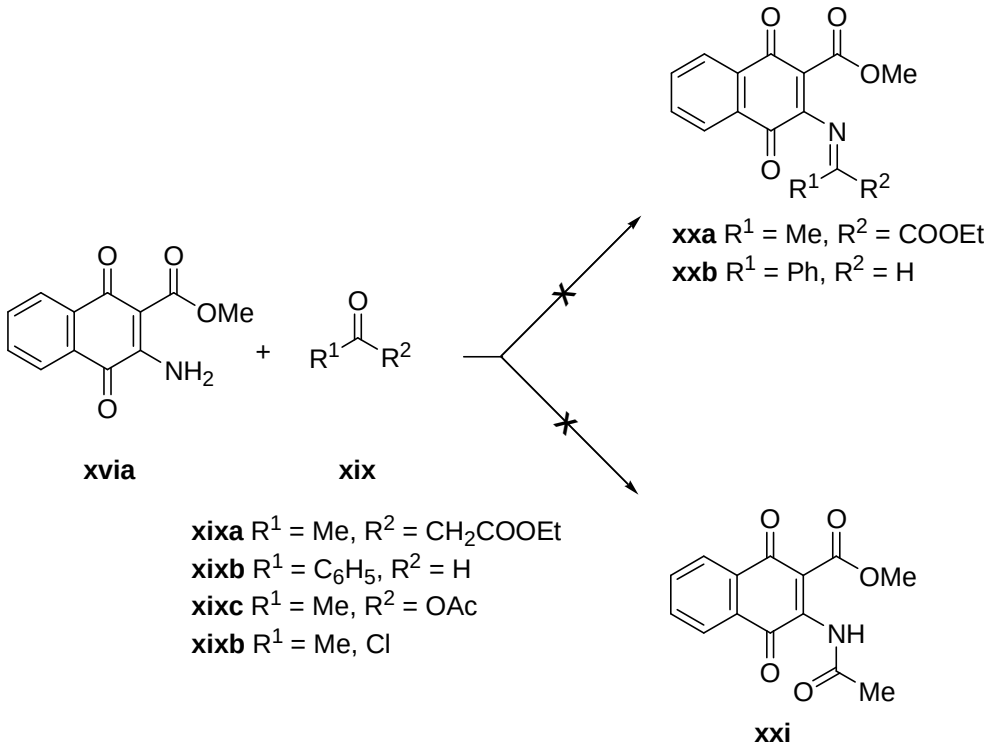
3-Alkylamino- en 3-arylamino-2-methoxycarbonyl-1,4-naftochinonen **xvi** werden bereid door geactiveerd naftochinon **xiii** en alkyl- of arylammoniumacetaten **xvii** te verhitten onder terugvloei in een rendement van 69-87% in de aanwezigheid van kleine hoeveelheden methyl-1,4-dihydroxynaftaleen-2-carboxylaat **xviii** (0-12%). Deze laatste verbinding **xviii** werd gevormd door autooxidatie-reductie van startmateriaal **xiii** en het hydrochinon gevormd na additie de aminogroep aan geactiveerd naftochinon **xiii**.



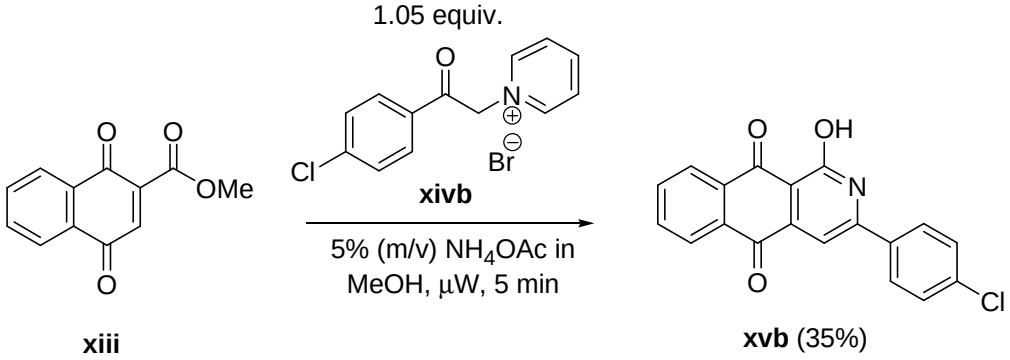
xiii **xvib-c** (69-87%) **xviii** (0-12%)

Het was onmogelijk om de aminogroep van 3-amino-2-methoxycarbonyl-1,4-naftochinon **xvia** te imineren of te acetyleren onder zure, neutrale of basische omstandigheden. Dit werd toegeschreven

aan het vinyloge karakter van de aminogroep en de mogelijkheid om intramoleculaire waterstofbindingen te vormen.

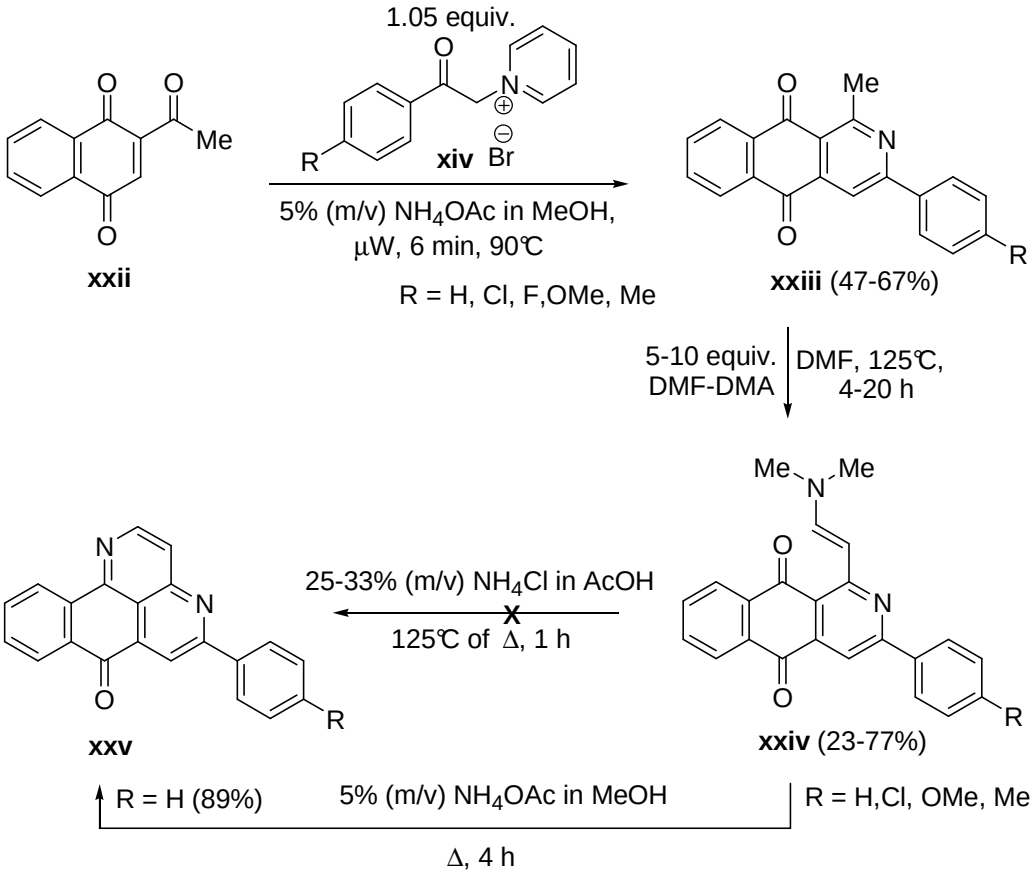


De vorming van het nevenproduct **xvia** kon vermeden worden door de synthese van 3-aryl-1-hydroxybenzo[*g*]isochinoline-5,10-dionen **xv** uit te voeren in een microgolfreactor onder omstandigheden die eerder werden geoptimaliseerd aan de Vakgroep Duurzame Organische Chemie en Technologie.

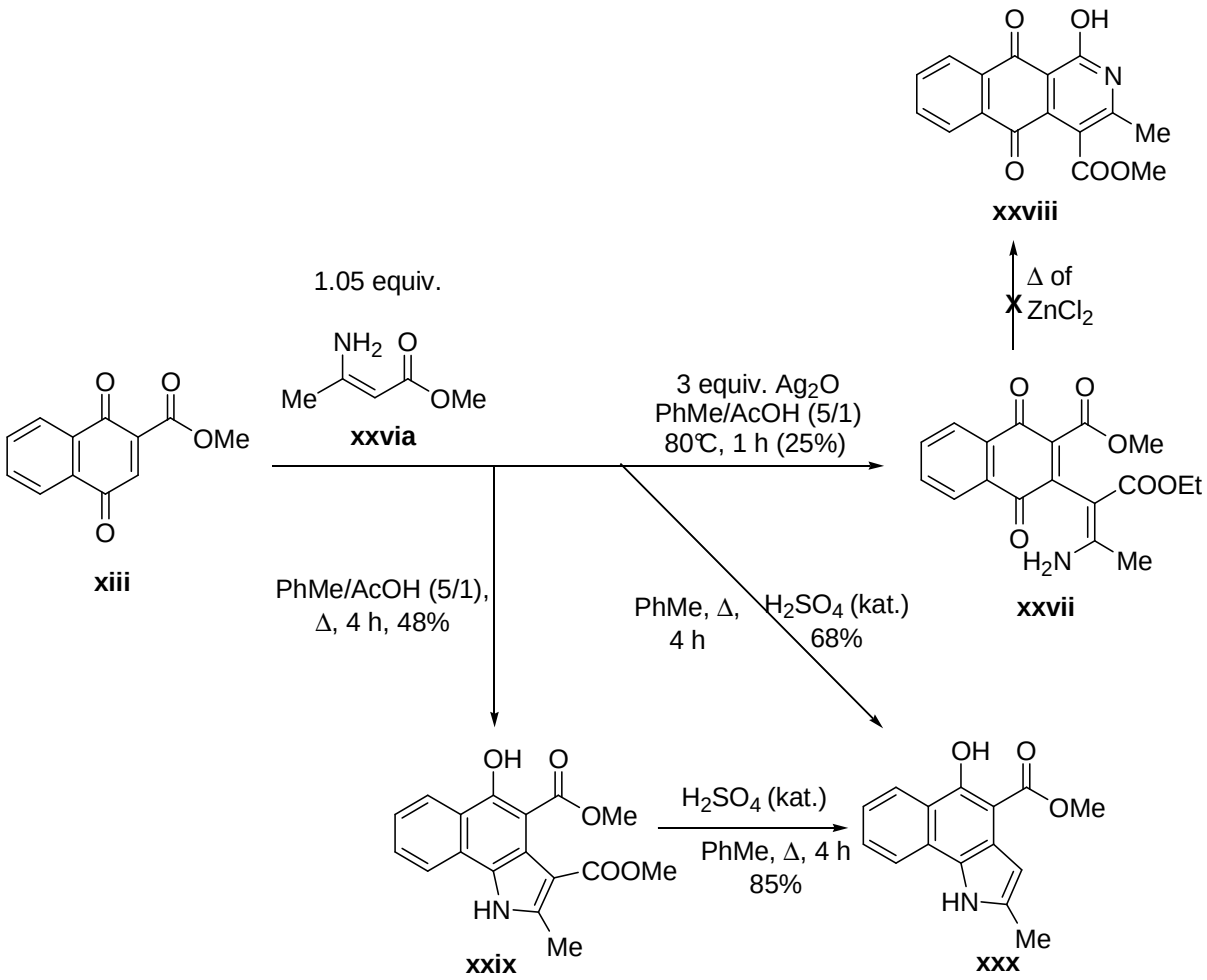


2-Acetyl-1,4-naftochinon **xxii** en pyridinium zouten **xiv** werden onder de hierboven vermelde microgolf geassisteerde Krönkhe omstandigheden behandeld met vorming van 3-aryl-1-methylbenzo[*g*]isochinoline-5,10-dionen **xxiii** in een rendement van 47-67%. Vervolgens werden 3-aryl-1-methylbenzo[*g*]isochinoline-5,10-dionen **xxiii** in reactie gebracht met een overmaat DMF-DMA, resulterend in 3-aryl-1-[2-(dimethylamino)vinyl]benzo[*g*]isochinoline-5,10-dionen **xxiv** in een rendement van 23-77%. Verscheidene pogingen om de overeenkomstige naftonaftyridinen **xxv** te bereiden volgens literatuurprocedures faalden. Desalniettemin leverde koken onder terugvloei van 3-aryl-1-

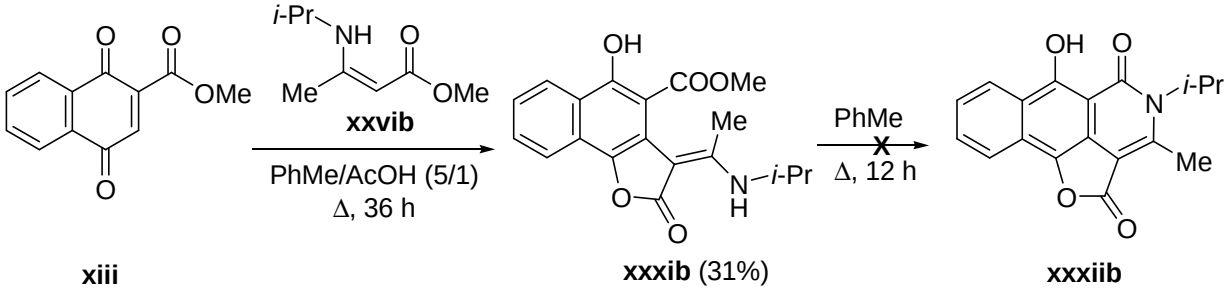
(dimethylaminovinyl)benzo[*g*]isochinoline-5,10-dion **xxiva** in methanol in de aanwezigheid van NH_4OAc het overeenkomstige 5-fenyl-7*H*-nafto[3,2,1-*de*]naftyridine-7-on **xxva** in een rendement van 89%.



De synthese van 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylantrachinon **xxxix** ging uit van 3-methoxycarbonyl-1,4-naftochinon **xxii** and enaminoesters **xxvi**. Om optimale reactieomstandigheden te vinden voor deze synthese werd de reactie van 3-methoxycarbonyl-1,4-naftochinon **xxiii** met methyl 3-aminocrotonaat **xxvia** gescreend. Deze reactie gaf 5-hydroxyindool **xxix** wanneer de verbindingen werden verhit onder terugvloei in een mengsel van tolueen en azijnzuur. Indool **xxx** werd bekomen in kokende tolueen in de aanwezigheid van een katalytische hoeveelheid zwavelzuur. Indool **xxx** kon eveneens bekomen worden door 5-hydroxyindool **xxix** te behandelen met een katalytische hoeveelheid zwavelzuur in kokende tolueen. Alleen Michaeladduct **xxvii** werd geïsoleerd in een rendement van 25% wanneer de reactie uitgevoerd werd bij 80°C. Pogingen om dit Michaeladduct **xxvii** te cycliseren tot het corresponderende methyl-1-hydroxy-3-fenylbenzo[*g*]isochinoline-5,10-dion-4-carboxylaat **xxviii** door middel van verhitting of $ZnCl_2$ faalden.

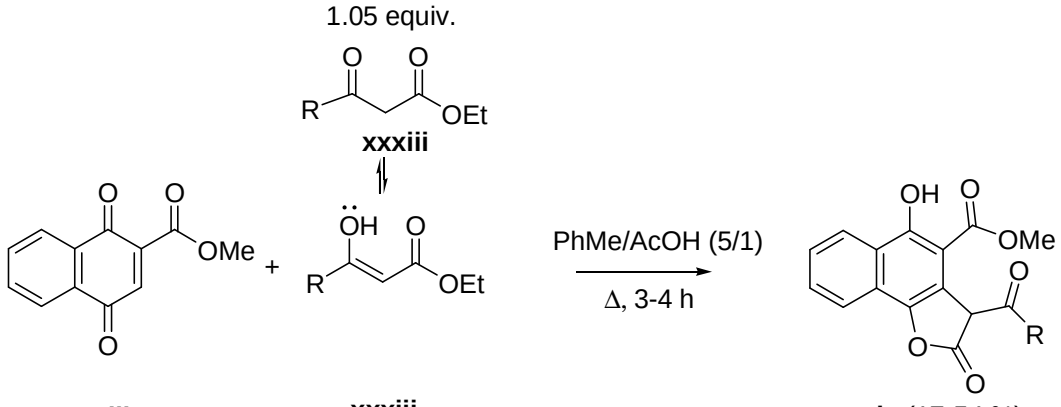


Teneinde de nucleofiliciteit van de aminogroep van enaminoesters **xxvi** beter te benutten, werd methyl-*N*-isopropyl-3-aminocrotonaat **xxvib** in reactie gebracht met geactiveerd naftochinon **xiii** in een mengsel van tolueen en azijnzuur. Na 36 uur werd alleen enaminolacton **xxxib** geïsoleerd. Daarom werd vooropgesteld dat *N*-isopropyl-3-methylbenzo[*g*]furo[4,3,2-*de*]isochinoline-1-on **xxxiib** bekomen kon worden door verhitting van enaminolacton **xxxib** als een sleutelintermediair in de synthese van benzo[*g*]isochinoline-1,5,10-(2*H*)-trionen **xxxix**. Helaas leverde langdurig verhitten niet het gewenste benzofuroisochinolinederivaat **xxxiib** op.

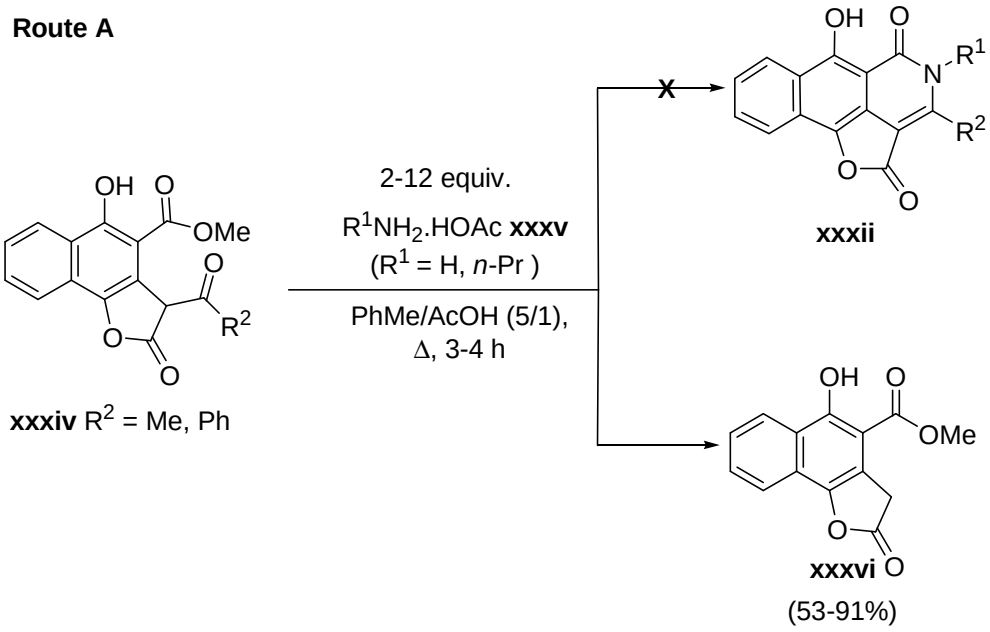


Daarom werden drie andere routes onderzocht om de beoogde 3-aryl-2-aza-1-hydroxy-4-methoxycarbonylantrachinonen **xxxix** te synthetiseren. Twee routes steunden op de synthese van *N*-gesubstitueerde 3-alkylbenzo[*g*]furo[4,3,2-*de*]isochinoline-1-onen **xxxii** als intermediairen. Deze werden

bereid door 2-methoxycarbonyl-1,4-naftochinon te behandelen **xiii** met ofwel β-ketoesters **xxxiii** en primaire amines **xxxv** (Route A) ofwel *N*-alkylenaminoesters **xxvi** (Route B). Een derde route bestond uit de oxidatieve additie van *N*-alkylenaminoesters **xxvi** aan methyl-1,4-dihydroxynaftaleen-2-carboxylaat **xviii** (Route C).



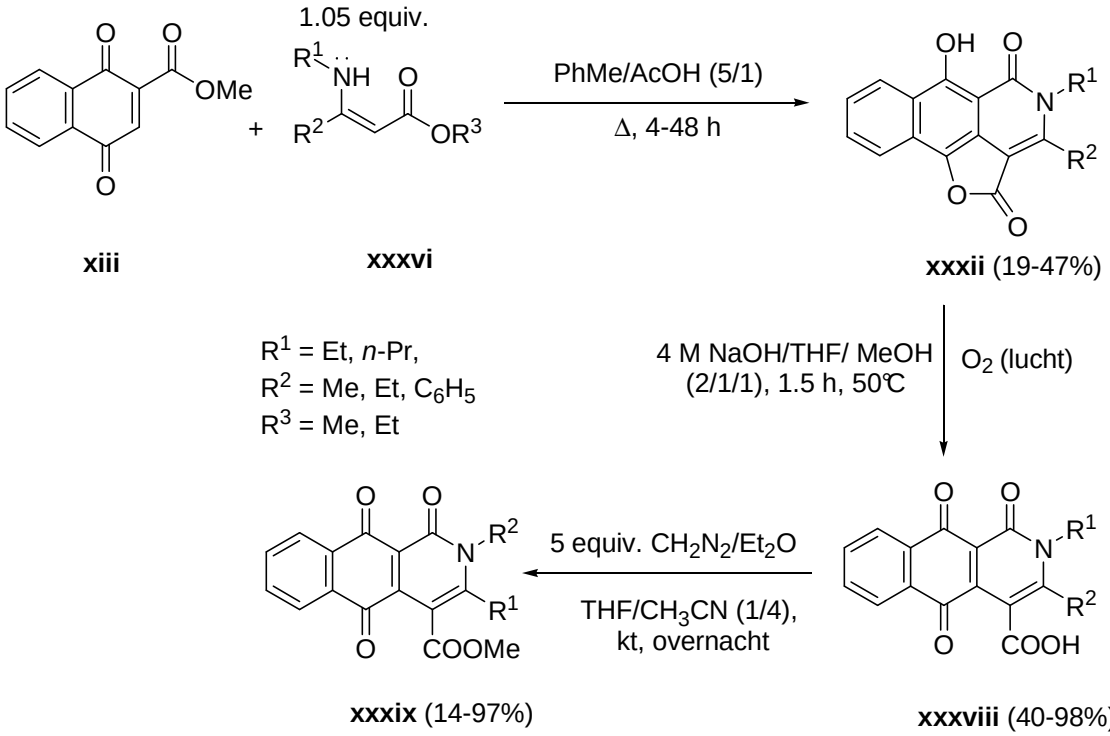
De eerste route vertrok van de reactie van 2-methoxycarbonyl-1,4-naftochinon **xiii** met 3-oxoesters **xxx** in zuur midden met vorming van naftofuranon **xxxiv**. Behandeling van dit naftofuran **xxxiv** met primaire amines **xxxv** in de aanwezigheid van azijnzuur faalde om benzo[*g*]furo[4,3,2-de]isochinoline-2,5(*4H*)-dionen **xxxii** te leveren maar gaf onverwacht methyl-2,3-dihydro-5-hydroxy-2-oxonafto[1,2-*b*]-furan-4-carboxylaat **xxxvi**.



De tweede route steunde op de Nenitzescureactie van 2-acetyl-1,4-naftochinon **xiii** met enaminoesters **xxvi** om benzo[*g*]furo[4,3,2-de]isochinoline-2,5(*4H*)-dionen **xxxii** te vormen. Deze laatste werden gehydrolyseerd tot de overeenkomstige carbonzuren **xxxviii**. Methylering met diazomethaan leverde

2,3-digesubstitueerde methyl-1,2,5,10-tetrahydro-1,5,10-trioxobenzo[*g*]isochinole-4-carboxylaten **xxxix** in een rendement van 14-97%.

Route B



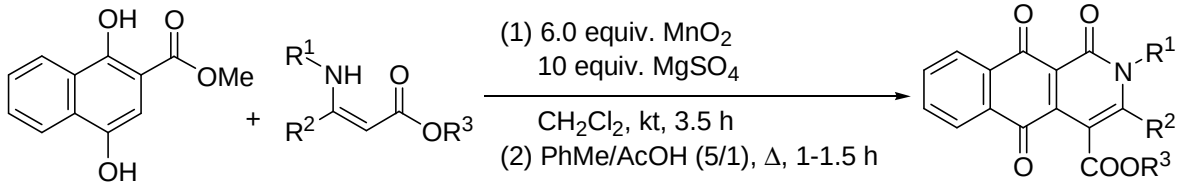
xiii **xxxvi** **xxxii** (19-47%)

R^1 = Et, *n*-Pr,
R^2 = Me, Et, C_6H_5
R^3 = Me, Et

xxxix (14-97%) **xxxviii** (40-98%)

Voor de derde route werd de reactie van methyl-1,4-dihydroxynaftaleen-2-carboxylaat **xviii** met enaminoester **xxvi** in de aanwezigheid van mangaan(IV)oxide bestudeerd om de reactieomstandigheden te optimaliseren. Een tweestapsprocedure bleek de beste manier te zijn waarbij *N*-gesubstitueerde benzo[*g*]isochinoline-1,5,10(2*H*)-trionen **xxxix** werden gesynthetiseerd in een rendement van 29-71%.

Route C

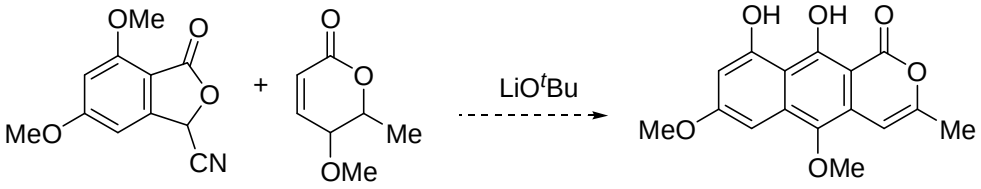


xviii **xxvi** **xxxix** (29-71%)

R^1 = Et, *n*-Pr
R^2 = Me, Et, C_6H_5
R^3 = Me, Et

In het huidige doctoraatsonderzoek was ook de eerste totaalsynthese van paepalantine **xlii** gepland aan de hand van een ftalide anneleringsreactie. Meer specifiek zou 3-cyaan-5,7-dimethoxy-3*H*-isobenzofuran-1-on **xl** in reactie gebracht worden met 6-hydroxy-2-methyl-6*H*-pyran-3-on **xli**. Alhoewel de synthese van 3-cyaan-5,7-dimethoxy-3*H*-isobenzofuran-1-on **xl** succesvol uitgevoerd werd, bleek de

in de literatuur gerapporteerde synthese van 6-hydroxy-2-methyl-6*H*-pyran-3-on **xli** niet te reproduceren. Bijgevolg blijft de eerste totaalsynthese van paepalantine **xlii** nog steeds een uitdaging.



xl **xli** **xlii**

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Curriculum vitae

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Primary:

- **1977-1983** Ecole Primaire de la Gare I - Kinshasa, RD Congo - Primary school certificate

Humanity:

- **1983-1989** College St-Joseph (ELIKYA) - Kinshasa, RD Congo -State diploma (Biology-Chemistry)

University:

- **1990-1995** University of Kinshasa - Kinshasa, RD Congo - Bachelor of Science (Chemistry)

  Dissertation: 'Contribution aux applications industrielles des charbons actifs'

- **1996-1999** University of Kinshasa - Kinshasa, RD Congo - Licensee (Organic-Chemistry)

  Dissertation: 'Epuration des eaux usées à l'aide de Charbons actifs de la bagasse à canne à sucre, de Ntola et de Lifaki'

- **2003-2005** University of Kwazulu-Natal, Durban, South Africa, Master of Science (Chemistry of Natural Products)

  Thesis: Chemical investigation of two South Africa *Vepris* species

  Promoter: Prof. D.A. Mulholland and Dr. P. Coombes

- **2007- 2011** Ghent University - Gent, Belgium, PhD student (Applied biology: Chemistry-Organic synthesis)

  PhD thesis: Synthesis of quinoid natural products and analogues.

  Promoter: Prof. Dr. ir. N. De Kimpe

III. Scientific publications

Peer-reviewed publications (SCI)

1. **Mbala, M.B**, Jacobs, J., Claes, P., Mudogo, V. and De Kimpe, N. Investigation towards the synthesis of benzo[*g*]isoquinoline-1,5,10(2*H*)-triones. *Tetrahedron* **2011***, 67,* 8747-8756.
2. Jacobs, J.; **Mbala, M.B.**; Kesteleyn, B.; Diels, G.; De Kimpe, N. Straightforward palladium-mediated synthesis of N-substituted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones. *Tetrahedron* **2009**, *64*, 6364-6371.
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Others

1. Mpiana, P.T.; Makelele, L.K.; Oleko, R.W.; Bokota, M.T.; Tshibangu, D.S.T. Ngbolua, K.N.; **Mbala, M.B.**; Atibu, E.K.; Nsimba, S.M. Antisickling activity of medicinal plants used in the management of Sickle cell Disease in Tshopo district, D.R.Congo. *Australian J. of Medical Herbalism* **2010**, *22*, 132-136.
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3. Mpiana, P.T.; Mudogo, V.; Kabangu, Y.F.; Tshibangu, D.S.T.; Ngbolua, K.N.; Atibu, E.K.; Mangwala, K.P.; **Mbala**, **M.B.**; Makelele, L.K.; Bokota, M.T. Antisickling activity and thermostability of anthocyanins extracts from a congolese plant, *Hymenocardia acida Tul*. (Hymenocardiaceae), *Int. J. Pharmacol.* **2009**, *5*, 65 -70.
4. Mpiana, P.T.; Mudogo, V.; Ngbolua, K.N., Tshibangu, D.S.T.; Shetonde, O.M.; **Mbala, M.B**. *In vitro* antisickling activity of anthocyanins from *Ocimum basilicum* L. (Lamiaceae). *Int. J. Pharmacol.* **2007**, 3: 371-374.

Local publications

1. **Mbala, M.B.**; Coombes, P.; Mullholand, D.A. Furoquinoline alkaloids from two South Africa *Vepris*. *Annales de la faculté des sciences-Unikin*, **2006**, *1*, 15-21.
2. Mbala, M.B.; Makambo, L.L.; Nsaka, L.S. Evaluation de l'Activité Antibactérienne de l'huile essentielle de Gingimbre (*Zingiber Officinalis*) croissant en République Démocratique de Congo. *Rev. Cong. Sc. Nuc.*, **2002**, ½, 145-149.

Submitted for publication

1. Mpiana, P.T.; Ngbolua, K.N.; Mudogo, V.; Tshibangu, D.S.T.; Atibu, E.K.; **Mbala, M.B.**; Tshilanda, D.D. Anti-sickle erythrocytes haemolysis properties and inhibitory effect of anthocyanins extracts of *Trema orientalis* (Ulmaceae) on the aggregation of human deoxyhemoglobin S *in vitro*.(*Blood transfusion*)
2. Mpiana, P.T.; Mudogo, V.; Tshibangu, D.S.T; Ngbolua, K.T.; Atibu, E.K.; **Mbala, M.B.**; Tshilanda, D.D.; Dianzenza, E.; Ilunga, A. M. *In vitro* antisickling activity, thermodegradation and photodegradation of the anthocyanins extracted from the leaves of *Annona senegalensis.* (*Asian Journal of Traditional Medicine*).

IV. Conference participations

Oral presentations

1. **Mbala, M.B.**; Coombes, P.; Mullholand, D.A. Furoquinoline alkaloids from two South Africa *Vepris*: Isolation, characterization and antiplasmodial activity. World Association of Young Scientists (WAYS-ROA). Regional meeting, Pretoria, South Africa. 21-22 March 2007.
2. **Mbala, M.B**.; Ngbolua, K.N.; Tshibangu, D.S.T.; Shetonde, O.M.; Mpiana, P.T.; Mudogo, V.C. *In vitro* anti-sickling activity of some congolese plants. TWAS Conference for Young Scientists. Nairobi, Kenya, December 2006.

Poster presentations

1. **Mbala, M.B.**; Jacobs, J.; De Kimpe, N. Unusual *N*-substituted 3-alkylbenzo[*g*]furo[4,3,2-*de*]isoquinoline-1-ones as key intermediates toward benzo[*g*]isoquinoline-1,5,10(*2H*)-triones. 13th Sigma-Aldrich Organic Synthesis Meeting. Spa; 2-3 December 2009.
2. Mudogo, V.; Mpiana, P.T. ; Tshibangu, D.S.T; Ngbolua, K.N.; Mangwala, K.P.; Atibu, E.K.; **Mbala, M.B**; Shetonde, O.M.; Kakule, M.K.; Makelele, L.K.; Bokota, M.T. Investigation into the structure, properties and reactivity of bioactive compounds. *In*: The Third World Academy of Science (TWAS) 11th General Conference, Durban, South Africa, 20-23 October 2009 (p22).
3. Mudogo, V.; Mpiana, P.T.; Tshibangu, D.S.T.; Shetonde, O.M.; Ngbolua, K.N.; **Mbala, M.B**. Antisickling activity of some medicinal plants from congolese biodiversity. African Issues Symposium: Food Security, Environmental Suitability & Human Health. Kansas State University USA, March 30 - April 1, 2009.
4. Mpiana, P.T., Mudogo, V.; Tshibangu, D.S.T.; Shetonde, O.M.; Ngbolua, K.N.; **Mbala, M.B.** Antisickling activity of some Congolese plants, In: Drug discovery from African flora, The 12th

Symposium of the Natural Product Research Network for Eastern and Central Africa, 22-26 July 2007, University of Makerere, Kampala, Uganda, p.45 (PS-6).